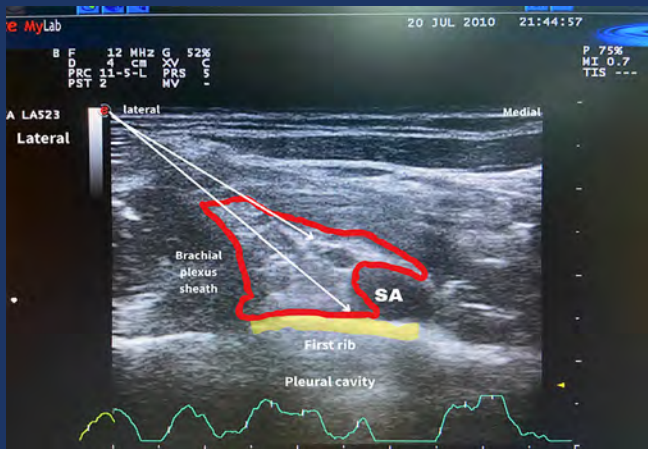
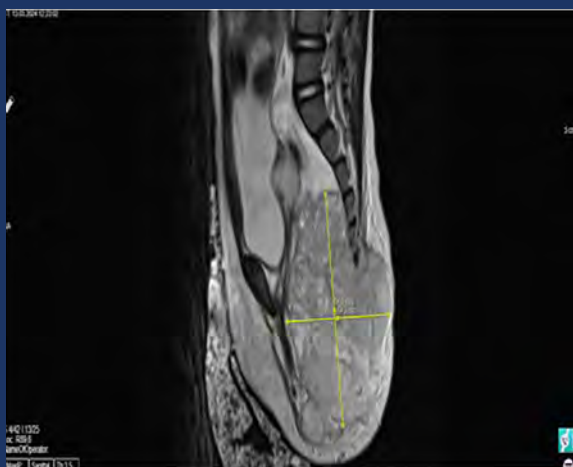


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Clinical Characteristics of Pediatric Germ Cell Tumors
Porcelain Gallbladder Missed on Preoperative Imaging
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Volume 17 Issue 4 October Year 2025

AIMS AND SCOPE

Comprehensive Medicine is the official publication of Kanuni Sultan Süleyman Training and Research Hospital. It is published regularly, four times a year, in January, April, July and October as an electronic journal.

The journal was published by Bakırköy Obstetrics and Gynecology Hospital in 1990s as JOPP (gynecology obstetrics, pediatric and pediatric surgery) and has reached the status of 'peer-reviewed journal' in 2009. The journal was changed to İstanbul Kanuni Sultan Süleyman Tıp Dergisi in 2014 and known as Comprehensive Medicine beginning from 2023.

The language of the journal is English. It is a peer-reviewed journal and does not charge any fee from readers or authors. All published articles are open access.

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Moreover, by conducting an objective evaluation within the framework of the ethical rules of the journal, the consultant aims to enable the reviewers to transfer their experiences to the authors, to give the author a perspective on how to write a scientific article, and to contribute to the elimination of the scientific value of the articles published in our country.

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COMPREHENSIVE MEDICINE

Formerly İstanbul Kanuni Sultan Süleyman Tıp Dergisi

CONTENTS

Volume 17 Issue 4 October Year 2025

RESEARCH ARTICLES

- 239** Social Approach to Human Papilloma Virus and Vaccine: Reflection of Knowledge, Attitudes and Costs
Melih Bestel, Elif Uçar
- 245** A Retrospective Evaluation of Acute Poisoning Cases in Emergency Departments: Focus on Suicide Attempts by Poisoning
Mehmet Gün
- 252** Evaluation of Fermented Food Consumption During Pregnancy and Breastfeeding in Mothers of Children with Egg Allergy
Halil Alkaya, Uğur Altaş, Seda Çevik, Zeynep Meva Altaş, Ebru Oğultekin Vazgeçer, Mehmet Yaşar Özkars
- 259** Outcomes of Screening for Retinopathy of Prematurity Using United Kingdom and United States Criteria at a Tertiary Referral Center in Türkiye
Cengiz Gül, Havvanur Bayraktar, Yusuf Berk Akbaş
- 265** Infodemiology Meets Pharmacoepidemiology: Search Trends and National Drug Use Patterns for Pain-related Medications in Türkiye
Sevtap Badıl Güloğlu, Gülsev Özen Yorgancıgil, Hatice Kübra Aşık, Demet Ferahman, Tuğba Şahbaz
- 271** Evaluation of Serum Lipid Profile as a Predictive Biomarker for Survival in Gastrointestinal Cancer Patients
Özgür Yılmaz, Sabin Göktaş Aydın, Osman Erinc, Ahmet Aydın, Hatice Telci, Şengül Aydın Yoldemir
- 279** Optimal Timing of Colostomy and Enterostomy Reversal: Insights from A 15-Year Retrospective Analysis
Emre Furkan Kırkan, Aylin Acar, Hasan Kumru, Tolga Canbak
- 286** Retrospective Analysis of Cardiac CT Angiography Applications in Pediatric Cardiology Clinic: Single Center Experience
Ali Nazım Güzelbağ, Burcu Çevlik, İsa Özyılmaz, Hatice Dilek Özcanoğlu, Selin Sağlam, Osman Nuri Bayrak, Behzat Tüzün, Ali Can Hatemi, Erkut Öztürk, Serap Baş
- 296** Maternal Obesity and Postpartum Hemorrhage in Women Undergoing Cesarean Delivery: A Retrospective Cohort Study
Nura Fitnat Topbaş Selçuki, Hikmet Tunç Timur, Meriç Kabakcı, Mustafa Göksu, Salih Yılmaz, Kerem Doğa Seçkin, Pınar Kadiroğulları
- 301** Clinical Characteristics and Treatment Patterns in Pediatric Localized Scleroderma: A Referral-center Experience
Gülşah Kavrul Kayaalp, Büşra Başer Taşkın, Aslı Dudaklı, Nuray Aktay Ayaz
- 309** Evaluation of Clinical, Radiological, and Pathological Efficacy Regarding Neoadjuvant Chemotherapy in Breast Cancer
Süleyman Büyükaşık, Yusuf Emre Altundal, Burak Kankaya, Cansu Esen, Selin Kapan
- 317** Retrospective Analysis of Emergency Laparotomy and Laparoscopy Outcomes: A Single-center Experience Comparing Etiologies and Early Postoperative Results in Geriatric and Adult Patients
İsmail Tırnova, Ahmet Serdar Karaca
- 323** Clinical and Treatment Characteristics of Pediatric Cranial/Extracranial Germ Cell Tumors and Literature Review
Hüseyin Avni Solgun, Duygu Özkorucu Yıldırğan, Ali Ayçiçek, Sibel Akpınar Tekgündüz
- 332** Ultrasound-guided Dextrose Prolotherapy for Refractory Piriformis Syndrome: A Retrospective Study
Mert Zure, Elif Özyiğit, Dilek Ün Oğuzhanasiltürk, Tugba Şahbaz
- 338** Comparison of Excessive Daytime Sleepiness Among Clinical Types of Obstructive Sleep Apnoea Syndrome
İşıl Yazıcı Gençdal, Mesrure Köseoğlu, Vasfiye Kabeloğlu, Oya Öztürk, Kürşat Nuri Baydili

REVIEW

- 346** Ultrasonography-guided Peripheral Nerve Blocks in Orthopedic Upper Extremity Surgery: A Narrative Review
Kadir Arslan, Ayça Sultan Şahin

CASE REPORT

- 358** Porcelain Gallbladder Undetected by Preoperative Imaging Findings: A Case Report and Literature Review
Sofia Barrientos-Villegas, Luis Felipe Cabrera-Vargas, Raquel Cardenas, Gabriela Prada-Zapata

COMPREHENSIVE MEDICINE

Formerly İstanbul Kanuni Sultan Süleyman Tıp Dergisi

Volume 17 Issue 4 October Year 2025

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Our journal has entered a new editorial term marked by renewal and progress. With the restructuring of the editorial board and the appointment of new section editors, we aim to enhance the scientific quality, ethical standards, and international visibility of our publication.

As a general medical journal, we publish qualified research articles, reviews, and case reports from both medical and surgical disciplines. While our journal is already indexed in national databases, our primary goal in this new term is to further strengthen its scientific value and achieve a more prominent position in reputable international indexing databases.

A rigorous peer-review process, the promotion of interdisciplinary collaboration, and the reinforcement of editorial transparency will remain our guiding principles. With the continued support of our authors, reviewers, and readers, we are confident that our journal will continue to evolve as a reliable platform for the advancement of medical science at both national and international levels.

Respectfully yours,

Assoc. Prof. Erkan Somuncu, MD

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Social Approach to Human Papilloma Virus and Vaccine: Reflection of Knowledge, Attitudes and Costs

✉ Melih Bestel, ✉ Elif Uçar

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ABSTRACT

Objective: The aim of this study was to evaluate the level of knowledge of the public about human papilloma virus (HPV) and the HPV vaccine, and to determine their attitudes towards HPV vaccination and the obstacles they encounter.

Materials and Methods: In this descriptive study, a structured questionnaire including questions about HPV infection, vaccine types, vaccination age ranges, and vaccine efficacy was applied to the participants. In addition, the effect of factors such as their attitudes towards vaccination, information sources, and the cost of vaccination were also evaluated.

Results: The results showed that there is a serious lack of knowledge about HPV and the HPV vaccine in the community. Most of the participants were not sufficiently familiar with the vaccine, did not know what HPV infection was, and had doubts about the protection of the vaccine. Lack of information, cost, lack of confidence, and inadequacies in the health system were the main reasons for not getting vaccinated.

Conclusion: Our study revealed that public awareness of HPV vaccination is low, and the cost of the vaccine is an important barrier. In order to implement an effective HPV vaccination programme, health policies should be established to raise public awareness, the cost of the vaccine should be reduced, and educational activities should be increased through health professionals.

Keywords: Human papilloma virus, HPV vaccine, opposition to vaccine, social awareness, student

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INTRODUCTION

Human papillomavirus (HPV) can cause condylomas in various parts of the body and is a public health problem closely related to head and neck cancers and cervical cancer. More than 500,000 newly diagnosed cases of cervical cancer are detected each year.^[1] It has been reported that cervical cancer caused more than 34,000 deaths after 2020.^[2] The majority of these deaths were observed in undeveloped or developing countries.^[3,4] In recent years, there has been a significant downward trend in the mortality and morbidity of cervical cancer with the widespread use of cervical cancer screening and vaccination programmes in developed countries.^[5] However, in undeveloped or developing countries, it is observed that there is an increasing trend in the morbidity and mortality of cervical cancer due to deficiencies in screening programmes and defects in the health system.^[6] Studies have

shown that HPV species in the high-risk group are the etiological agents of cervical cancer with persistent infection.^[7] In their study, Ngo-Metzger et al.^[7] found that high-risk strains were present in 99.7% of patients with cervical cancer.

HPV is quite common in sexually active men and women. It can often resolve spontaneously without requiring any treatment or giving any symptoms. However, some types cause permanent infections that may lead to cervical cancer.^[8] There are more than 200 defined types of HPV.^[9] HPV 16 and HPV 18 types are the most common types in terms of cervical cancer risk. These HPV species play an important role in the aetiology of cervical intraepithelial neoplasia and then invasive cervical cancer by integrating into the genomic DNA of the individual. It may cause cancer through oncogenic activations and disruptions in the tumour suppressor mechanism.^[10,11]



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Cervical cancer is recognised as one of the most preventable and treatable cancer types worldwide. In the prevention of this disease, the HPV vaccine stands out as the primary protection method and regular screening tests as the secondary protection method. If the HPV vaccine is included in national immunisation programmes, vaccination of adolescent girls and boys before they start sexual life will be one of the most effective ways to prevent the spread of HPV infection.^[11]

In this study, it was aimed to measure the level of awareness of the public about HPV in a developing country and to evaluate their perspectives on the vaccination programme.

MATERIALS and METHODS

In 2024, 560 people consisting of women and their male partners who came to the obstetrics and gynaecology department of a private hospital for examination for any reason were included in the study. The study was prospectively designed, and the participants were randomly and voluntarily selected. The patients were first informed about the study, and the questionnaire was applied before their examination. The results were recorded. Pregnant patients were not included in the study. This study was approved by the Ethics Committee of Istanbul Esenyurt University (07.09.2023 date and 2023/08-04, Number: E-12483425-299-35342). The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Descriptive statistics were used in the study. Statistical analyses were performed using SPSS (IBM SPSS Statistics 27; IBM Corporation, Armonk, NY, USA) package programme. Frequency tables and descriptive statistics were used to interpret the findings.

RESULTS

Of the 560 people included in this study, 475 (84.9%) were in the 18–30 age group, 466 (83.2%) were female, 364 (65.0%) had an associate degree, and 551 (98.4%) lived in the city. 234 (41.7%) had a monthly income of <10,000 TL, 373 (66.6%) had health insurance, and 482 (86.1%) did not receive HPV vaccination (Table 1). The results of the answers given to the questions in the questionnaire are shown in Tables 2 and 3.

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Level of Knowledge

Most of the patients (64.5%) who came for examination knew that cervical cancer is the most common gynaecological cancer. However, only 25.1% knew that smoking was a risk factor for this type of cancer. Only 53.4% of the patients knew that HPV can be prevented by barrier methods such as condoms.

Table 1. Demographic data					
Variable (n=560)			Variable (n=560)		
	n	%		n	%
Age			License	90	16.1
Under 18	10	1.8	Master's Degree	14	2.5
18–30	475	84.8	Region of Residence		
31–40	58	10.4	City	551	98.4
41–50	11	2.0	Rular	9	1.6
50 years and over	6	1.0	Monthly income level		
Gender			Less than 10.000 TL	234	41.7
Female	466	83.2	10.000–20.000 TL	202	36.1
Male	94	16.8	More than 60.000 TL	124	22.2
Education			Health Insurance		
Illiterate	3	0.5	Yes	373	66.6
Primary School	11	2.0	No	187	33.4
Secondary Education	15	2.6	HPV vaccine		
High School	63	11.3	Yes	78	13.9
Associate Degree	364	65.0	No	482	86.1

HPV: Human papillomavirus

Table 2. HPV awareness level

Variable	Yes		No		I don't know	
	n	%	n	%	n	%
1. Cervical cancer is the most common gynaecological cancer in the population.	361	64.5	61	10.9	138	24.6
2. The prevalence of cervical cancer in Türkiye is lower than the world average.	162	29.0	157	28.0	241	43.0
3. The majority of cervical cancer cases are seen in developed regions	214	38.2	143	25.5	203	36.3
4. A history of sexually transmitted diseases is a risk factor for cervical cancer.	417	74.5	46	8.2	97	17.3
5. Smoking is not a risk factor for cervical cancer.	141	25.1	268	47.9	151	27.0
6. Oral contraceptive use (birth control pill) is a risk factor for cervical cancer.	197	35.2	141	25.2	222	39.6
7. Having many births is protective for cervical cancer.	147	26.3	216	38.5	197	35.2
8. HPV can be protected by barrier methods such as condoms.	299	53.4	105	18.8	156	27.8
9. HPV can be prevented by birth control methods such as birth control pills and monthly injections.	180	32.1	187	33.4	193	34.5
10. HPV has been detected in most of the cervical cancer cases.	225	40.2	68	12.1	267	47.7
11. HPV is a sexually transmitted infectious agent.	372	66.4	86	15.4	102	18.2
12. HPV can cause genital and extragenital (mouth, throat) warts.	352	62.8	62	11.1	146	26.1
13. There is no screening programme for cervical cancer in our country.	142	25.4	171	30.5	247	44.1
14. Pap-smear test and detection of high-risk HPV types are used in screening.	253	45.1	90	16.1	217	38.8
15. Screening reduces the incidence and mortality of cervical cancer.	213	38	111	19.9	236	42.1
16. HPV is not a serious enough infection to require vaccination.	121	21.6	323	57.7	116	20.7
17. HPV vaccine is protective against some types of cancer in both men and women.	300	53.6	92	16.4	168	30
18. The virus type-specific protection of HPV vaccine in HPV infection is close to 100%.	177	31.6	117	20.9	266	47.5
19. The protection of HPV vaccine against cervical cancer is around 70%.	235	42	76	13.6	249	44.4
20. The ideal age group recommended for HPV vaccination is 11–12 years.	185	33	113	20.2	262	46.8
21. HPV vaccine is included in the routine vaccination programme of the Ministry of Health.	196	35	152	27.1	212	37.9
22. HPV vaccines in Türkiye are of three types: 2, 4, 9-valent and these vaccines are administered in 3 doses.	224	40	39	7	297	53
23. There is no need for screening with pap smear in people who have received HPV vaccine.	111	19.8	184	32.9	265	47.3
24. There is less need for people who have been vaccinated against HPV to use or have a condom used during sexual intercourse.	142	25.4	195	34.8	223	39.8
25. The price of a dose of HPV vaccine is around 1.000 TL	180	32.1	91	16.3	289	51.6

HPV: Human papillomavirus

Table 3. Willingness to be vaccinated

Variable	Yes		No		Ambivalent	
	n	%	n	%	n	%
I'll get the HPV vaccine	331	59.1	54	9.6	175	31.3
If I had a daughter. I would have her vaccinated against HPV	331	59.1	42	7.5	187	33.4
If I had a son. I would have him vaccinated against HPV	308	55	55	9.8	197	35.2
I buy the HPV vaccine for a fee and get it done	230	41.1	96	17.1	234	41.8
I will get the HPV vaccine if it is covered by social security	339	60.5	51	9.1	170	30.4

Table 4. Motivators

Motivators	n	%
Where did you learn about the vaccine?		
Social media	122	21.8
Television	30	5.3
Doctors	76	13.6
Friend	55	9.8
I didn't know about the vaccine	277	49.5
Which lesions does the vaccine protect against?		
Condyloma (wart)	185	33
Cancer	102	18.2
None of them	47	8.4
All of them	226	40.4

67.9% did not know that OCS and monthly injections were not protective. 69.5% of the patients did not know that there is a screening programme for cervical cancer in our country, and 54.9% did not know that smear and high-risk HPV types are investigated in screening. 53.6% knew that vaccination protects both men and women. 60% of the patients did not know that there are 3 types of vaccines in our country (Table 2).

Willingness

In addition, the perspective of the patients on vaccination was evaluated. 59.1% of the patients stated that they would have the vaccine, 59.1% said that they would have the vaccine for their daughters, and 55% said that they would have the vaccine for their sons. While 41.1% of the patients stated that they would have the vaccine even if it was paid, this rate increased to 60.5% if the vaccine was included in the scope of insurance payment by the state (Table 3).

Motivating Factors

21.8% of the patients stated that they learned about the vaccine from social media, and 13.6% from doctors or health workers. 33% of the patients stated that the vaccine was protective against condyloma, 18.2% stated that it was protective against cancer, and 40.4% stated that it was protective against both (Table 4).

DISCUSSION

In this study, we aimed to evaluate the level of knowledge of the public about HPV and to reveal their attitudes towards HPV vaccination. Our results show that there is a serious lack of knowledge among the public and that opposition to vaccination is widespread. Opposition to vaccination is not only due to lack of knowledge but also due to financial concerns

and inadequacies of healthcare providers. With the introduction of the 9-valent HPV vaccine in our country, it has been observed that clinicians have started to recommend this vaccine more frequently. In this study, it was aimed to determine the public's perspective and negative motivations towards HPV vaccination, to reveal the correctable factors, and to contribute to health policies on cervical cancer prevention.

The American Academy of Paediatrics recommends that HPV vaccination should be initiated between the ages of 9–12 years.^[12] In 2007, Australia was the first country to implement the HPV vaccination programme for girls, and in 2013 for boys, with full funding.^[13] Although this practice has been successful, it is reported that efforts to increase the impact of the programme are still ongoing. In Türkiye, even the 4-variant HPV vaccine is not yet fully financed by the public, and vaccination is carried out through individual initiatives and the efforts of healthcare professionals. Again, in a study conducted by Akcaoglu et al.^[14] in Türkiye, it was found that vaccination rates were quite low even in adults, let alone in the paediatric age group. In our study, we found that the rate of those who received the HPV vaccination was only 13.9%. However, even if the HPV vaccine is covered by the social security institution, the rate of those who want to have HPV vaccination remains at only 60.5%. However, the rate of those who said that they would definitely not get the HPV vaccine even if the health system covered it was found to be 9.1%. Approximately 59% of the participants said that they would have their children vaccinated regardless of their gender. These data show that almost 4 out of every 10 people do not have confidence in the HPV vaccine.

In a study conducted in the USA, it was aimed to increase the level of knowledge of medical and dental students about HPV.^[15] In the same country, a survey conducted among women of reproductive age revealed that both the level of knowledge about HPV was low, and vaccination rates were insufficient.^[16] Similarly, studies conducted in Algeria, Romania, and Morocco revealed that the level of knowledge of university students, high school students, parents, and healthcare workers about HPV and the HPV vaccine was inadequate; it was emphasized that national vaccination programmes should target the young population and should be supported by educational policies.^[17–19] In order to increase the effectiveness of HPV vaccination at the community level, it is of great importance for healthcare professionals to increase information activities and raise awareness of families.^[20] In our study, we questioned where they learned the information about vaccination. 49.4% of the participants stated that they did not know about vaccination, 21.8% stated that they learned

from social media, and 13.6% stated that they learned from doctors. Therefore, we think that in addition to using modern communication tools such as social media to increase vaccine education and awareness, healthcare professionals, especially starting from primary healthcare institutions, should inform the public in detail for vaccine awareness.

HPV vaccine provides effective protection against cervical cancer and its precursor lesions. In our study, the rate of those who knew the role of HPV in cervical cancer was found to be 40.2%. However, 66.4% of the participants knew that HPV is sexually transmitted, but only 33% of the participants thought that vaccination should start at the age of 11–12. According to the studies, vaccination should be carried out before the first contact with HPV to ensure immunity. Studies have revealed that infected women benefit less from vaccination and therefore the importance of prophylactic vaccination should be emphasized.^[21] In addition, a positive correlation was found between education level and vaccine uptake. This shows that public health campaigns should especially target individuals with low education levels.^[22] In our study, although 94.9% of the participants had an education level of high school and above, the vaccination rate was found to be 13.9%. When we evaluate these data together, it suggests that the cost of the vaccine and the difficulties in accessing the vaccine cause the vaccination rate to remain low even though the level of education is high.

The effectiveness of prophylactic HPV vaccines has been clearly demonstrated in studies conducted worldwide. In countries such as Australia, Europe, and North America, reductions of up to 90% in infections against HPV 6, 11, 16, and 18 types and genital wart cases have been reported after vaccination.^[23–26]

Two- and four-valent HPV vaccines specifically target high-risk types such as HPV-16 and HPV-18. Systematic reviews have reported that these vaccines significantly reduce the incidence of cervical precancerous lesions and cancer.^[27] More than 270 million doses have been administered worldwide and a strong safety profile has been found.^[28] In our study, only 31.6% of the participants stated that they were informed about the protection of the HPV vaccine. However, only 42% were aware of its protection against cervical cancer.

In our study, it was determined that lack of information, lack of confidence in vaccination, and especially cost concerns were the basis of the participants' negative attitudes towards vaccination.

Our study was conducted only in a private tertiary care hospital. In addition, the fact that we could not compare the opinions between age groups and genders are the limitations of our study.

More detailed studies at all health levels and in all segments of society, as well as studies comparing the opinions of individuals who comply with the national vaccination calendar and those who do not comply with the national vaccination calendar, may reveal the social approach to HPV vaccination more clearly.

CONCLUSION

Despite the proven efficacy of the HPV vaccine, access and cost remain significant barriers. Especially in low-income countries, sustainable health policies should be developed to reduce costs and make the vaccine widespread. In order to increase vaccination rates, it is essential to increase the level of knowledge of the public, use communication tools such as social media more frequently, increase confidence in the vaccine, inform individuals in detail at all health levels, and ensure financial accessibility. Otherwise, the social and financial burden of HPV-related diseases will continue, and public health will remain under threat in terms of preventable cancer types. In order to fully utilise the preventive potential of the HPV vaccine, decisive steps should be taken at the global and national level to reduce prices, educate the public, and ensure public financing.

Disclosures

Ethics Committee Approval: The study was approved by the Istanbul Esenyurt University Ethics Committee (No: 2023/08-04, Date: 07/09/2023).

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A Retrospective Evaluation of Acute Poisoning Cases in Emergency Departments: Focus on Suicide Attempts by Poisoning

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ABSTRACT

Objective: Identifying poisoning and suicidal characteristics in a country or specific region is crucial for determining risks, implementing necessary precautions, and managing affected individuals. This study aimed to examine the demographic, etiologic, and clinical features of patients with acute poisoning and identify factors associated with suicide attempts by poisoning.

Materials and Methods: One hundred thirty-eight patients with acute poisoning who were admitted to the emergency department of Tokat-Turhal State Hospital between July 2021 and June 2023 were retrospectively included in this study. The patients were divided into two groups based on suicidal intent.

Results: The incidence of poisoning over the study period was 0.048%. The median age was 28.5 (range: 15–47) years, and 81 (58.7%) patients were female. Poisoning cases were most frequent during summer, particularly in June. Thirty patients (21.74%) presented following suicide attempts by poisoning. The most common causes of poisoning were mushrooms (34.26%) and corrosive agents (32.41%) in the non-suicidal group. In contrast, 80% of suicide attempts involved drug poisoning ($p<0.001$), primarily analgesics and psychiatric drugs. Patients in the suicide attempt group had higher rates of psychiatric history ($p<0.001$), poorer health status ($p=0.009$), and more frequent ICU admissions ($p<0.001$).

Conclusion: Suicide attempts mostly occurred via drug overdose, especially among individuals with psychiatric illness, resulting in poorer outcomes and greater need for intensive care. Early intervention, follow-up, and increased public awareness may help improve prognosis and reduce complications.

Keywords: Drug intoxication, emergency department, poisoning, suicide attempt

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INTRODUCTION

Acute poisoning is one of the most common reasons for emergency department (ED) referrals and represents a significant public health issue due to its potential morbidity and mortality.^[1] Poisoning occurs from exposure to harmful substances in quantities capable of causing toxic effects, either accidentally or intentionally.^[2] Exposure routes include ingestion, inhalation, injection, or dermal absorption. Admission rates due to acute poisoning vary globally and within countries, influenced by socioeconomic status, geography, culture, and seasonal factors.^[3] Poisoning may occur accidentally, especially in young children, or intentionally as a suicide attempt, particularly in adolescents and adults. Among suicide meth-

ods, poisoning is one of the most frequently used, alongside hanging and firearms. Understanding regional poisoning trends and suicide attempt characteristics is essential for risk assessment and preventive strategies.^[4,5] With advances in modern medicine, technology, and changing sociocultural conditions, the epidemiology of poisoning may vary over time. Recording cases, especially those with suicidal intent, and regularly updating demographic and clinical data are crucial to improve prevention and management.^[6,7]

This study aimed to examine the demographic, etiologic, and clinical characteristics of acute poisoning patients admitted to the emergency department and identify factors associated with suicide attempts by poisoning.

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MATERIALS and METHODS

This study was designed as a single-center, retrospective, and descriptive study conducted between July 2021 and June 2023 in the Tokat-Turhal State Hospital. A total of 288,461 patients were admitted to the emergency department for any reason during this period, and 138 of them were diagnosed with acute poisoning of various origins. Demographic data including age and sex, seasonal and monthly variation, causes of poisoning, route of exposure, clinical features, follow-up, and outcomes were obtained from patient records and hospital databases.

The diagnosis of poisoning was based on information provided by the patient, family members, or companions regarding the substances involved. The identity of the substance was confirmed when possible, based on the statements of conscious patients or by the physical presence of the substance near the patient. Suicidal intent, thoughts, and plans were identified from interviews with patients or their relatives. The national poison control center was consulted for all cases, and its recommendations were implemented.

All patients received standard poisoning management protocols and were followed up for at least one month. When indicated, combination therapy with gastric lavage, activated charcoal, and decontamination with water and soap was applied. Continuous monitoring, specific antidotes, and elimination techniques were administered as needed. In cases of suicide attempts, additional measures such as continuous observation, prevention of self-harm, psychiatric consultation, and supportive care were applied during and after hospitalization. The time interval between poison intake and hospital admission, as well as mortality data, were also recorded.

All research procedures were reviewed and approved by the Tokat Gaziosmanpaşa University Clinical Research Ethics Committee (Approval Number: 23-KAEK-181, Date: 17/08/2023) and were conducted in accordance with the ethical principles of the Declaration of Helsinki.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Histogram and Q-Q plots were used to assess the distribution of continuous variables. Continuous variables are presented as mean±standard deviation or median (1st–3rd quartile) depending on distribution, and categorical variables as frequency (percentage). Normally distributed variables were analyzed using the Student's t-test. Non-normally

distributed variables were analyzed using the Mann–Whitney U test. Categorical variables were analyzed using the Chi-square test, Fisher's exact test, or Fisher–Freeman–Halton test, as appropriate. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 138 patients with acute poisoning were included in this study. The incidence of poisoning during the entire study period was 0.048%. The median age was 28.5 years (range: 15–47), and 97 patients (70.29%) were older than 18 years. Eighty-one patients (58.7%) were female. The highest number of poisoning cases occurred in summer, particularly in June. Most patients (78.99%, n=109) were admitted to the hospital within 0–4 hours of exposure. Thirty patients (21.74%) had attempted suicide. Based on suicidal intent, patients were categorized into two groups. No significant differences were found between the groups in terms of age, sex, or seasonal/monthly distribution (all, p>0.05). Demographic data are summarized in Table 1.

Among patients without suicide attempts, the most common causes of poisoning were mushrooms (34.26%), corrosive agents (32.41%), carbon monoxide (15.74%), insecticides or pesticides (4.63%), and other agents such as drugs, food, or methanol (2.78%). In contrast, 80% of patients who attempted suicide were poisoned by drugs (p<0.001), including analgesics (n=12), psychiatric drugs (n=9), cardiovascular drugs (n=8), and multiple drugs (n=6). In the non-suicidal group, corrosive substances used included laundry bleach (n=13) and detergent (n=17) (p=0.032). All patients in the suicide attempt group were exposed orally (p=0.002), while in the non-attempt group, 71.3% were exposed orally, 28.7% by inhalation, and 3.7% by dermal route (p=0.002). Details of causes and exposure routes are shown in Table 2 and Figure 1.

Symptom rates were higher in the non-suicidal group (p=0.025). Nausea and vomiting were the most frequent symptoms in this group, while nausea and somnolence were more common among those who attempted suicide. Blackout and somnolence were significantly more frequent in the suicide group (p=0.039 and p=0.027, respectively). Gastric lavage was used in 49.35% of non-suicidal cases and 73.33% of suicide cases (p=0.043). Ten patients (33.3%) in the suicide group had a known psychiatric disorder (p<0.001). A greater proportion of patients in the suicide group (96.67%) presented within 0–4 hours compared to the non-suicidal group (p=0.015). There were no significant

Table 1. Demographic and seasonal characteristics of poisoning cases by suicidal intent

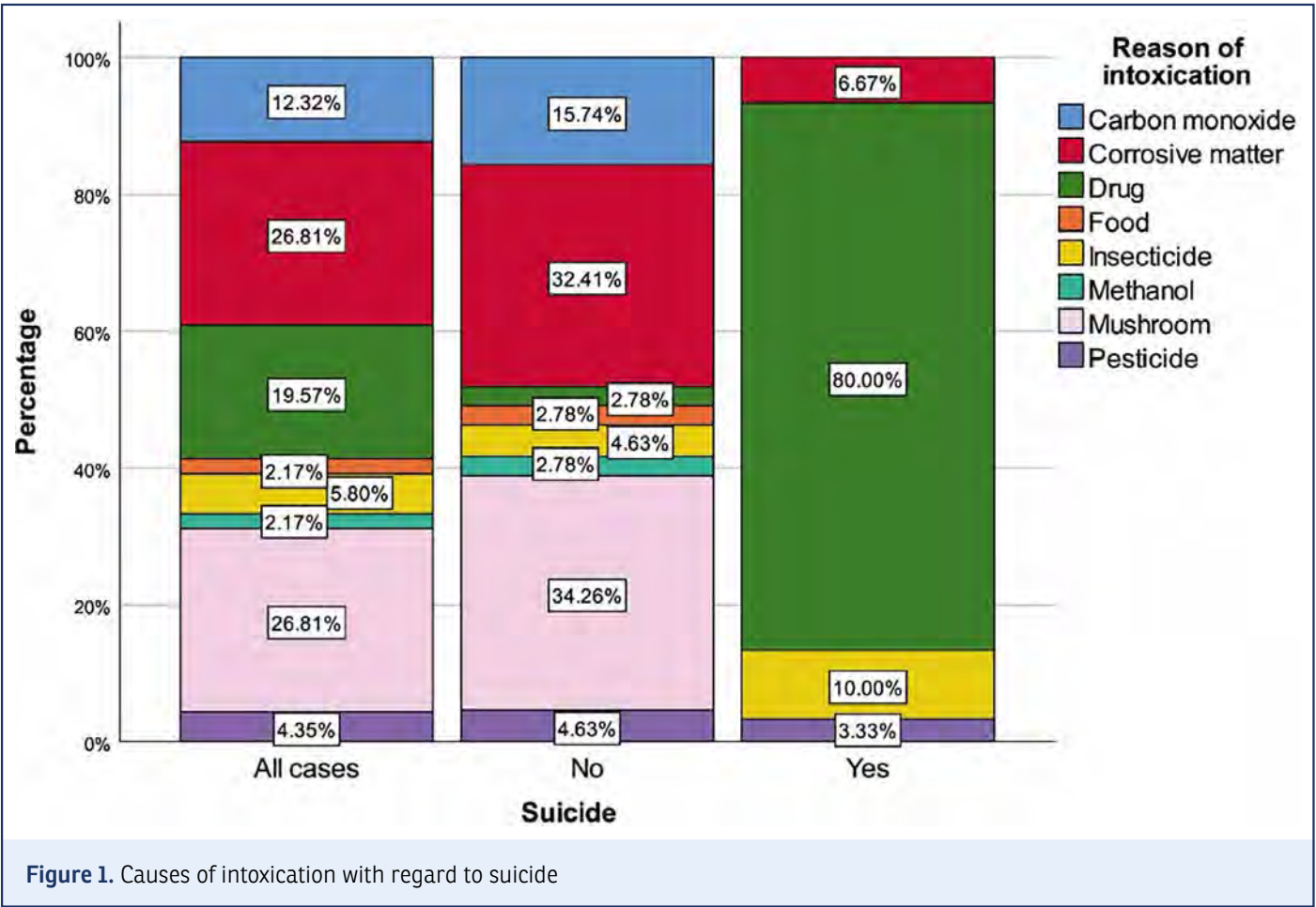
Variables	All cases (n=138)		No suicide attempt (n=108)		Suicide attempt (n=30)		p
	n	%	n	%	n	%	
Age (years), median (IQR)	28.5 (15–47)		30 (13–51)		23.5 (18–42)		0.722
<18 years	41	29.7	34	31.5	7	23.3	0.523
≥18 years	97	70.3	74	68.5	23	76.7	0.523
Sex - male	57	41.3	47	43.5	10	33.3	0.428
Sex - female	81	58.7	61	56.5	20	66.7	
Season - winter	38	27.5	30	27.8	8	26.7	0.066
Season - spring	22	15.9	17	15.7	5	16.7	
Season -summer	53	38.4	46	42.6	7	23.3	
Season -autumn	25	18.1	15	13.9	10	33.3	

Data are presented as n (or median (IQR) unless otherwise specified. IQR: Interquartile range

Table 2. Causes and routes of poisoning in all patients and comparison by suicidal intent

Variables	Suicidal attempts						p
	All cases (n=138)		No (n=108)		Yes (n=30)		
	n	%	n	%	n	%	
Causes of Poisoning (n=138)							
Carbon monoxide	17	12.32	17	15.74	0	0.00	<0.001
Corrosive matter	37	26.81	35	32.41	2	6.67	
Drug	27	19.57	3	2.78	24	80.00	
Food	3	2.17	3	2.78	0	0.00	
Insecticide	8	5.80	5	4.63	3	10.00	
Methanol	3	2.17	3	2.78	0	0.00	
Mushroom	37	26.81	37	34.26	0	0.00	
Pesticide	6	4.35	5	4.63	1	3.33	
The use of corrosive substances (n=37)							
Laundry bleach	13	35.14	13	37.14	0	0.00	0.032
Detergent	17	45.95	17	48.57	0	0.00	
Other	7	18.92	5	14.29	2	100.00	
Type of drug used for poisoning (n=27) (1)							
Cardiovascular drugs	8	29.63	0	0.00	8	33.33	0.532
Analgesics	13	48.15	1	33.33	12	50.00	1.000
Psychiatric drugs	10	37.04	1	33.33	9	37.50	1.000
Other drugs	5	18.52	1	33.33	4	16.67	0.474
Multiple drugs	6	22.22	0	0.00	6	25.00	1.000
Exposure route (n=138) (1)							
Intravenous	0	0.00	0	0.00	0	0.00	N/A
Oral	107	77.54	77	71.30	30	100.00	0.002
Dermal	4	2.90	4	3.70	0	0.00	0.577
Inhalation	31	22.46	31	28.70	0	0.00	0.002

Data are given as mean±standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. (1) Individuals may have more than one of the followings. N/A: Not applicable



differences in vital signs or other cardinal findings (all, $p>0.05$). Clinical features are provided in Table 3.

Poor or fair health status was more common among patients in the suicide group ($p=0.009$). This group also had lower rates of discharge with full recovery and higher rates of intensive care unit admission ($p<0.001$). Thirteen patients in the non-suicidal group were referred to another hospital. Two deaths occurred due to methanol ingestion in the non-suicidal group, both admitted more than 4 hours after exposure. Clinical outcomes are presented in Table 4.

DISCUSSION

This study aimed to examine the demographic, etiologic, and clinical characteristics of patients with acute poisoning and to identify factors associated with suicide attempts. We found a poisoning incidence of 0.048% over the study period, which is relatively low. In Turkey, reported rates of poisoning-related ED admissions range between 0.8% and 5%.^[6] The lower rate in our study may reflect local and regional differences. Our study was conducted in Turhal, a

small town with a mixed rural–urban population of 78,219. To investigate local poisoning patterns and the impact of geography, we included all acute poisoning cases over a two-year period.

Female patients made up 58.7% of the study population, consistent with national data. However, sex distribution varies by region. Studies have reported female predominance in cities such as Diyarbakır (74.1%), Düzce (63.2%), and İstanbul (66%).^[7,8] In contrast, the U.S. National Poison Data System reported equal sex distribution in over 2.7 million cases.^[9] Due to variation in sample sizes, patient profiles, and regional factors, it is difficult to draw a definitive conclusion about sex distribution in acute poisoning cases.

Seasonal variation also appeared relevant. In our study, poisoning cases peaked in summer, while suicide attempts occurred more frequently in autumn. Similar seasonal patterns were observed in previous research. Baydin et al.^[10] found increased poisoning cases in summer. while Doğanay et al.^[11] linked suicide attempts with temperature, humidity, and sunlight duration. International data show variability: in

Table 3. Clinical characteristics of patients and comparison by suicidal intent

Variables	Suicidal attempts						p
	All cases (n=138)		No (n=108)		Yes (n=30)		
	n	%	n	%	n	%	
Symptoms (n=138) (1)	116	84.06	95	87.96	21	70.00	0.025
Dizziness	18	13.04	16	14.81	2	6.67	0.361
Headache	19	13.77	17	15.74	2	6.67	0.247
Abdominal pain	20	14.49	19	17.59	1	3.33	0.075
Nausea	72	52.17	59	54.63	13	43.33	0.374
Vomiting	36	26.09	30	27.78	6	20.00	0.533
Diarrhea	3	2.17	3	2.78	0	0.00	1.000
Skin burning	5	3.62	5	4.63	0	0.00	0.585
Burning mouth/throat	16	11.59	15	13.89	1	3.33	0.194
Blackout	10	7.25	5	4.63	5	16.67	0.039
Dyspnea	12	8.70	11	10.19	1	3.33	0.462
Somnolence	18	13.04	10	9.26	8	26.67	0.027
Syncope	4	2.90	2	1.85	2	6.67	0.206
Gastric lavage (n=107)	60	56.07	38	49.35	22	73.33	0.043
Activated charcoal (n=107)	60	56.07	39	50.65	21	70.00	0.111
The history of Psychiatric disease (n=138)	10	7.25	0	0.00	10	33.33	<0.001
Systolic blood pressure (n=138)	120.93±18.77		120.97±18.70		120.77±19.35		0.958
Diastolic blood pressure (n=138)	74.62±10.87		75.06±11.04		73.00±10.25		0.359
Body temperature (n=138)	36.66±0.21		36.66±0.21		36.69±0.21		0.518
Oxygen saturation (n=138)	99 (97–99)		99 (97–99)		98.5 (97–99)		0.910
Heart rate (n=138)	89 (78–100)		87 (77–100)		91 (78–100)		0.414
Time of admission to hospital (n=138)							
0–4 hours	109	78.99	80	74.07	29	96.67	0.015
>4 hours	29	21.01	28	25.93	1	3.33	

Data are given as mean±standard deviation or median (1st quartile–3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. (1) Individuals may have more than one of the followings.

Finland, female poisoning peaked in autumn,^[12] and in Italy, suicides by poisoning peaked in spring and late autumn.^[13] Thus, seasonal asymmetry appears to vary with age, sex, and regional or methodological factors.

Suicide and suicide attempts are major global health concerns with personal, familial, and societal impact. According to the WHO, over 700,000 suicide deaths occur annually, accounting for 1.3% of all global deaths.^[14] In Türkiye, common suicide methods include hanging, drug ingestion, sharp tools, jumping from heights, and firearms.^[2] Recent studies and meta-analyses have shown an increasing rate of suicide attempts by poisoning, particularly among ado-

lescents and young adults.^[15] In our study, the median age of patients attempting suicide was 23.5 years, with 80% using medications. Analgesics and psychiatric drugs were the most common agents, consistent with national data. This may be linked to prescription trends and accessibility.

In contrast to Turkish data, Värnik et al.^[16] reported that hanging was the most common suicide method in Europe (49.5%), followed by drug poisoning (12.7%). Additionally, in rural regions like South Africa, pesticide-related suicides were more prevalent than drug-related ones due to greater availability.^[17] These findings highlight how suicide methods vary with geography and access to substances.

Table 4. Clinical outcomes of patients and comparison by suicidal intent

Variables	Suicidal attempts						p
	All cases (n=138)		No (n=108)		Yes (n=30)		
	n	%	n	%	n	%	
Health status (n=138)							
Good	103	74.64	87	80.56	16	53.33	0.009
Fair	24	17.39	15	13.89	9	30.00	
Poor	11	7.97	6	5.56	5	16.67	
Status (n=138)							
Discharged with full recovery	29	21.01	28	25.93	1	3.33	<0.001
Hospitalized, service	77	55.80	63	58.33	14	46.67	
Hospitalized, intensive care unit	32	23.19	17	15.74	15	50.00	
Mortality (n=138)	2	1.45	2	1.85	0	0.00	1.000
Refuse to hospitalization (n=109)	20	18.35	18	22.50	2	6.90	0.114
Referred to another hospital (n=138)	13	9.42	13	12.04	0	0.00	0.071
Referral indication (n=13)							
Gastroenterology	3	23.08	3	23.08	0	0.00	
Pediatric gastroenterology	1	7.69	1	7.69	0	0.00	
Hyperbaric oxygen therapy	4	30.77	4	30.77	0	0.00	
Dialysis	1	7.69	1	7.69	0	0.00	
Intensive care unit	1	7.69	1	7.69	0	0.00	
Pediatric intensive care unit	1	7.69	1	7.69	0	0.00	
Intensive care unit with dialysis	2	15.38	2	15.38	0	0.00	

Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

Psychiatric conditions are key risk factors for suicide. Various studies have identified associations with disorders such as depression, anxiety, PTSD, and personality disorders.^[18,19] In our study, 33.3% of patients who attempted suicide had a known psychiatric illness, suggesting a strong correlation. Psychiatric deterioration, such as behavioral change or withdrawal, should be closely monitored by healthcare providers and family members. Patients with suicidal ideation should be directly questioned to assess risk and guide timely intervention.

Suicide attempters face increased risk of repeat attempts or completion. Understanding patterns and trends helps inform public health strategies. Poisoning is a growing public health issue requiring intensive care and long-term monitoring.^[20] In our study, patients who attempted suicide had poorer clinical status, higher ICU admission rates, and lower discharge rates, though no deaths occurred. This may reflect the availability of close monitoring and sufficient resources.

This study has limitations. First, it is a retrospective, single-center design, which may introduce bias. Second, specific toxins could not be confirmed due to lack of toxicological screening. Third, variables such as comorbidities, dosage, time to ED arrival, poisoning severity, and physician experience may have influenced outcomes.^[21] Lastly, as a hospital-based study, the results may reflect more severe cases and may not be generalizable to the broader population.

CONCLUSION

In conclusion, suicide attempts via drug poisoning were common in our study, particularly among those with psychiatric illnesses. These patients had worse clinical outcomes and required more intensive care. Early intervention, psychiatric evaluation, and increased public awareness may improve outcomes and reduce suicide-related complications and mortality.

Disclosures

Ethics Committee Approval: The study was approved by the Tokat Gaziosmanpaşa University Clinical Research Ethics Committee (No: 23-KAEK-181, Date: 17/08/2023).

Informed Consent: Informed consent was obtained from all participants or their caregivers, where applicable.

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Evaluation of Fermented Food Consumption During Pregnancy and Breastfeeding in Mothers of Children with Egg Allergy

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ABSTRACT

Objective: Fermented foods, such as yogurt and kefir, provide health benefits. This study explores how fermented food consumption during pregnancy and breastfeeding may affect the development of egg allergy in children.

Materials and Methods: The study included mothers of 50 children diagnosed with egg allergy and a control group of mothers of 52 healthy children of the same age group. Retrospective analysis was performed on data such as the mothers' consumption of fermented foods during pregnancy and breastfeeding, sociodemographic characteristics, and family history of allergies.

Results: It was observed that the case and control groups were similar in terms of age, gender, gestational age, maternal weight gain during pregnancy, and mode of delivery ($p>0.05$). However, the mean age of mothers in the case group was significantly lower than that in the control group ($p=0.008$). There was a significant difference in maternal education level between the groups ($p=0.044$). No statistically significant differences were found between the groups in terms of fermented food consumption, including yogurt, cheese, kefir, tarhana, pickles, and fermented sausage (sucuk), during pregnancy and breastfeeding ($p>0.05$).

Conclusion: The findings indicate that the fermented food consumption habits of mothers of children with egg allergy during pregnancy and breastfeeding were not different from those of mothers in the control group. These results suggest no relationship between fermented food consumption and the development of egg allergy in children. However, further extensive studies are needed on this subject.

Keywords: Allergic diseases, breastfeeding, egg allergy, fermented food consumption, pregnancy

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INTRODUCTION

Fermentation is defined as the food processing process that occurs through the activity of enzymes within microorganisms.^[1] Foods resulting from the fermentation process have been one of the main components of human nutrition for thousands of years.^[2] The ability of fermented foods to be well-preserved due to the fermentation process has made them an essential part of the diet.^[3]

Fermented foods are widely consumed in Turkish cuisine. Yogurt is made through the fermentation of milk and contains streptococci and lactobacilli. Tarhana is produced by fermenting a mixture of dough, vegetable purée, yogurt, flour, and spices for a period of 1 to 7 days. Kefir is a fermented product composed of diacetyl and acetaldehyde.^[1] Fermented foods generally originate from lactic acid and some acetic acid bacteria, such as *Lactobacillus*, *Streptococcus*, and *Pediococcus*.

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cus.^[4,5] It has been demonstrated that fermented foods have protective effects against various gastrointestinal diseases, obesity, cardiovascular diseases, and metabolic disorders.^[6]

Egg allergy is a significant health issue and one of the most common food allergens encountered in childhood. Egg white proteins are more allergenic than yolk proteins and tend to cause more severe reactions, although the body may react to both.^[7] The prevalence of egg allergy is increasing in Western countries, making it one of the most common food allergies, typically emerging in the first year of life.^[8,9] Previous studies have shown that cow's milk is the most common allergy, followed by egg allergy, which affects approximately 0.8% of children and 1.3% of those aged 0–5 years.^[10] Moreover, egg has been identified as the most frequent cause of anaphylaxis in the first year of life.^[11] Egg allergy has been associated with conditions such as urticaria, angioedema, eosinophilic esophagitis, and enteropathy.^[12] A strong link between egg allergy and atopic dermatitis has also been established, with egg allergy detected in two out of three patients with atopic dermatitis undergoing food provocation tests.^[13]

Regular consumption of fermented foods such as yogurt, kefir, and tarhana during pregnancy may beneficially alter the balance of lactic acid bacteria in the maternal gut microbiota, leading to increased production of short-chain fatty acids. These metabolites can modulate immune signals transmitted to the fetus via the placenta, strengthening T-cell tolerance mechanisms and reducing early-life sensitization to allergens. While existing studies have shown that probiotic use in pregnancy lowers the risk of atopic dermatitis, eczema, and food allergies, data specific to egg allergy are scarce. Accordingly, our study seeks to offer a novel scientific perspective on nutrition-based allergy prevention by both quantitatively and qualitatively assessing the relationship between maternal fermented food intake frequency and the development of egg allergy in offspring.

MATERIALS and METHODS

This analytical case-control study was conducted between October 1, 2024, and December 1, 2024, at the Pediatric Health and Diseases, and Pediatric Allergy and Immunology outpatient clinics of , Health Sciences University, Ümraniye Training and Research Hospital. The study included mothers of children aged 0–2 years diagnosed with egg allergy, whose consumption of homemade fermented foods during pregnancy was evaluated. It also involved mothers of healthy children in the same age group with no history of allergies. The control group consisted of mothers of children attending the well-child outpatient clinic for routine check-ups. The children in the control group had no history of allergic diseases.

The study included mothers of children aged 0–2 years diagnosed with egg allergy by positive skin prick test and/or specific IgE results and confirmed by oral egg provocation testing, as well as mothers of healthy children in the same age group with no history of allergies. Exclusion criteria comprised mothers who provided incomplete information about their fermented food consumption during pregnancy and individuals whose children had a history of other allergic conditions. Sampling was performed from eligible participants attending the outpatient clinics during the study period.

Participant data were reviewed and included in the study through surveys. The survey included questions regarding the frequency of consumption of homemade fermented foods such as yogurt, cheese, kefir, tarhana, pickles, and fermented meat products during pregnancy and breastfeeding. Additionally, information about the children's allergy history, age at symptom onset, family allergy history, and other environmental factors was recorded.

Consumption of fermented dairy products (FDPs), including yogurt, cheese, tarhana, kefir, pickles, and sucuk, was calculated separately for pregnancy and breastfeeding periods in grams or milliliters. The frequency of consumption was categorized into four groups: daily, every other day, every three days, and less frequently. Weekly consumption was calculated by multiplying the daily consumption amount by the number of days consumed per week and expressed in milliliters for kefir and grams for other foods.

Statistical Analysis

Statistical analysis and data recording were carried out using SPSS version 25.0 for Windows (SPSS25; Armonk, New York). Descriptive statistics were expressed as medians, ranges (minimum and maximum values), frequencies (n), and percentages (%). The assessment of normality was performed through the Kolmogorov–Smirnov/Shapiro–Wilk tests, Q-Q plots, and boxplots. The Mann–Whitney U test was utilized for comparing two independent groups with non-normally distributed data, while categorical variables were analyzed using the Chi-square test. A p-value below 0.05 was considered to indicate statistical significance.

Ethical Committee Approval

The study received ethical approval from the , University of Health Sciences, Ümraniye Training and Research Hospital's Ethics Committee (decision number: 287, dated 05/09/2024). All participants provided informed consent prior to their inclusion in the study. The research adhered to the principles outlined in the Declaration of Helsinki.

Table 1. Sociodemographic characteristics of case and control groups and method of birth with gestational age

	Group				p
	Case		Control		
	n	%	n	%	
Child's age, median (min-max)	13.0 (1.0–24.0)		10.0 (2.0–32.0)		0.117
Mother's age, median (min-max)	29.0 (21.0–42.0)		31.0 (20.0–43.0)		0.008
Gestastional week, median (min-max)	38.0 (36.0–41.0)		38.0 (30.0–41.0)		0.208
Gestational weight gain, median (min-max)	15.0 (5.0–70.0)		14.0 (5.0–25.0)		0.129
Maternal education					
Primary School	3	6.5	8	16.3	0.044
High School	17	37.0	8	16.3	
University	26	56.5	33	67.3	
Child gender					0.436
Female	25	50.0	22	42.3	
Male	25	50.0	30	57.7	
Method of birth					
Cesarean	21	42.0	18	34.6	0.443
Vaginal (NSD)	29	58.0	34	65.4	

Min: minimum; Max: maximum; NSD: Normal spontaneous delivery.

RESULTS

Data from 50 participants in the case group and 52 participants in the control group were analyzed. The two groups were comparable in terms of age, gender, gestational age, maternal weight gain during pregnancy, and delivery method ($p>0.05$) (Table 1-3).

No significant differences were found between the groups regarding a family history of food allergies or respiratory allergies ($p=0.156$ and $p=0.649$, respectively). Similarly, there were no notable differences in other variables.

The consumption of yogurt during pregnancy was lower in the case group when compared to the lactation period, but this difference was not statistically significant ($p=0.510$). Likewise, there were no significant differences between the groups regarding fermented food consumption during lactation ($p>0.05$).

DISCUSSION

Various studies have investigated the relationship between the consumption of fermented foods during pregnancy and egg allergy. These studies suggest that the foods consumed during pregnancy may influence the immune system of the unborn child and their predisposition to allergic diseases. For

instance, one study reported a close association between egg allergy and asthma risk.^[14] In the study by Leduc et al.,^[15] yogurt consumption during pregnancy was found to reduce the incidence of atopic dermatitis, allergic rhinitis, and asthma, but it had no significant effect on food allergies. This finding partially aligns with our study, as we also observed lower yogurt consumption during pregnancy in the case group; however, this difference did not reach statistical significance. On the other hand, this discrepancy may be attributed to cultural dietary habits or nuances in maternal immune responses.

Another study reported that 9.5% of children reacted to raw egg by the age of one, but this rate declined to 1.2% by the age of four.^[16] In a study conducted in the United States, it was shown that half of the children outgrew egg allergy by the age of six, while a similar study reported a remission rate of only 12% initially, which increased to 68% by the age of sixteen.^[17,18] These studies suggest that egg allergy tends to decrease over time; in contrast, our study contributes to the literature by examining the impact of maternal dietary habits during pregnancy on the development of egg allergy.

A previous study on children with cow's milk protein allergy (CMPA) analyzed 80 cases and 80 controls, identifying cheese, yogurt, and tarhana (a traditional fermented soup) as the most frequently consumed FDPs. In that study, FDP

Table 2. Family history, place of residence, pets, family smoking, and antibiotic use

	Group				p
	Case		Control		
	n	%	n	%	
Family food allergy					
None	39	78.0	46	88.5	0.156
Present	11	22.0	6	11.5	
Family respiratory allergy					
None	32	64.0	31	59.6	0.649
Present	18	36.0	21	40.4	
Family allergic rhinitis (AR)					
None	40	80.0	47	90.4	0.139
Present	10	20.0	5	9.6	
Family asthma					
None	43	86.0	47	90.4	0.492
Present	7	14.0	5	9.6	
Family atopic dermatitis (AD)					
None	42	84.0	49	94.2	0.096
Present	8	16.0	3	5.8	
Pets					
None	48	96.0	48	92.3	0.678
Present	2	4.0	4	7.7	
Place of Residence					
Rural	3	6.0	1	1.9	0.358
Urban	47	94.0	51	98.1	
Maternal smoking during pregnancy					
Yes	1	2.0	6	11.5	0.113
No	49	98.0	46	88.5	
Maternal smoking during breastfeeding					
Yes	3	6.0	7	13.5	0.319
No	47	94.0	45	86.5	
Paternal smoking during pregnancy					
Yes	28	56.0	27	51.9	0.680
No	22	44.0	25	48.1	
Paternal smoking during breastfeeding					
Yes	29	58.0	25	48.1	0.316
No	21	42.0	27	51.9	
Maternal antibiotic use during pregnancy					
Yes	9	18.0	12	23.1	0.526
No	41	82.0	40	76.9	

consumption during pregnancy and lactation was significantly lower in the case group than in the control group.^[19] In our study, although yogurt consumption during pregnancy was lower in the case group compared to the lactation period, this difference was not statistically significant. Moreover, no sig-

nificant difference was found between the two groups in terms of FDP consumption during lactation. In this regard, our study differs from the CMPA study, and this discrepancy may stem from the type of allergy studied (egg vs. milk), sample size, methodology, or cultural differences in dietary habits.

Table 3. Consumption of fermented dairy products during pregnancy and breastfeeding

	Group						p
	Case			Control			
	Median	Minimum	Maximum	Median	Minimum	Maximum	
Pregnancy							
Yogurt (gr/wk)	700	0	1400	840	0	1750	0.510
Cheese (gr/wk)	385	0	1000	350	70	1750	0.121
Tarhana (gr/wk)	38	0	1750	70	0	2450	0.733
Kefir (mL/wk)	0	0	3500	35	0	2800	0.483
Pickles (gr/wk)	70	0	2100	0	0	1260	0.248
Fermented Sausage (gr/wk)	700	0	2100	305	0	2100	0.053
Breastfeeding							
Yogurt (gr/wk)	700	0	2100	700	100	2800	0.302
Cheese (gr/wk)	350	0	2000	280	0	2000	0.210
Tarhana (gr/wk)	0	0	2100	0	0	1750	0.924
Kefir (mL/wk)	0	0	3500	0	0	3500	0.243
Pickles (gr/wk)	140	0	700	0	0	2100	0.119
Fermented Sausage (gr/wk)	410	0	3500	210	0	2100	0.183

gr/wk: Gram/week; mL/wk: Mililitre/week

To our knowledge, no studies in the literature have evaluated the relationship between egg allergy and FDP consumption habits. In this respect, our study aims to fill a critical gap in the field and highlights the need for larger-scale and prospective studies to better understand the potential effects of FDP consumption during pregnancy and lactation on the development of egg allergy. Considering the potential protective effects of FDP diversity against allergic diseases, future high-quality studies in this area are expected to make valuable contributions to the literature.

In our study, the gestational age and maternal weight gain during pregnancy were similar for both the case and control groups. This similarity suggests that we excluded the effects of these two factors from the results, and other variables might be more decisive. While factors like gestational age and maternal weight gain during pregnancy have been studied in relation to pregnancy and allergic diseases, their specific association with egg allergy has not been addressed in the literature. This highlights our study's potential to fill a significant knowledge gap in this area and contribute uniquely to the field.

The case and control groups in our study were also statistically similar regarding gender. No differences were found between the groups regarding the presence of food allergies, asthma, allergic rhinitis, and respiratory allergies in the fam-

ily, as well as for other factors. However, maternal education level showed a significant difference between the groups ($p=0.044$). No significant differences were observed for other variables. In a similar study on FDP consumption during pregnancy, CMPA was found to be more prevalent in male children. The risk of CMPA was higher in children of parents with a history of asthma and allergic rhinitis, and it was also greater in mothers with higher education levels. Moreover, maternal smoking during pregnancy and having pets in the household during the child's first year were linked to a decreased risk of CMPA in children.^[20] The lack of gender-based differences in our study suggests that gender does not play a significant role in the development of egg allergy. Furthermore, the absence of differences between groups regarding family histories of food allergy, asthma, allergic rhinitis, atopic dermatitis, and respiratory allergies indicates that these factors do not directly influence the development of egg allergy. The significant difference in maternal education levels suggests that higher education levels in mothers may be associated with differences in allergy and dietary habits in their children. This finding aligns with previous studies that link higher education levels with increased allergy risks and more conscious dietary choices by mothers. Given the limited data in the literature, broader research is needed to fill this gap and provide valuable insights into this field.

Our study also showed no statistical differences between the case and control groups regarding delivery method and maternal smoking during pregnancy. In another study on children with allergic proctocolitis, vaginal delivery and maternal smoking during pregnancy were more prevalent in the allergic proctocolitis group compared to the control group.^[21] These findings suggest that our results were not influenced by demographic factors, making them more reliable. The association of maternal smoking with both allergic proctocolitis and other allergic diseases is a common finding in the literature. Smoking is proposed to influence the fetal immune system, predisposing it to allergic diseases. However, the lack of an association between these factors and allergic reactions (specifically egg allergy) in our study suggests that the impact of maternal smoking on allergic diseases may not be uniform across all disease groups. For instance, specific diseases like egg allergy may be less sensitive to the effects of maternal smoking, or these effects may manifest differently. This underscores the complexity of the etiology of allergic diseases and the need for an integrated evaluation of genetic, environmental, and immunological factors.

In our study, no differences were found between groups regarding a family history of atopic dermatitis. In a study of 2,371 participants, it was observed that mothers who consumed yogurt in the later stages of pregnancy had infants with a lower incidence of eczema at 3–6 months and a reduced risk of recurrent eczema during the first 6 months.^[22] The absence of a significant difference between groups concerning a family history of atopic dermatitis suggests that genetic predisposition is not a decisive factor in this context. Instead, environmental or nutrition-based factors, particularly maternal-related variables, might play a more significant role in the development of eczema and atopic dermatitis in infants, providing a novel perspective on the etiology of these conditions. Consequently, specific dietary interventions during pregnancy, such as yogurt and other fermented food consumption, could be considered potential protective factors against the development of atopic dermatitis in infants.

The statistical similarity of the case and control groups regarding gestational age, maternal weight gain during pregnancy, gender, family history of allergic diseases, and maternal smoking enabled an independent evaluation of our results, emphasizing the significance of nutrition-based factors. Despite the lower yogurt consumption during pregnancy in the case group, the lack of a significant difference and the absence of differences during the lactation period contribute to an underexplored area in the literature. Additionally, maternal environmental and nutrition-based factors appear to

play a more decisive role in the development of egg allergy than genetic factors. Although our study is one of the initial investigations into the link between FDP consumption during pregnancy and breastfeeding and egg allergy, it underscores the importance of conducting large-scale studies to explore the possible impact of FDP on allergic conditions.

CONCLUSION

The findings demonstrate that maternal consumption patterns of fermented foods during pregnancy and lactation among mothers of children diagnosed with egg allergy did not differ significantly from those observed in the control group. These results do not support a potential association between the intake of fermented foods and the development of egg allergy in offspring. Although our study did not establish a clear relationship between the consumption of fermented foods during pregnancy and the development of egg allergy in children, previous literature has shown that fermented foods rich in probiotics may reduce the overall risk of allergies. Due to their potential to decrease the development of certain allergic conditions, particularly atopic dermatitis, the consumption of such foods during pregnancy can still be considered a recommended approach. It is believed that consuming at least one serving (150–200 grams) of yogurt or kefir per day during pregnancy may be beneficial in terms of general probiotic support. However, it should be clearly stated that this recommendation is not supported by sufficient evidence specifically regarding egg allergy and, therefore, should not replace current diagnostic or therapeutic approaches. There is a need for future descriptive and interventional studies with larger sample sizes, designed prospectively and utilizing validated dietary intake questionnaires. Such studies would allow for a more accurate evaluation of the impact of maternal nutrition during pregnancy on the development of childhood allergies.

Among the limitations, the single-center nature of the study restricts the generalizability of the findings. The relatively small sample size may affect the statistical power, and reliance on self-reported dietary habits introduces a risk of recall bias. Additionally, the study focused solely on fermented dairy products, excluding other potential dietary factors, and did not comprehensively evaluate variables such as socioeconomic status or environmental influences.

Nevertheless, the study also has significant strengths. Being one of the pioneering studies to investigate the relationship between fermented dairy consumption during pregnancy and lactation and the development of egg allergy highlights its originality in this field. The similarity of the case and con-

trol groups regarding key variables such as gestational age, maternal weight gain, gender, and smoking status enhances the reliability of the results. Furthermore, by focusing on a topic that has not been adequately addressed in the literature, the study provides a unique and valuable contribution to the field. It underscores the potential role of maternal nutrition in the development of allergic diseases and paves the way for more comprehensive future research on this subject.

Mothers may have difficulty recalling their dietary habits from previous months, which could lead to systematic bias.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences, Ümraniye Training and Research Hospital Ethics Committee (No: 287, Date: 05/09/2024).

Informed Consent: Written informed consent forms were obtained from the patients, as this was a prospective study.

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Outcomes of Screening for Retinopathy of Prematurity Using United Kingdom and United States Criteria at a Tertiary Referral Center in Türkiye

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ABSTRACT

Objective: To investigate the impact of using United Kingdom (UK) or United States (US) criteria instead of Turkish criteria for retinopathy of prematurity (ROP) screening on infants who require ROP treatment.

Materials and Methods: Four hundred and twenty-two infants underwent ROP screening. ROP screening was performed in all infants with a gestational age of less than 34 weeks or a birth weight of less than 1,700 g. Gestational age, birth weight, stages of ROP, treatments administered, and treatment outcomes were documented.

Results: ROP was diagnosed in 136 (32.2%) of 422 infants. Of these, 60 (14.2%) required treatment due to either type 1 ROP or aggressive ROP (A-ROP). If the UK screening criteria had been used, only 245 infants would have been screened, resulting in a 41.9% reduction compared to the screening criteria used in Türkiye. Thirteen (9.5%) cases of ROP developed in the 167 infants who were excluded from screening. Of these cases, five (8.3%) required treatment. If the screening criteria used in the US had been applied, the number of screened infants would have been reduced by 49.3% compared to the screening criteria used in Türkiye. Of the 208 infants who were not screened, 20 (14.7%) developed ROP, with 8 (13.3%) requiring treatment.

Conclusion: The use of the US or UK screening criteria for ROP in our center has led to the underdiagnosis and undertreatment of ROP. Increased awareness of ROP in intensive care units may lead to further standardization of screening criteria in the future.

Keywords: Birth weight, gestational age, retinopathy of prematurity, screening criteria

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INTRODUCTION

The establishment of clear criteria for the screening of ROP, a condition that can potentially result in blindness among preterm infants, is crucial for ensuring its early detection and effective management. The guidelines consider various risk factors, including the infant's gestational age (GA) and birth weight (BW), as well as the specific environment within NICUs. To reduce the likelihood of severe visual impairment or blindness in newborns, each country has developed tailored screening protocols that emphasize early identification and timely intervention. The primary determinants of these screening guidelines are GA and BW (Table 1).

An extensive and comprehensive study conducted across 69 NICUs in Türkiye revealed that newborns with a BW of up to

1,700 grams and a GA of up to 34 weeks are particularly vulnerable to developing more severe forms of ROP—conditions that, in many cases, necessitate urgent and targeted medical intervention.^[1] In alignment with the 2021 guidelines set forth by the Turkish Neonatology Society ROP Study Group and the Turkish Ophthalmology Society ROP Commission, it is strongly recommended that all infants with a GA below 34 weeks and a BW of 1,700 g or less should undergo ROP screening.

On the other hand, the 2008 United Kingdom (UK) guidelines recommend ROP screening for all infants born at or before 31 weeks and 6 days, or with a BW below 1,501 g.^[2] Similarly, the 2018 guidelines provided by the American Academy of Pediatrics and the American Academy of Ophthalmology recommend ROP screening for all newborns in the United



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States (US) who weigh 1,500 g or less at birth, or are born at 30 weeks of gestation or earlier.^[3] However, research has shown that these screening criteria, as utilized in the US and the UK, may not be universally applicable across different populations and settings.^[4-9] It is imperative to ascertain the underlying causes of this situation to achieve the more optimal developed-country screening criteria.

According to the "Early Treatment of Retinopathy of Prematurity" (ETROP) and International Classification of Retinopathy of Prematurity (ICROP) criteria, ROP requiring treatment consists of two main conditions: type 1 ROP and aggressive ROP (A-ROP).^[10,11] The aim of this study was to compare cases of ROP requiring treatment using the screening criteria of the UK or the US, as opposed to those of our country, among patients admitted to our ROP diagnosis and treatment center. Furthermore, the underlying reasons for any observed disparities were sought to be identified.

MATERIALS and METHODS

This retrospective study aimed to evaluate preterm infants monitored at the ROP clinic of Basaksehir Cam and Sakura Hospital, with the study period spanning from January 1, 2023, to January 1, 2024. The study was approved by the institutional review board and the local ethics committee (E-96317027-514.10-238025866). Informed consent, both verbal and written, was obtained from the parents or legal guardians of all participating infants, in full compliance with the ethical principles outlined in the Declaration of Helsinki.

Routine ROP screenings were performed on all infants born with a BW below 1,700 g or a GA under 34 weeks. The follow-up period ended when the infants either achieved complete retinal vascularization or showed no signs of sub-threshold or more severe stages of ROP by 45 weeks postmenstrual age. For those who achieved full retinal vascularization before reaching 45 weeks postmenstrual age, follow-up was concluded earlier. Infants who failed to meet these follow-up criteria or who passed away during the study were excluded from the analysis.

The infants were stratified into two cohorts: those monitored in our hospital's NICU and followed up at the ROP clinic constituted the internal NICU group, while those monitored in other hospitals' NICUs and referred to our ROP clinic comprised the external NICU group. The data collected included BW, GA, the most advanced stages of ROP observed, the treatments administered, and their corresponding outcomes. The documentation of ROP findings followed the international classification criteria for ROP.^[11] Infants diagnosed with A-ROP or type 1 ROP were treated.

Table 1. Key differences in ROP screening criteria

Country	Gestational age (GA) threshold	Birth weight (BW) threshold
Türkiye	≤34 weeks	≤1700 g
United Kingdom (UK)	≤31 weeks 6 days	≤1500 g
United States (US)	≤30 weeks	≤1500 g

ROP: Retinopathy of Prematurity

This research explores the discrepancies between ROP cases detected or missed based on the screening criteria used in the UK and those identified or missed under the screening guidelines in the US. The study assessed the number of cases requiring treatment under each set of criteria and compared the effectiveness of these screening approaches. The present study also examined the association of differences in ROP diagnosis and treatment between screening criteria and NICU type.

Statistical Analysis

Data analysis was conducted using IBM SPSS Version 20 (IBM Corporate, USA) software. The normality of the data was assessed using the Shapiro–Wilk test. Descriptive statistics of the data are presented as median and interquartile range (IQR). For data with a normal distribution, intergroup comparisons were performed using the independent sample t-test, while the Mann–Whitney U test was applied for data that did not follow a normal distribution. The relationship and differences between categorical variables were analyzed using the chi-square test. A p-value of less than 0.05 was considered statistically significant. The statistical analyses aimed to thoroughly examine the characteristics of the groups, their distributions, and potential relationships between variables within the dataset.

RESULTS

Throughout the course of the study, a total of 422 premature infants were systematically evaluated in accordance with the current screening criteria established by Türkiye. Among these infants, 224 (53.1%) were identified as male, while 198 (46.9%) were female. The median GA of the participants was found to be 32 weeks, with the observed range spanning from 22 weeks and 6 days to 33 weeks and 6 days. In terms of BW, the median value was recorded at 1,540 g, with a broad range extending from 370 g to 3,140 g. It was ascertained that all infants included in the study successfully completed their final ROP screening as part of the follow-up procedures. This comprehensive screening process ensured that all relevant data were collected, facilitating the thorough examination of the infants' ROP findings during the study period.

Table 2. Demographics and clinical characteristics of the infants

	ALL		Internal NICU		External NICU		p
	n	%	n	%	n	%	
n, %	422		245	58.1	177	41.9	
Female	198	46.9	131	53.5	67	37.9	0.001
Gestational age (week), median (range)	32 (22.6–33.6)		32 (22.6–33.6)		31.3 (23–33.6)		0.008
Birth weight (gram), median (range)	1540 (370–3140)		1530 (370–3000)		1550 (500–3140)		0.401
With any stage ROP	136	32.2	61	24.9	75	42.4	0.001
Gestational age (week), median (range)	28.1 (22.6–33.6)		27.5 (22.6–33.6)		29 (23–33.6)		0.182
Birth weight (gram), median (range)	1040 (370–2400)		1040 (370–1860)		1020 (500–2400)		0.204
With Type 1 ROP/A-ROP	60	14.2	23	9.4	37	20.9	0.001
Gestational age (week), median (range)	26.4 (22.6–33.6)		26 (22.6–29.6)		28 (23–33.6)		0.029
Birth weight (gram), median (range)	930 (370–2400)		800 (370–1400)		980 (500–2400)		0.022

NICU: Neonatal Intensive Care Unit; ROP: Retinopathy of Prematurity

Out of a total of 136 infants (32.2%) diagnosed with ROP, 14.2% (60 infants) exhibited either type 1 ROP or A-ROP and were subsequently treated. The median GA of infants diagnosed with ROP was 28 weeks and 1 day, with a range between 22 weeks and 6 days to 33 weeks and 6 days. The median BW for these infants was 1,040 g, with the lowest being 370 g and the highest reaching 2,400 g. The median GA of infants with ROP requiring treatment was 26 weeks and 4 days. The GA for this group spanned from 22 weeks and 6 days to 33 weeks and 6 days. Regarding BW for this specific group, the median was found to be 930 g, with a range that spanned from 370 g to 2,400 g (Table 2).

The median GA of infants undergoing ROP screening in the internal NICU is 32 weeks, with a range spanning from 22 weeks and 6 days to 33 weeks and 6 days. In contrast, the median GA for infants screened in external NICUs is 31 weeks and 3 days, with a range from 23 weeks to 33 weeks and 6 days ($p=0.008$). The average BW of infants screened in the internal NICU is 1,530 g, ranging from 370 g to 3,000 g, while the average BW for those screened in external NICUs is 1,550 g (range: 500 g to 3,140 g) ($p=0.401$) (Table 2).

In our study, the group of infants who developed ROP in the internal NICU had a median GA of 27 weeks and 5 days, with the range spanning from 22 weeks and 6 days to 33 weeks and 6 days. The median BW for this cohort was 1,040 g, while the range of weights varied from 370 g to 1,860 g. In infants from external NICUs who also developed ROP, the median GA was 29 weeks, with a range extending from 23 weeks to 33 weeks and 6 days. The median BW for this group was 1,020

Table 3. Comparison of United Kingdom and United States screening criteria with Türkiye criteria

	Türkiye (a)	UK (b)	US (c)	b/a (%)	c/a (%)
Total number of infants screened	422	245	214	58.1	50.7
ROP detected	136	123	116	90.4	85.3
Type 1 ROP detected	60	55	52	91.7	86.7

g, and their weight distribution ranged from 500 g to 2,400 g. No statistically significant differences were found between the groups in terms of GA ($p=0.182$) or BW ($p=0.204$) (Table 2).

The infants in the internal NICU with ROP requiring treatment had a median BW of 800 g, with the observed range between 370 g and 1,400 g. The median GA for this cohort was 26 weeks, and the range of GA varied from 22 weeks and 6 days to 29 weeks and 6 days. In contrast, infants in external NICUs with ROP requiring treatment had a median BW of 980 g, with the range extending from 500 g to 2,400 g. The median GA in this group was 28 weeks, ranging from 23 weeks to 33 weeks and 6 days. The differences in GA ($p=0.029$) and BW ($p=0.022$) between the two groups were statistically significant (Table 2).

Had the screening criteria applied in the UK been adopted, 245 infants would have undergone screening, reflecting a 41.9% reduction when compared to the criteria used in Türkiye. Of the 167 infants excluded from screening, 13 cases of ROP developed, with 5 of these cases progressing to type 1 ROP or A-ROP, necessitating treatment (Table 3).

Had the US screening criteria been applied, 214 infants would have been screened, resulting in a 49.3% decrease compared to the screening criteria followed in Türkiye. Among the 208 infants excluded from screening, 20 cases of ROP developed, with eight of these cases progressing to type 1 ROP or A-ROP, which required treatment (Table 3).

DISCUSSION

The findings of this study indicate that the ROP screening guidelines applied in the US and UK are unsuitable for the premature infant population examined. The analysis demonstrates that 8.3% of infants requiring ROP treatment would be overlooked under the UK screening criteria, while the rate would increase to 13.3% under the US criteria. The primary rationale for this predicament is that more mature infants treated in external NICUs, who are not subject to screening according to the criteria established by developed countries, nevertheless require treatment for ROP.

In the multicenter TR-ROP study carried out in our country, 27% of the infants screened were diagnosed with some stage of ROP, and 6.7% required treatment for severe ROP.^[1] In our study, 32.4% of the infants were diagnosed with some stage of ROP, and 14.2% of them required treatment. The TR-ROP study divided hospitals into private and public and found that severe ROP cases occurred more frequently in infants who were more mature in private hospitals. In our patient population under study, infants treated in external NICUs and referred to our center were from private hospital NICUs. In our study, all infants requiring treatment but non-compliant with the US criteria were monitored in the NICUs of private hospitals. The rates of ROP diagnosis and treatment in our study were notably higher than those documented in the TR-ROP study. This inconsistency may have arisen due to only specific cases being referred from private hospitals to our hospital, rather than all infants. These selected cases may not fully reflect the general population. These findings indicate a need for increased awareness of ROP development among NICUs in private hospitals in Istanbul.

The establishment of ROP screening criteria is contingent upon the developmental stage of countries.^[12] Research carried out in developed countries has demonstrated that infants born at or beyond 32 weeks of GA face a markedly lower likelihood of developing ROP. Furthermore, the majority of infants born at over 28 weeks' gestation who do develop ROP tend to manifest mild forms of the disease that often resolve spontaneously without requiring treatment.^[13] Research conducted in developing countries has yielded findings that

are consistent with those observed in our study.^[14] Research conducted in Hong Kong revealed that if the UK criteria were replaced with the US criteria, no cases of ROP requiring treatment would have been missed.^[15] Similarly, had we confined our examination to infants treated in our NICU, no infant outside the US screening criteria would have required treatment. This is comparable to the ROP screening criteria in developed countries. Nevertheless, it is evident that the US and UK screening criteria are not universally applicable across Istanbul. Moreover, the division of ROP centers into two distinct categories—those dedicated solely to diagnosis and those offering both diagnosis and treatment—has created a significant challenge in managing ROP effectively.

A multitude of studies have been conducted on a global scale with the objective of evaluating the suitability of the criteria utilized in the US and the UK.^[8,15-18] The primary aim of these studies is twofold: firstly, to evaluate the efficiency of the screening guidelines used in developed countries within their respective regions; and secondly, to explore ways in which these criteria can be made applicable in other contexts.

The application of UK screening criteria to the study conducted in China revealed that 9.4% of ROP cases requiring treatment would have been overlooked if these criteria had been used. The same study revealed that if the US screening criteria were applied, 14.7% of cases would have been overlooked.^[6] Research conducted in Iran showed that 25.4% of ROP cases and 8.4% of cases that needed treatment would not have been detected if the US criteria had been used.^[16] Studies conducted in Pakistan and Saudi Arabia found no cases of ROP requiring treatment in infants born with a GA higher than 32 weeks and a BW exceeding 1,500 g.^[17,18]

A prior study conducted in Türkiye found that 3.8% of infants born at or after 32 weeks and 6.5% of infants born at or after 1,500 g developed severe ROP.^[19] In the more recent TR-ROP study, 1.2% of babies born over 1,500 g and over 32 weeks developed severe ROP that required treatment.^[1] In our study, the rate was found to be 8.3%. A possible reason for this difference is that a considerable number of infants transferred to our hospital from private hospitals were later referred for treatment.

To establish more optimal ROP screening criteria in Istanbul, it may be necessary to increase the educational levels of NICUs in private hospitals regarding ROP. In our country, a neonatologist is typically the head of the NICU in public hospitals. However, in private hospitals, the responsibility for NICUs can also fall upon general pediatricians. Ensuring the presence of a neonatologist in all NICUs could potentially lead to a decline in the rate of ROP treatment.

This study has certain limitations. Firstly, its retrospective design limited the evaluation of other potential factors that may play a role in the development of ROP. Secondly, the study did not include all public and private hospitals in Istanbul. Consequently, it is not possible to extrapolate the current results to all private and public hospitals. Thirdly, the conditions of care and the nurse-to-patient ratio for infants treated in external NICUs are not available for analysis. Furthermore, there were instances where information was missing for infants who had recently passed away or were treated at other facilities without recorded ROP outcomes.

CONCLUSION

In conclusion, applying ROP screening criteria in Istanbul based on those developed in the US or UK led to underdiagnosis and insufficient treatment of ROP cases. By enhancing the educational standards and intensive care practices regarding ROP in private hospitals, it may be feasible to implement screening criteria derived from developed countries. Furthermore, the strategic transformation of hospitals from mere diagnosis centers to comprehensive diagnosis and treatment facilities has the potential to enhance awareness regarding ROP. This approach may prevent the performance of unnecessary examinations and treatments.

Disclosures

Ethics Committee Approval: The study was approved by the Basaksehir Cam and Sakura Hospital Ethics Committee (No: E-96317027-514.10-238025866, Date: 06/03/2024).

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Infodemiology Meets Pharmacoepidemiology: Search Trends and National Drug Use Patterns for Pain-related Medications in Türkiye

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ABSTRACT

Objective: Musculoskeletal system diseases are a significant global health burden, frequently requiring long-term pharmacological management. While conventional databases offer reliable drug consumption data, they often fail to reflect dynamic public interest. Google Trends, as a real-time digital surveillance tool, can provide complementary insights by capturing health-related online search behaviors. This study aimed to evaluate the association between national pharmaceutical consumption and public interest in musculoskeletal and nervous system drugs in Türkiye between 2015 and 2022.

Materials and Methods: This retrospective descriptive study integrated OECD pharmaceutical consumption statistics with Google Trends data for selected keywords. Drug use was assessed via per capita expenditure and percentage of total pharmaceutical sales. Relative search volume values were extracted and normalized for keywords such as "painkiller," "muscle relaxant," and "osteoarthritis."

Results: Strong positive correlations were identified between analgesic consumption and RSVs for keywords including "painkiller" and "muscle relaxant" ($r=0.922$, $p=0.001$), "muscle pain" ($r=0.898$, $p=0.002$), and "joint pain" ($r=0.826$, $p=0.011$). No significant associations were found for musculoskeletal or anti-inflammatory drugs. In turnover-based analyses, certain keywords—especially "joint rheumatism" and "osteoarthritis"—were associated with specific drug categories. Negative correlations between musculoskeletal drug sales and general pain-related searches may suggest a public inclination toward symptom-based treatment.

Conclusion: Google Trends data closely mirror analgesic consumption patterns, indicating their potential as digital proxies for pharmaceutical demand. Integrating such digital tools with traditional data sources may enhance public health surveillance and guide policy decisions.

Keywords: Digital epidemiology, drug utilization, google trends, musculoskeletal system drugs, pharmaceutical consumption

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INTRODUCTION

Musculoskeletal system diseases represent a substantial and growing health concern globally, contributing to significant levels of disability, healthcare expenditure, and social burden.^[1,2] Disorders such as chronic pain syndromes, osteoarthritis, neuropathic pain, and related neurological conditions frequently require long-term pharmacological management, leading to increased use of analgesics, anti-inflamma-

tory agents, muscle relaxants, and centrally acting drugs.^[1,3,4] Monitoring pharmaceutical consumption for these drug categories is thus essential to inform public health strategies, ensure rational drug use, and support resource allocation at both national and international levels.^[1,3,5]

Comprehensive, standardized pharmaceutical data are critical for understanding drug utilization patterns and for cross-national comparisons. The Organization for Econom-



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ic Co-operation and Development (OECD) Health Statistics database provides robust, comparable data on drug consumption in member and partner countries, supporting international benchmarking and research.^[1] In parallel, the Anatomical Therapeutic Chemical (ATC) classification and defined daily dose (DDD) methodology, coordinated by the World Health Organization (WHO), offers a gold standard for classifying drugs and measuring consumption, facilitating analyses of trends, appropriateness of use, and policy impacts.^[2] However, such traditional surveillance systems primarily reflect drug supply or dispensing at the healthcare system level and may not fully capture dynamic changes in public interest, awareness, or unmet informational needs regarding pharmaceuticals.^[3,5,6]

In recent years, the rapid expansion of internet access and digital platforms has transformed health information-seeking behaviors worldwide. It is now estimated that over 90% of internet users have searched for health-related information online, including topics related to symptoms, diagnoses, and drug therapies.^[6,7] Google Trends, a publicly accessible tool provided by Google, enables the analysis of the frequency and temporal distribution of search queries, offering real-time, population-level insights into public interest in specific health topics.^[7,8] The methodology of Google Trends is well-defined and widely accepted in the fields of infodemiology and infoveillance, allowing researchers to normalize search activity data and compare trends across time, regions, and languages.^[6–8] This approach has proven especially valuable for detecting emerging health trends, monitoring the public's response to health policies, and identifying potential mismatches between information demand and service provision.^[3,5,8]

A growing body of research supports the use of Google Trends as a complementary tool to traditional pharmaceutical surveillance. Studies have shown that internet search activity can closely reflect and, in some instances, predict actual drug consumption patterns for diverse therapeutic classes, including antibiotics, opioids, antidepressants, and anti-inflammatory drugs.^[9–12] For example, investigations from Europe, North America, and Asia have demonstrated strong correlations between increases in web searches for specific medications and subsequent rises in their prescription or sales figures, often in the context of new clinical guidelines, public health campaigns, or widespread events such as the COVID-19 pandemic.^[9,11,12] Google Trends has also been employed to track shifts in public interest following new legislation or policy interventions, as well as to mon-

itor the effects of seasonal changes and media coverage on health information-seeking behavior.^[9–12]

Despite the increasing use of digital data sources in pharmacoepidemiology, few studies have focused specifically on musculoskeletal system drugs, and the relationship between internet search trends and national drug utilization in these categories remains largely unexplored—particularly in middle-income countries such as Türkiye. Understanding this interplay is critical, as the burden of musculoskeletal system disorders continues to rise and health systems are challenged to meet growing needs for effective, safe, and evidence-based pharmacological interventions.^[1,4,9,12]

Türkiye has experienced a significant evolution in its healthcare system and pharmaceutical market over the past two decades, including expanded access to medications, changes in prescribing practices, and increased public engagement with digital health information. However, it remains unclear to what extent internet search behavior reflects or anticipates real-world trends in drug consumption for musculoskeletal system conditions within this setting.^[9,12]

Therefore, the objective of this study is to investigate the association between national pharmaceutical consumption statistics and Google Trends search data for selected musculoskeletal system drug categories in Türkiye from 2015 to 2022. By integrating standardized national drug utilization data with normalized digital search metrics, this study aims to provide a comprehensive, multidimensional understanding of both actual consumption patterns and public information-seeking behavior. The findings may help identify gaps in health communication, support more targeted public health interventions, and inform future pharmaceutical and digital health policies.

MATERIALS and METHODS

This retrospective and descriptive study aimed to investigate the relationship between pharmaceutical consumption patterns and public interest in musculoskeletal and nervous system-related drug categories in Türkiye, using national pharmaceutical statistics and Google Trends data from 2015 to 2022. The year 2022 was selected as the upper limit for the analysis because it was the most recent year with complete data available from both sources at the time of the study.

Pharmaceutical data were obtained from the OECD Health Statistics database. The Organization for Economic Co-operation and Development (OECD) is an international organization that provides reliable and standardized data across member countries to support evidence-based policymaking in areas such as health, education, and economics. From this

source, annual data on pharmaceutical sales volume (in millions of packages), sales value (in local currency), and defined daily doses (DDD) per 1,000 inhabitants per day were extracted.^[1,2] The data were filtered specifically for Türkiye and analyzed for two main therapeutic groups and their respective subcategories: musculoskeletal system drugs, including anti-inflammatory and antirheumatic products (non-steroids), and nervous system drugs, including analgesics.

Google Trends was used to obtain the relative search volume (RSV) for selected keywords that reflect public interest in each drug category. Google Trends is a publicly available web-based tool developed by Google that analyzes the popularity of top search queries in Google Search across various regions and time periods. It provides a normalized index of search volume ranging from 0 to 100, where 100 represents the peak popularity of a term within the selected time frame and region.^[6,7]

For this study, search queries were limited to Türkiye and the period between January 2015 and December 2022. Keyword selection was conducted carefully to ensure that the terms accurately represented layperson terminology related to each pharmacological group. This process involved reviewing commonly used Turkish expressions in media, patient forums, and health-related platforms. As a result, representative keywords were selected to reflect public interest in musculoskeletal system drugs, anti-inflammatory products, and analgesics. These included "ağrı kesici" (painkiller), "kas gevşetici" (muscle relaxant), "kas ağrısı" (muscle pain), "eklem ağrısı" (joint pain), "romatizma ilacı" (rheumatism drug), "eklem romatizması" (joint rheumatism), "kireçlenme" (osteoarthritis), and "iltihap giderici" (anti-inflammatory).^[6,13]

To enhance reliability, the search terms were entered using the "Search Term" setting in Google Trends rather than the "Topic" option, ensuring that the RSV data corresponded to exact keyword matches. RSV values were then exported as annual averages for each term and normalized on a scale from 0 to 100 for direct comparison across years and drug categories. This approach allowed for an objective assessment of temporal shifts in public online interest that could be compared to national pharmaceutical consumption trends.^[6,7,13]

This study complies with the principles of the Declaration of Helsinki. It was based solely on publicly available and anonymized data (Google Trends and OECD pharmaceutical statistics) and did not involve any human participants, interventions, or personal health information. Since only publicly available, anonymized data were used, ethical approval was not required.

Statistical Analysis

Statistical analyses were conducted using SPSS Statistics software (version 25; IBM Corp., Armonk, NY, USA). Pearson correlation coefficients were calculated to assess the strength and direction of linear associations between normalized relative search volume (RSV) values and pharmaceutical consumption indicators (i.e., per capita expenditure and percentage of total turnover). Prior to conducting correlation analysis, the assumptions of linearity and normal distribution of variables were visually inspected using scatterplots and Shapiro-Wilk tests, respectively. A two-tailed p-value of <0.05 was considered statistically significant.

RESULTS

In this study, we analyzed the relationship between national pharmaceutical consumption data and public interest, as reflected in Google search trends for selected keywords related to musculoskeletal and nervous system drugs in Türkiye between 2015 and 2022.

Per capita pharmaceutical expenditures (in PPP-adjusted USD) were as follows: for musculoskeletal system drugs, the mean was 13.83 (SD=1.17; range: 11.90–15.90); for anti-inflammatory and antirheumatic products (non-steroids), 5.93 (SD=0.70; range: 5.00–7.30); and for analgesics, 5.46 (SD=0.99; range: 3.90–7.10). The corresponding median values were 14.00, 5.75, and 5.50, respectively.

Regarding the percentage share of total pharmaceutical sales turnover, musculoskeletal system drugs had a mean of 5.59% (SD=0.53; range: 4.80–6.20), anti-inflammatory and antirheumatic products (non-steroids) had 2.39% (SD=0.26; range: 2.00–2.70), and analgesics had 2.19% (SD=0.21; range: 1.90–2.60). The respective median values were 5.85%, 2.45%, and 2.20%.

To explore the potential associations between online public interest and pharmaceutical consumption, correlation analyses were conducted using PPP-adjusted per capita drug expenditure and Google Trends data. The keywords "painkiller" and "muscle relaxant" showed strong positive correlations with analgesic consumption ($r=0.922$, $p=0.001$). "Muscle pain" ($r=0.898$, $p=0.002$), "joint pain" ($r=0.826$, $p=0.011$), "rheumatism drug" ($r=0.814$, $p=0.014$), and "osteoarthritis" ($r=0.790$, $p=0.020$) also demonstrated statistically significant positive correlations with analgesic consumption. No statistically significant correlations were found between any keyword and musculoskeletal system drugs or anti-inflammatory non-steroids. "Joint rheumatism" ($r=0.500$, $p=0.207$) and "osteoarthritis" ($r=0.452$,

Table 1. Correlation between Google Search Trends and Drug consumption (US dollars per person, PPP-adjusted)

Keyword	Musculo-skeletal system	Anti-inflammatory non-steroids	Analgesics
Painkiller	r=0.143 (p=0.736)	r=0.095 (p=0.823)	r=0.922 (p=0.001)
Muscle relaxant	r=0.143 (p=0.736)	r=0.095 (p=0.823)	r=0.922 (p=0.001)
Muscle pain	r=0.119 (p=0.779)	r=0.190 (p=0.651)	r=0.898 (p=0.002)
Joint pain	r=0.167 (p=0.693)	r=0.310 (p=0.456)	r=0.826 (p=0.011)
Rheumatism drug	r=0.167 (p=0.693)	r=0.381 (p=0.352)	r=0.814 (p=0.014)
Joint rheumatism	r=0.500 (p=0.207)	r=0.190 (p=0.651)	r=-0.323 (p=0.435)
Osteoarthritis	r=0.452 (p=0.260)	r=0.143 (p=0.736)	r=0.790 (p=0.020)
Anti-inflammatory	r=0.190 (p=0.651)	r=0.310 (p=0.456)	r=0.922 (p=0.001)

PPP: Purchasing power parity

Table 2. Correlation between Google Search Trends and drug category sales share (% of total turnover)

Keyword	Musculo-skeletal system	Anti-inflammatory non-steroids	Analgesics
Painkiller	r=-0.778 (p=0.023)	r=-0.655 (p=0.078)	r=0.634 (p=0.091)
Muscle relaxant	r=-0.778 (p=0.023)	r=-0.655 (p=0.078)	r=0.634 (p=0.091)
Muscle pain	r=-0.802 (p=0.017)	r=-0.606 (p=0.111)	r=0.586 (p=0.127)
Joint pain	r=-0.778 (p=0.023)	r=-0.558 (p=0.151)	r=0.464 (p=0.247)
Rheumatism drug	r=-0.814 (p=0.014)	r=-0.436 (p=0.280)	r=0.342 (p=0.408)
Joint rheumatism	r=0.826 (p=0.011)	r=0.570 (p=0.140)	r=0.171 (p=0.686)
Osteoarthritis	r=-0.263 (p=0.528)	r=-0.206 (p=0.624)	r=0.805 (p=0.016)
Anti-inflammatory	r=-0.778 (p=0.023)	r=-0.449 (p=0.265)	r=0.586 (p=0.127)

p=0.260) showed non-significant positive correlations with musculoskeletal system drugs. The keyword "joint rheumatism" showed a non-significant negative correlation with analgesics (r=-0.323, p=0.435). "Anti-inflammatory" was strongly correlated with analgesic consumption (r=0.922, p=0.001), but not significantly associated with the other drug groups (Table 1).

A second correlation analysis was performed to evaluate the relationship between Google search trends and the percentage share of each drug category in total pharmaceutical turnover. The keywords "painkiller" and "muscle relaxant" exhibited significant negative correlations with musculoskeletal system drugs (r=-0.778, p=0.023). "Muscle pain" (r=-0.802, p=0.017), "joint pain" (r=-0.778, p=0.023), and "rheumatism drug" (r=-0.814, p=0.014) also showed significant negative correlations with this category. In contrast, "joint rheumatism" was positively correlated with musculoskeletal drug turnover (r=0.826, p=0.011), while "osteoarthritis" showed a statistically significant correlation with analgesics (r=0.805, p=0.016). Other correlations were not statistically significant (Table 2).

DISCUSSION

This study analyzed the relationship between national pharmaceutical consumption data and public interest, as reflected in Google search trends for selected keywords related to musculoskeletal and nervous system drugs in Türkiye between 2015 and 2022.

The analysis revealed strong and statistically significant positive correlations between keywords such as "painkiller," "muscle relaxant," and "muscle pain" and per capita analgesic consumption, suggesting a parallel between digital interest and real-world demand for pain relief. No statistically significant associations were identified for musculoskeletal or anti-inflammatory drugs. In terms of sales turnover, certain search terms showed negative correlations with musculoskeletal drug sales, while "joint rheumatism" and "osteoarthritis" indicated positive trends within their respective categories.

Negative correlations observed between public search interest and the sales share of musculoskeletal drugs suggest an inverse relationship between online search behavior and financial turnover in this category. This may reflect the pub-

lic's greater focus on general pain relief and symptomatic management, favoring analgesic consumption over musculoskeletal-specific medications. Variations in terminology and public understanding of drug categories may also contribute to these findings. Such inverse associations have been reported in previous studies examining the complex dynamics between public interest, clinical needs, and medication consumption.^[6,14,15]

Several recent studies support the use of Google Trends as a proxy for public health interest and pharmaceutical consumption patterns. For example, Spyrtatos et al.^[14] demonstrated that Google Trends reflected seasonal fluctuations in over-the-counter analgesic sales in Greece during the COVID-19 pandemic. Rognoni et al.^[15] found that search trends in Italy correlated with changes in opioid prescription policies and public interest in pain medications. Mavragani^[6] emphasized the methodological value and growing adoption of infodemiology approaches using search data in pharmacovigilance and public health surveillance. Additionally, Gokdemir et al.^[16] validated the applicability of Google Trends data for monitoring medication use in Türkiye, aligning with our study's context and findings.

Recent advances in digital epidemiology have highlighted the value of Google Trends as a real-time proxy for monitoring public health interest and anticipating pharmaceutical demand. For example, one study demonstrated the utility of search engine data in forecasting drug consumption patterns, particularly for over-the-counter analgesics.^[17] Another analysis of pandemic-driven fluctuations in medication searches revealed shifts in public behavior that closely mirrored pharmaceutical sales.^[18] These findings support and extend our observations on the correlation between online interest in pain relief and analgesic consumption.

Moreover, a separate investigation into the role of Google Trends in tracking opioid prescription patterns amid the opioid crisis underscored the potential of digital tools in shaping public health responses and policymaking.^[19]

Collectively, these studies reinforce the significance of integrating digital search data with pharmaceutical statistics, enabling more responsive and informed health system planning. Our study contributes to this growing body of evidence by focusing on musculoskeletal and nervous system medications in Türkiye, highlighting region-specific dynamics and cultural considerations in digital health behavior.

These findings suggest potential implications for public health planning, particularly regarding health information

dissemination and medication literacy. As the data indicate a strong public tendency to search for general pain-related symptoms rather than specific drug categories, tailored health education programs emphasizing rational drug use and clarifying treatment options may be beneficial. Policymakers could consider investing in digital health awareness campaigns to bridge the information gap and improve public engagement with accurate pharmaceutical guidance.

CONCLUSION

This study demonstrates a significant association between public interest, as measured by Google search trends, and pharmaceutical consumption patterns for analgesics in Türkiye. The strong correlations observed suggest that online search behavior may serve as an early indicator of real-world drug demand, particularly for pain-related medications. However, the relationship between search trends and other drug categories, such as musculoskeletal and anti-inflammatory drugs, appears less direct.

These findings support the integration of digital epidemiology tools like Google Trends into public health monitoring and pharmaceutical policy planning.^[6,8,14,16–18] Future research should expand keyword selection, extend the study period, and consider additional drug classes to further validate and refine these insights. The integration of Google Trends into pharmacoepidemiologic monitoring offers opportunities for shaping proactive public health policies. Initiatives such as national medication literacy campaigns and digital platforms that provide accessible drug-related information may help align public interest with evidence-based pharmaceutical practices.

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Evaluation of Serum Lipid Profile as a Predictive Biomarker for Survival in Gastrointestinal Cancer Patients

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ABSTRACT

Objective: Altered lipid metabolism is increasingly recognized as a hallmark of cancer progression and may serve as a prognostic biomarker. While individual lipid components such as total cholesterol, LDLc, HDLc, and triglyceride have been evaluated in various malignancies, their prognostic relevance in gastrointestinal (GI) cancers remains unclear. This study aimed to assess the association between baseline lipid profiles and overall survival (OS) in GI cancer patients.

Materials and Methods: A retrospective analysis was conducted on 103 patients with histologically confirmed gastric, colorectal, rectal, or esophageal cancer treated between January 2024 and March 2025. Pre-treatment fasting lipid profiles, including total cholesterol, LDLc, HDLc, and triglyceride, were recorded. Optimal cut-off values were determined by receiver operating characteristic analysis, and OS was analyzed using Kaplan–Meier survival curves and log-rank tests.

Results: At a median follow-up of 22 months, 26 patients (25.2%) had died. Low baseline total cholesterol (<135 mg/dL), LDLc (<76.5 mg/dL), and HDLc (<40 mg/dL) were each significantly associated with reduced median OS (all $p < 0.01$). Triglyceride levels did not significantly correlate with survival ($p = 0.400$). Cancer type, stage, liver metastasis, sex, and diabetes status showed no significant association with OS.

Conclusion: Lower baseline total cholesterol, LDLc, and HDLc levels predict worse survival in GI cancer patients, highlighting the prognostic relevance of lipid metabolism. Routine lipid profiling may serve as an accessible tool for risk stratification in oncology. Prospective studies are warranted to validate these findings and explore lipid modulation as a therapeutic adjunct.

Keywords: Cholesterol, gastrointestinal cancer, HDLc, lipid profile, LDLc, triglyceride

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INTRODUCTION

Lipid metabolism plays an important role in cancer biology and systemic health. Dyslipidemia, involving changes in serum lipids like total cholesterol, low-density lipoprotein cholesterol (LDLc), high-density lipoprotein cholesterol (HDLc), and triglyceride, is recognized as a metabolic issue and potential prognostic factor in cancer.^[1–2] In cancers such as colorectal, gastric, and hepatocellular, serum lipid changes relate to tumor progression, immune response, and inflammation, indicating baseline lipid profiles may have prognostic value.^[3]

Cholesterol is crucial for maintaining cell membrane integrity, supporting hormone production, and facilitating intracellular signaling, functions that are vital for the growth and survival of cancer cells.^[4] It facilitates lipid raft formation, clustering signaling molecules like receptor tyrosine kinases, and activating oncogenic pathways such as PI3K/AKT and MAPK.^[5,6] Additionally, hypocholesterolemia may reflect malnutrition, cancer-related cachexia, or high tumor burden, particularly in gastrointestinal (GI) malignancies. A large nationwide cohort study by Lim et al.^[7] demonstrated



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that lower serum cholesterol levels were inversely associated with gastric cancer risk among postmenopausal women, highlighting the potential role of cholesterol as a biomarker linked to cancer susceptibility and progression.

HDLc exerts protective anti inflammatory and antioxidant effects by removing cholesterol from tissues, modulating cytokines, and reducing oxidative stress.^[8,9] LDLc may promote tumor growth by supplying cholesterol for dividing cells and membrane synthesis.^[10] Disrupted HDLc and LDLc balance links to higher cytokines, endothelial dysfunction, and tumor angiogenesis, leading to poorer prognosis.^[11,12] Thus, low HDLc and LDLc levels may indicate the host's metabolic and tumor microenvironment status, affecting survival. On the other hand, studies have shown that reduced lipid levels are linked to chronic inflammation, with elevated IL-6 and TNF- α suppressing hepatic lipoprotein production and increasing lipoprotein catabolism, potentially worsening prognosis by promoting tumor growth.^[13,14]

Likewise, Gu et al.^[15] (n=1,303) found that a higher preoperative HDLc/LDLc ratio was independently predictive of improved progression-free survival (HR 0.65; 95% CI 0.50–0.84; p=0.001) and overall survival (OS) (HR 0.60; 95% CI 0.45–0.80; p<0.001) in resectable colorectal cancer patients. Similarly, Tao et al.^[16] demonstrated that lower serum HDLc levels were significantly correlated with larger tumor size (>5 cm) and advanced stage (p<0.01), and that elevated expression of cholesterol metabolism genes such as LDLcR (HR 3.12), ABCA1 (HR 1.66), and OSBPL1A (HR 1.38) independently predicted poorer disease-free survival. In a comprehensive meta-analysis by Zhou et al.,^[17] low serum HDLc and total cholesterol were significantly associated with poorer OS across various malignancies, with the strongest effects observed in GI cancers. In a large cohort of 59,217 newly diagnosed cancer patients, Kim et al.^[18] demonstrated a U shaped relationship between baseline total cholesterol and LDLc levels and all cause mortality. Specifically, both very low total cholesterol (≤ 97 mg/dL; aHR 1.54, 95% CI 1.43–1.66) and very low LDLc (≤ 57 mg/dL; aHR 1.38, 95% CI 1.14–1.68) were independently associated with increased risk of death.

In a comprehensive meta-analysis of 156 studies including gastric, colorectal, and hepatocellular carcinoma patients, Peng et al.^[19] found that higher HDLc, TC, and ApoA1 levels were significantly associated with improved OS and DFS. Notably, LDLc and TG levels did not show consistent prognostic value. Conversely, the relationship between hypertriglyceridemia and cancer prognosis remains inconsistent. Some studies have reported that elevated triglyceride

levels are associated with worse survival outcomes, potentially reflecting the complex interplay between lipid metabolism, metabolic syndrome, insulin resistance, and cancer-related cachexia. For example, Lee et al.^[20] found that in terminal cancer patients, high triglyceride levels were independently linked to shorter survival, particularly when combined with low LDLc levels, suggesting that altered lipid metabolism may reflect both tumor-driven catabolic processes and systemic metabolic dysfunction.

Most studies on lipids in GI cancers are limited by narrow focus and lack of survival-optimized thresholds, leaving the prognostic value of major lipid parameters inadequately defined. The present study aims to examine the prognostic significance of baseline lipid profile parameters, including total cholesterol, LDLc, HDLc, and triglyceride, on OS in patients with GI cancers. Using a retrospective cohort design with receiver operating characteristic (ROC)-derived cut-off values and survival analysis, this study seeks to determine whether lipid abnormalities act as modifiable prognostic markers that can aid in risk stratification and guide future therapeutic strategies.

MATERIALS and METHODS

Study Design and Settings

This retrospective cohort study included patients diagnosed with GI cancers who presented to the medical oncology outpatient clinic of our hospital between 1 January 2024 and 31 March 2025. Patient data were obtained from the institutional electronic medical record system. Baseline demographic and clinical characteristics, including age, sex, tumor type (gastric, esophageal, colon, or rectal), stage at diagnosis, presence of liver metastases, and comorbid conditions such as diabetes mellitus and hypertension, were systematically recorded.

The exclusion criteria were as follows: history of any other malignancy, use of lipid-lowering medications (including statins, fibrates, ezetimibe, omega-3 fatty acids, or PCSK9 inhibitors), presence of active infection or acute inflammatory conditions at the time of diagnosis, known familial hypercholesterolemia or other genetic dyslipidemia syndromes, uncontrolled endocrine or metabolic diseases affecting lipid metabolism (such as hypothyroidism or nephrotic syndrome), chronic kidney disease stage ≥ 3 (eGFR <60 mL/min/1.73 m²), chronic liver disease, current use of corticosteroids, immunosuppressive drugs, or hormonal agents known to interfere with lipid levels, prior initiation of cancer treatment before lipid measurement, and incom-

plete or missing clinical or laboratory data. A total of 103 patients were included in the final cohort for analysis.

Ethics Approval and Consent to Participate

This study was carried out in compliance with the Declaration of Helsinki. Informed consent was obtained from all patients or their caregivers. The Local Ethics Committee of Istanbul Medipol University approved the study (decision date: 19.06.2025, number: E-10840098-202.3.02-4097).

Lipid Profile Measurement

Fasting blood samples were obtained at cancer diagnosis, prior to any oncologic treatment, following an overnight fast of ≥ 8 hours. Serum lipid levels, including total cholesterol, LDLc, HDLc, and triglyceride, were measured using enzymatic colorimetric methods on the Roche Cobas 8000 analyzer. All assays were performed in the central biochemistry lab per institutional protocols. Lipid parameters were categorized as “low” or “high” based on cohort-specific ROC-derived cut-offs for OS: 135 mg/dL (total cholesterol), 76.5 mg/dL (LDLc), 40 mg/dL (HDLc), and 150 mg/dL (triglyceride).

Outcomes

The primary outcome was the association between baseline lipid parameters (total cholesterol, LDLc, HDLc, and triglyceride) and OS, defined as the time from diagnosis to death or last follow-up. Secondary analyses assessed OS across cancer types and by liver metastases, sex, diabetes status, and disease stage.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize patient demographics and clinical characteristics. The normality of distribution for continuous variables was assessed using the Kolmogorov–Smirnov test. ROC curve analysis was conducted to evaluate the predictive value of lipid profile parameters for OS, with area under the curve (AUC) and 95% confidence intervals (CI) reported. Kaplan–Meier survival curves were constructed to estimate OS, and group differences were tested using the log-rank (Mantel–Cox) test. OS was defined as the time from the date of cancer diagnosis to the date of death or last available follow-up. Median OS and corresponding 95% CIs were calculated. A two-sided p-value of less than 0.05 was considered statistically significant. Optimal cut-off values were determined by ROC analysis using the Youden index to maximize the sum of sensitivity and specificity. Pairwise

Table 1. Demographic and clinical characteristics of the patients

Patient characteristic	Value	
	n	%
Age, years	56 (39–81)	
Gender		
Female	50	48.5
Male	53	51.5
Cancer type		
Colorectal	39	37.9
Rectal	22	21.4
Gastric	24	23.3
Esophageal	18	17.5
Cancer stage		
Stage 1	6	5.8
Stage 2	26	25.2
Stage 3	32	31.1
Stage 4	39	37.9
Presence of hepatic metastasis	29	28.2
Exitus	26	25.2

comparisons between cancer types were evaluated using a chi-square test where appropriate.

RESULTS

The median age was 56 years (range: 39–81). The cohort consisted of 53 males (51.5%) and 50 females (48.5%). By cancer type, the cohort comprised 39 colorectal cancer patients (37.9%), 24 gastric cancer (23.3%), 22 rectal cancer (21.4%), and 18 esophageal cancer patients (17.5%). At diagnosis, 6 patients (5.8%) were in stage I, 26 (25.2%) in stage II, 32 (31.1%) in stage III, and 39 (37.9%) in stage IV. Comorbid diabetes mellitus was present in 26 patients (25.2%), and hypertension in 29 (28.2%). Liver metastases were documented in 29 patients (28.2%). At a median follow-up of 22 months, 26 patients (25.2%) had died. Key demographic and clinical features are summarized in Table 1.

Patients with low baseline total cholesterol levels (<135 mg/dL) had a markedly shorter median OS compared to those with higher levels (≥ 135 mg/dL). Specifically, at a median follow-up of 22 months, the median OS in the low total cholesterol group was 7.0 months (95% confidence interval [CI]: 0.0–14.5), while the median OS was not reached in the high total cholesterol group (indicating that more than half of the patients in this group were still alive at the end of the

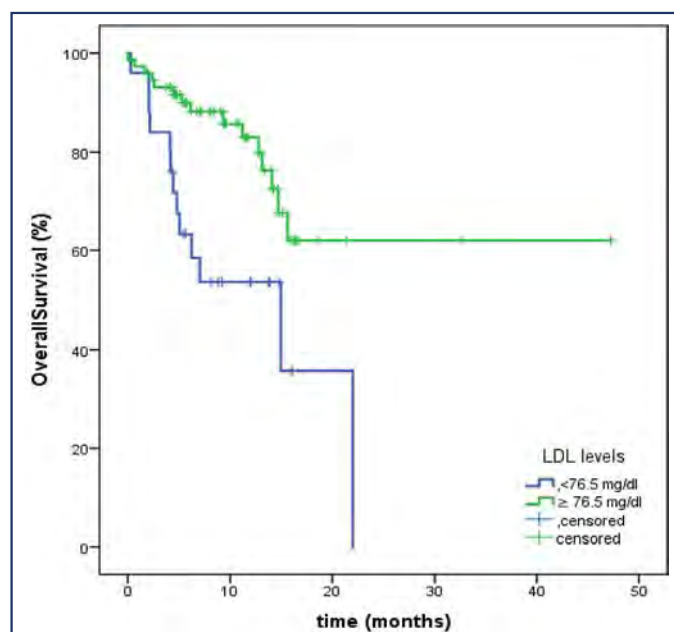


Figure 1. Kaplan–Meier overall survival curves for patients stratified by baseline LDLc levels (cut-off=76.5 mg/dL). The blue curve represents patients with LDLc <76.5 mg/dL and the green curve represents those with LDLc ≥76.5 mg/dL

LDLc: Low-density lipoprotein cholesterol

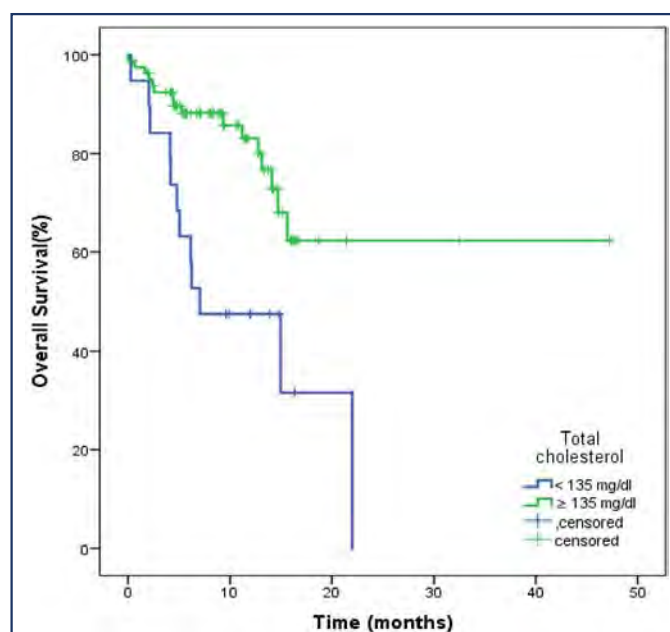


Figure 2. Kaplan–Meier overall survival curves for patients stratified by baseline total cholesterol levels (cut-off=135 mg/dL). The blue curve represents patients with total cholesterol <135 mg/dL, and the green curve represents those with total cholesterol ≥135 mg/dL

follow-up period). This difference was statistically significant (log-rank $p=0.001$). Similarly, patients with LDLc <76.5 mg/dL had a median OS of 14.97 months (95% CI: 2.76–27.17), compared to a not-reached median OS in those with LDLc ≥76.5 mg/dL ($p=0.002$). A comparable survival advantage was observed in patients with higher HDLc levels (≥40 mg/dL), as the median OS was not reached in this group, while it was 14.7 months (95% CI: 3.01–26.39) in the lower HDLc group ($p=0.002$). In contrast, triglyceride levels did not show a significant association with survival. When stratified by a cut-off value of 150 mg/dL, the median OS was 22.0 months (95% CI: 11.1–32.8) in the low triglyceride group (<150 mg/dL) and 14.7 months (95% CI: 13.4–16.0) in the high triglyceride group (≥150 mg/dL), but this difference did not reach statistical significance (log-rank $p=0.4$) (Figs. 1-3).

Despite no statistical significance, rectal cancer patients had a numerically shorter survival than those with colon cancer ($\chi^2=1.902$, $p=0.168$), gastric cancer ($\chi^2=2.406$, $p=0.121$), and esophageal cancer ($\chi^2=1.324$, $p=0.250$), but these comparisons did not reach statistical significance. Similarly, the survival difference between colon and gastric cancers ($\chi^2=0.304$, $p=0.581$) and between colon and esophageal cancers ($\chi^2=0.045$, $p=0.832$) was not statistically significant.

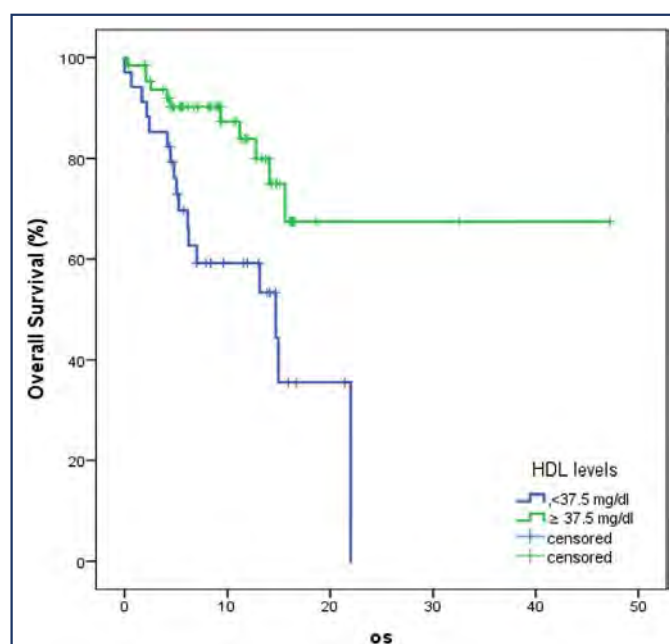


Figure 3. Kaplan–Meier overall survival curves for patients stratified by baseline HDLc levels (cut-off=40 mg/dL). The blue curve corresponds to patients with HDLc <40 mg/dL, and the green curve to those with HDLc ≥40 mg/dL

HDLc: High-density lipoprotein cholesterol

Cancer type was not a statistically significant determinant of OS (log-rank $p > 0.05$); however, median OS was observed as follows: 25.6 months in gastric (95% CI: 18.7–32.6), 22.3 months in colon (95% CI: 16.1–28.5), 20.1 months in esophageal (95% CI: 13.9–26.2), and 17.4 months in rectal cancer (95% CI: 9.2–25.6).

Disease stage at diagnosis showed a non-significant trend toward poor OS in patients with stage IV disease compared to those with stage I–III (log-rank $p = 0.1$).

Median OS was 19.3 months in patients with liver metastases ($n = 29$, 28.2%) and 25.7 months in those without ($n = 52$, 50.5%) (log-rank $p = 0.087$). Sex (female: $n = 50$, 48.5%; male: $n = 53$, 51.5%; $p = 0.438$) and diabetes status ($n = 26$, 25.2%; $p = 0.503$) were not significantly associated with OS.

DISCUSSION

This study evaluated the prognostic significance of baseline lipid profile parameters, including total cholesterol, LDLc, HDLc, and triglyceride, on OS in patients with GI malignancies such as gastric, esophageal, colorectal, and rectal cancers. This concept is further supported by the comprehensive review of Pavlova and Thompson,^[21] who emphasized that tumor-specific alterations in lipid metabolism, particularly shifts in fatty acid oxidation and cholesterol biosynthesis, represent key drivers of cancer progression and therapeutic resistance.

Several studies have highlighted the prognostic relevance of baseline lipid parameters in various GI malignancies, supporting the emerging view that dyslipidemia may influence not only cancer-related inflammation and nutritional status but also tumor progression and patient survival. For instance, Shen et al.^[3] retrospectively evaluated 358 gastric cancer patients and found that patients with low preoperative HDLc (< 54.2 mg/dL) exhibited deeper tumor invasion, more nodal metastasis, and advanced stage at presentation ($p < 0.05$), suggesting a link between hypolipidemia and tumor aggressiveness, albeit without significant impact on OS.

Similarly, a comprehensive meta-analysis by Yang et al.^[22] evaluated more than 15,000 non-metastatic colorectal cancer patients across 20 cohort studies and concluded that higher baseline HDLc levels were significantly associated with improved disease-free and OS (RR 0.86; 95% CI 0.77–0.97). In esophageal squamous cell carcinoma, Chen et al.^[23] retrospectively analyzed 214 patients undergoing esophagectomy and found that low preoperative LDLc (< 3.23 mmol/L, ~ 125 mg/dL) correlated with more advanced tumor stage. Multivariate analysis showed these patients had significantly shorter survival: median DFS was 17.7 vs. 55.3 months and

median OS was 25.8 vs. 60.4 months for low versus high LDLc groups ($p < 0.001$). The proposed mechanism involves HDLc's role in modulating oxidative stress and suppressing inflammation within the tumor microenvironment.

In a retrospective cohort study comprising 712 patients who underwent curative resection for colorectal cancer, Chen et al.^[24] investigated the prognostic significance of preoperative serum triglyceride levels. Patients were stratified based on their preoperative TG concentrations into low and high groups. The survival outcomes were analyzed using multivariate Cox proportional hazards models, adjusting for potential confounders including tumor stage, BMI, and systemic inflammatory markers.

Their findings demonstrated that higher preoperative triglyceride levels were independently associated with both improved OS and disease-free survival (DFS). This suggests that adequate lipid reserves may play a protective role in sustaining metabolic homeostasis and energy supply during cancer progression. Furthermore, these results align with the broader concept that lipid metabolism is intricately linked to tumor biology and host resilience, highlighting the potential prognostic relevance of metabolic biomarkers in oncological outcomes.^[24]

Recent high-quality retrospective studies have provided compelling evidence that serum lipid profiles carry prognostic value in GI cancers. For instance, Nam et al.^[25] conducted a retrospective analysis on esophageal squamous cell carcinoma (ESCC) patients and found that lower preoperative LDLc levels were significantly correlated with poorer OS, presumably due to LDLc's role in maintaining cell membrane structure and supporting immune competence. For gastric cancer, Pih et al.^[26] analyzed patient lipid profiles and reported that individuals with low HDLc and/or high LDLc/HDLc ratios exhibited more advanced disease stages and poorer prognosis, supporting the notion that dysregulated lipid transport may exacerbate tumor progression. In a retrospective study, Zhang and colleagues investigated the prognostic value of lipid profiles in 306 patients with esophageal squamous cell carcinoma undergoing curative esophagectomy. They evaluated preoperative serum lipid levels and demonstrated that low LDLc concentrations were independently associated with worse OS, even after adjusting for tumor stage and systemic inflammation, suggesting that LDLc plays a critical role in maintaining membrane stability and supporting immune competence in cancer patients.^[27]

Our findings revealed that lower levels of total cholesterol, LDLc, and HDLc at diagnosis were significantly associated

with reduced OS. Specifically, patients with total cholesterol <135 mg/dL had a median OS of 7.0 months, while the median OS was not reached in those with higher levels (≥ 135 mg/dL). Similarly, patients with LDLc below 76.5 mg/dL and HDLc below 40 mg/dL had markedly shorter survival times compared to those with higher levels in each category. In contrast, triglyceride levels did not show a statistically significant association with OS.

In our cohort, OS did not differ significantly across GI cancers, yet rectal cases fared worst. Sánchez Martínez et al.^[28] demonstrated in colon cancer cell models and clinical samples that overexpression of ACSL1/4 and SCD enzymes activates epithelial–mesenchymal transition, enhances invasive behavior, and correlates with poor outcomes in stage II colon cancer patients, suggesting that dysregulated lipid metabolism may similarly contribute to aggressive biology in rectal tumors.

In our cohort, stage IV disease showed a non-significant OS disadvantage versus stage I–III ($p=0.109$). Surveillance, epidemiology, and end results (SEER) program data cite 5-year survival rates of 91.5%, 73.4%, and approximately 15% for localized, regional, and distant colorectal cancer.^[29,30] In metastatic gastric cancer, median OS has been reported as 6–13 months, whereas resectable stages yield 25–40 months, according to international consensus data.^[31,32] Small early-stage patient numbers, a low number of events, and biologic/treatment heterogeneity likely underpowered our analysis, underscoring the need for larger, stage-balanced cohorts.^[33]

Previous studies have consistently indicated that liver metastases significantly worsen OS in GI malignancies. However, Engstrand et al.^[34] reported no statistically significant difference in OS between patients with synchronous versus metachronous liver metastases in colorectal cancer, suggesting that the timing of hepatic spread may be less important than its mere presence. In contrast, Sun et al.,^[35] using SEER data on newly diagnosed gastric cancer patients with liver metastases, found median OS to be only 4.0 months in untreated individuals versus 12.0 months in those receiving multimodal therapy, emphasizing the poor prognosis associated with hepatic involvement and the potential benefits of treatment. In line with these findings, median OS was 19.3 months in patients with liver metastases ($n=29$, 28.2%) and 25.7 months in those without ($n=52$, 50.5%) (log-rank $p=0.087$) in our cohort. Although the difference did not reach statistical significance, likely due to sample size limitations, the trend aligns with prior

literature suggesting the adverse prognostic impact of hepatic dissemination. Sex (female: $n=50$, 48.5%; male: $n=53$, 51.5%; $p=0.438$) and diabetes status ($n=26$, 25.2%; $p=0.503$) were not significantly associated with OS, consistent with meta-analyses indicating only modest or non-significant survival effects of these variables in GI cancers. These observations suggest that, in the context of GI malignancies, metastatic burden, particularly liver involvement, may exert a stronger influence on survival outcomes than baseline demographic or metabolic factors.

Our study has several limitations. As a retrospective, single-center analysis, it might introduce selection bias and limited generalizability. Lipid parameters were measured once before cancer treatment, preventing assessment of changes over time. We also did not collect data on diet, nutrition, BMI, or genetics that could influence lipid metabolism and outcomes. The study's observational nature means causality cannot be confirmed. Additionally, progression-free and recurrence-free survival were not assessed due to the inclusion of patients across all disease stages (I–IV), making OS the primary endpoint. However, with longer follow-up, including progression-free survival and relapse-free survival could offer useful prognostic insights. Additionally, inflammatory markers such as C-reactive protein or interleukin-6 (IL-6) were not assessed, which might have further clarified the role of systemic inflammation in lipid alterations.

Even with its retrospective, single-center scope and modest sample size, this study is the first to apply survival-optimized lipid cut-offs across four major GI cancers, showing that low baseline total cholesterol, LDLc, and HDLc reliably flag poorer OS. By providing clinically actionable thresholds derived from routine blood tests, it supplies a practical risk-stratification tool and builds a rationale for prospective trials of lipid-modulating strategies in GI oncology. Furthermore, routine assessment of serum lipid profiles may aid in early risk stratification, particularly in resource-limited oncology settings, due to its accessibility and low cost.

CONCLUSION

Our study demonstrates that lower baseline levels of total cholesterol, LDLc, and HDLc are significantly associated with reduced OS in patients with GI cancers. These findings suggest that lipid profile parameters, particularly cholesterol-related indices, may serve as simple and accessible prognostic biomarkers. Prospective studies are needed to confirm these associations and to explore their potential role in individualized cancer management.

Disclosures

Ethics Committee Approval: The study was approved by the Istanbul Medipol University Non-interventional Clinical Research Ethics Committee (No: E-10840098-202.3.02-4097, Date: 19/06/2025).

Informed Consent: Informed consent was obtained from all participants.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: Concept – S.G.A., Ö.Y.; Design – Ö.Y., S.G.A.; Supervision – Ş.A.Y.; Data collection and/or processing – O.E., Ö.Y., A.A., H.T., S.A.Y.; Data analysis and/or interpretation – S.G.A., A.A.; Literature search – Ö.Y.; Writing – Ö.Y.; Critical review – Ö.Y., S.G.A.

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Optimal Timing of Colostomy and Enterostomy Reversal: Insights from A 15-Year Retrospective Analysis

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ABSTRACT

Objective: This study aimed to evaluate the impact of optimal timing of enterostomy (particularly ileostomy) and colostomy closures on postoperative complications. The goal was to compare early versus late closures to inform surgical strategies and improve patient outcomes.

Materials and Methods: Data from 474 patients who underwent ostomy closure between 2008 and 2023 were retrospectively analyzed. Based on prior literature, enterostomy patients were grouped as early (<12 weeks) or late (>12 weeks), and colostomy patients as early (<12 weeks), intermediate (13–20 weeks), or late (>20 weeks). Only patients with complete clinical records were included.

Results: Among 366 patients with enterostomy closure, 27.5% (n=101) underwent closure within 12 weeks, while 72.4% (n=265) had closure after 12 weeks. Overall complication rate was 8.4%, with serosal injury (58.1%) and perforation (38.7%) being the most frequent. Late closure was significantly associated with malignant indications (OR = 7.208), preoperative rectoscopy (OR=2.063), and adjuvant therapy (OR=1.735). In 108 patients with colostomy closure, the complication rate was 23.2%, with serosal damage (52.0%) and perforation (40.0%) being most common. Malignancy was less common in patients closed within 12 weeks, but significantly higher in the >20-week group (p<0.001). Malignancy increased the risk of delayed closure by 4.9 times according to logistic regression.

Conclusion: Optimal timing of ostomy closure is critical, especially in malignancy-related cases. Delayed closure is linked to increased complication rates. When early closure is applied to selected low-risk patients, outcomes may improve. Surgical timing should be guided by comorbidities, underlying disease, and oncologic treatment history.

Keywords: Colostomy, enterostomy, postoperative complications

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INTRODUCTION

A stoma is a surgically created opening that allows intestinal contents to exit through the abdominal wall when the continuity of the gastrointestinal tract is disrupted. The term, derived from the Greek word for “opening,” was first used in the 18th century to address intestinal obstruction in emergency settings.^[1] Today, colostomy and ileostomy are widely used in the management of various clinical conditions such as trauma, inflammatory bowel disease, and malignancy.^[2] Indications for stoma formation include bowel obstruction, perforation, diverticulitis, and protection of low anastomoses after rectal cancer surgery.^[3] In these contexts, a stoma may

be created temporarily or permanently to enhance patient outcomes and reduce the risk of complications.^[4]

The goal of stoma closure is to reestablish intestinal continuity. However, this procedure carries the risk of several complications, including anastomotic leakage, wound infection, bowel obstruction, and intra-abdominal adhesions.^[5] The likelihood of such complications is influenced by factors like surgical expertise, the patient's general condition, and the suitability of the chosen technique.^[6]

Prior studies have investigated the effects of early versus late stoma closure, reporting mixed results. Early closure has been associated with shorter hospital stays and fast-



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er wound healing,^[7] and some evidence suggests a lower rate of wound infections, although the risk of postoperative bowel obstruction may be increased.^[8] On the other hand, late closure allows inflammation to subside and provides a safer surgical field but prolongs the psychosocial burden of living with a stoma.^[9] Moreover, while late closure may be technically safer, it delays definitive restoration of function.^[10] This study aimed to evaluate the impact of closure timing on outcomes and complications through a retrospective analysis, with the goal of providing evidence-based guidance for optimal surgical planning.

MATERIALS and METHODS

Ethical Approval and Study Design

The study was conducted in accordance with the principles of the Helsinki Declaration. Approval from the Umraniye Training and Research Hospital ethics committee was obtained prior to the study (Date: 17/10/2024, Decision No: 364). The study evaluated patients between January 2008 and June 2023.

Patients aged 18 years and older who had undergone complete postoperative follow-up were included. Patients under 18 or those whose postoperative data could not be obtained were excluded. The study was conducted at a single centre.

Study Population and Grouping

A total of 474 patients were included in the study, of whom 366 underwent enterostomy (jejunostomy or ileostomy) closure and 108 underwent colostomy closure. In line with classifications used in similar studies in the literature, enterostomy patients were divided into two groups based on the timing of stoma reversal: those who underwent closure within 12 weeks postoperatively were categorized as the early group, while those who underwent closure after 12 weeks were categorized as the late group.

For colostomy cases, again based on existing literature, three subgroups were defined: early, intermediate, and late. Patients whose colostomies were closed within 12 weeks after formation were defined as the early group; those closed between 13 and 20 weeks as the intermediate group; and those closed after 20 weeks as the late group. All patients were followed for a period of one year after ostomy closure. Mortality was defined as any death occurring within 30 days following the closure procedure (Fig. 1).

Data Collection and Variables

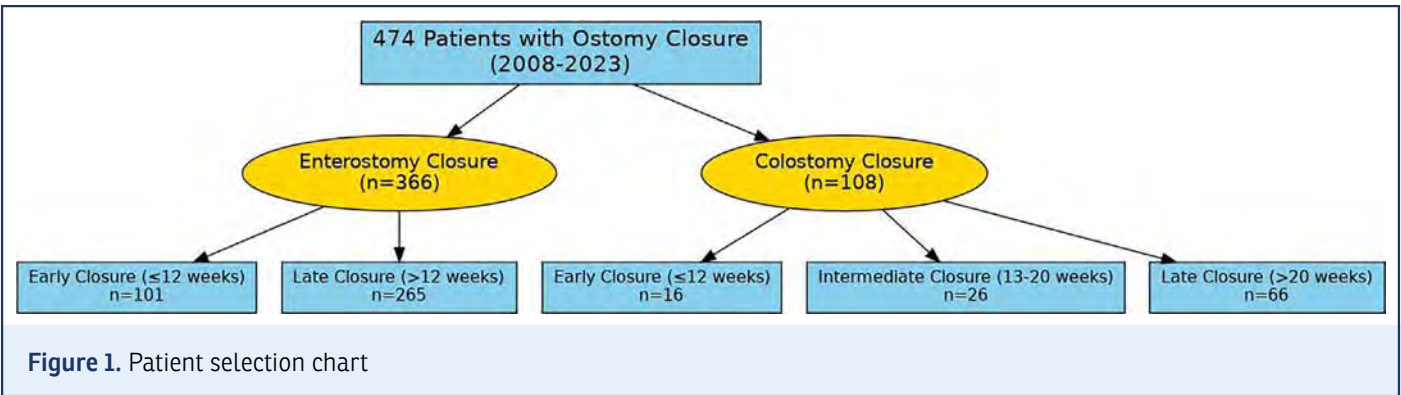
Patients with enterostomy and colostomy were compared using various demographic and clinical parameters, including age, sex, duration of hospitalization, length of ICU stay, timing of stoma closure, and total duration of stoma presence. Additional variables included the underlying indication for stoma creation (benign vs. malignant), stoma type (anatomical and functional), preoperative endoscopy findings, use of neoadjuvant or adjuvant therapies, and surgical details such as hand-sewn or stapled anastomosis, and the use of supporting sutures during closure.

Postoperative complications were classified according to the Clavien–Dindo system. These included anastomotic leakage, wound infection, intestinal obstruction, and other relevant events. Mortality and morbidity rates were also recorded and analysed.

Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics version 21.0 software (IBM Corporation, Armonk, NY, USA) and Microsoft Excel 2007. A p-value of <0.05 was considered statistically significant.

The distribution of continuous variables was assessed using graphical methods and the Shapiro–Wilk test. Descriptive statistics were presented as mean ± standard deviation or median (minimum–maximum), as appropriate.



Comparative analysis of continuous variables—including patient age, postoperative hospital stay, and postoperative third-level intensive care unit (ICU) stay—was performed using the Mann–Whitney U test. In patients who underwent enterostomy (jejunostomy or ileostomy) closure, the anastomosis level (cm) was analysed in relation to anal access in the prior surgery and the timing of stoma closure.

In the colostomy group, age, postoperative hospital stay, ICU stay, anastomosis level according to anal access, and stoma closure timing were compared using the Kruskal–Wallis test.

Categorical variables were compared based on stoma closure timing using cross tabulations, frequencies (n), percentages (%), and the chi-square (χ^2) test. Potential risk factors for delayed closure were analysed using both univariate and multivariate logistic regression models. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs).

RESULTS

A total of 366 patients underwent enterostomy (jejunostomy or ileostomy) closure; 65.3% (n=239) were male and 34.7% (n=127) were female. The mean age was 58.0±14.6 years, and the median postoperative hospital stay was 9.0 (range: 2–64) days. Forty patients (11.0%) required admission to a third-level intensive care unit (ICU), with a mean ICU stay of 2.7±2.0 days. Closure occurred within 12 weeks in 27.5% (n=101) and after 12 weeks in 72.4% (n=265).

Indications for ostomy formation were benign in 21.0% (n=77) and malignant in 79.0% (n=289); benign causes included diverticular disease (1.3%), inflammatory bowel disease (39.0%), perforation (36.3%), mesenteric ischaemia (11.7%), and other (11.7%), while malignant cases comprised colon (17.3%), rectal (79.2%), and other organ malignancies (3.5%).

Ostomy configurations were loop (85.6%), tip (10.3%), and double-barrel (4.1%). Anastomosis types were ileoileal (87.4%), ileocolic (8.7%), colorectal (0.5%), ileorectal (1.4%), jejunocolic (0.5%), and jejunojejunal (1.4%); configurations were side-to-side (86.9%), end-to-side (9.8%), and end-to-end (3.3%).

Stapled anastomosis was used in 92.7% (n=339) (linear 96.2%, circular 3.8%), while 7.3% (n=27) underwent hand-sewn closure; support sutures were applied in 70.5% (n=258).

Intraoperative complications occurred in 8.4% (n=31), comprising serosal injury (58.1%), perforation (38.7%), and stenosis (3.2%), and ostomy reestablishment was required in 2.7% (n=10).

Preoperative rectoscopy findings (performed in 26.7% of cases) included polypoid lesions (32.4%), strictures (23.2%),

diversion colitis (10.1%), fistulas (8.1%), nonspecific colitis (7.1%), and other (19.1%), with a mean anastomosis level of 7.4±6.0 cm.

Neoadjuvant therapy was given to 16.7% (n=61) and adjuvant therapy to 32.0% (n=117). The postoperative 30-day mortality rate was 3.0% (n=11) and morbidity rate 15.0% (n=55); according to Clavien–Dindo classification, 49.0% were Grade I, 18.1% Grade II, 1.9% Grade III, 1.9% Grade IV, with further subgrades of 3a (n=1), 3b (n=6), 4b (n=2), and 5 (n=8) (Appendix 1).

The mean age of patients with ostomy closure ≤12 weeks was 60.3±15.9 years, while it was 57.2±14.1 years in those with closure >12 weeks. ICU admission occurred in 17.8% (n=18) of the early group and in 8.3% (n=22) of the late group. A statistically significant difference was found between groups in terms of postoperative third-level ICU admission ($\chi^2=6.808$, $p=0.009$).

Among patients with a malignant cause, 17.1% (n=13) had colon cancer, 73.7% (n=56) rectal cancer, and 9.2% (n=7) other malignancies in the early group, compared to 17.4% (n=37), 81.2% (n=173), and 1.4% (n=3), respectively, in the late group.

Intraoperative complications in the early group included serosal injury (25.0%, n=2) and perforation (75.0%, n=6). In the late group, serosal injury occurred in 69.6% (n=16), perforation in 26.1% (n=6), and stenosis in 4.3% (n=1).

Preoperative rectoscopy was performed in 16.8% (n=17) of patients with closure ≤12 weeks and in 30.6% (n=81) of those with closure >12 weeks. This difference was statistically significant ($\chi^2=8.256$, $p=0.016$). Adjuvant therapy was administered to 23.8% (n=24) in the early group and 35.1% (n=93) in the late group ($\chi^2=4.318$, $p=0.038$). No other variables showed statistically significant differences ($p>0.05$) (Appendix 2).

Univariate logistic regression showed that patients with ICU admission had a 58.3% lower risk of late closure. The risk of late closure was 6.641 times higher in patients with colon malignancy and 7.208 times higher in those with rectal malignancy, compared to other malignancies. Serosal injury during ostomy closure increased the risk of late closure 8.000-fold compared to perforation. Pathological findings on preoperative rectoscopy increased the likelihood of late closure 2.063-fold, while adjuvant therapy was associated with a 1.735-fold increased risk (Table 1).

In the enterostomy group, multivariate logistic regression did not reveal any statistically significant independent predictors of delayed closure. Although malignancy, preoperative rectoscopy, and adjuvant therapy were significant in univariate analysis, these associations were no longer present after adjusting for potential confounders. This may be attributed

Table 1. Potential risk factors associated with late closure (>12 weeks) in univariate logistic regression model

Variables	β	SD	Wald	p	OR	95% CI for OR	
						Bottom	Top
Age	-0.015	0.008	3.188	0.074	0.985	0.969	1.001
Postop 3 rd step ICU hospitalization (available)	-0.874	0.342	6.512	0.011	0.417	0.213	0.817
Malignancy type			7.807	0.020			
Colon	1.893	0.762	6.179	0.013	6.641	1.492	29.551
Rectum	1.975	0.707	7.806	0.005	7.208	1.803	28.815
Type of complication during ostomy closure (serosal injury)	2.079	0.946	4.827	0.028	8.000	1.252	51.137
Preop rectoscopy specialised case (available)	0.724	0.302	5.739	0.017	2.063	1.141	3.730
Adjuvant chemotherapy-radiotherapy (yes)	0.551	0.267	4.261	0.039	1.735	1.028	2.927

SD: Standard deviation; OR: Odds ratio; CI: Confidence interval; ICU: Intensive care unit

to the marked imbalance in group sizes, potential multicollinearity between clinical variables, and limited statistical power. Therefore, the multivariate findings should be interpreted cautiously, and the univariate associations should not be overgeneralized without further validation ($p>0.05$).

Colostomy closure was performed in 108 patients, of whom 62.0% ($n=67$) were male and 38.0% ($n=41$) were female. The mean age was 54.6 ± 15.8 years, and the median was 56 (range: 18–89) years. The mean postoperative hospital stay was 12.8 ± 7.6 days (median: 11.0, range: 1–42), and ICU admission occurred in 14.8% ($n=16$) of patients, with a mean ICU stay of 4.6 ± 6.0 days and a median of 2.0 (range: 1–25). Ostomy closure timing was ≤ 12 weeks in 14.8% ($n=16$), 13–20 weeks in 24.0% ($n=26$), and >20 weeks in 61.2% ($n=66$).

The indication for ostomy creation was benign in 51.8% ($n=56$) and malignant in 48.2% ($n=52$); among benign causes, diverticular disease (28.5%), perforation (32.3%), mesenteric ischaemia (7.1%), and IBD (5.3%) were reported, while among malignancies, 73.0% ($n=38$) were colon, 23.0% ($n=12$) rectal, and 4.0% ($n=2$) other types. The ostomy configuration was tip in 79.7%, loop in 17.6%, and double-barrel in 2.7%.

Anastomosis types included colocolic (52.7%), colorectal (29.7%), ileocolic (9.2%), ileoileal (4.6%), and ileorectal (3.7%). End-to-end anastomosis was used in 73.2% of cases, followed by side-to-side (24.0%) and end-to-side (2.8%). Stapler-assisted anastomosis was performed in 80.6% ($n=87$) of cases (70.1% circular, 29.9% linear), while 19.4% ($n=21$) underwent manual anastomosis. Support sutures were used in 56.5% ($n=61$).

Intraoperative complications occurred in 23.2% ($n=25$) of patients: serosal injury (52.0%), perforation (40.0%), and

ischaemia (4.0%). Ostomy reestablishment was required in 4.7% ($n=5$), and postoperative anastomotic leakage occurred in 5.6% ($n=6$). The mean anastomosis level observed on preoperative rectoscopy was 17.7 ± 8.9 cm (median: 19.0, range: 2–40). Rectoscopy findings were absent in 68.5%, positive in 20.3%, and undocumented in 11.2% of cases.

Neoadjuvant therapy was not administered in 77.8% ($n=84$), while 22.2% ($n=24$) received it; adjuvant therapy was given to 41.7% ($n=45$), while 58.3% ($n=63$) did not receive it. The postoperative 30-day mortality rate was 3.7% ($n=4$), and morbidity occurred in 25.0% ($n=27$). According to the Clavien–Dindo classification, 66.7% ($n=18$) were Grade I, 7.4% ($n=2$) Grade IIb, and 25.9% ($n=7$) Grade V (Appendix 3).

No patients with ostomy closure ≤ 12 weeks required postoperative third-level ICU admission. In contrast, ICU admission occurred in 23.1% ($n=6$) of patients closed at 13–20 weeks and 15.2% ($n=10$) of those closed after 20 weeks. A statistically significant difference was observed in ICU admission rates among the three groups ($\chi^2=6.374$, $p=0.041$).

The indication for ostomy creation was benign in 81.3% ($n=13$) and malignant in 18.7% ($n=3$) of patients with closure ≤ 12 weeks. Among patients closed at 13–20 weeks, benign and malignant causes were each observed in 50.0% ($n=13$). For patients closed >20 weeks, 34.8% ($n=23$) had benign and 65.2% ($n=43$) had malignant causes. The difference in underlying indication according to closure time was statistically significant ($\chi^2=19.728$, $p<0.001$). No other variables showed significant differences ($p>0.05$) (Appendix 4).

Univariate logistic regression analysis revealed that the risk of late closure was 4.938 times higher in patients with malignant indications compared to those with benign conditions.

Table 2. Potential risk factors associated with late closure (>12 weeks) in univariate/multivariate logistic regression model

Variables	β	SD	Wald	p	OR	95% CI for OR	
						Bottom	Top
Postop 3 rd step ICU hospitalization (available) ^a	19.645	10048.24	0.001	0.998	3400999	0.001	–
Reason for ostomy opening ^a	1.597	0.674	5.618	0.018	4.938	1.318	18.494
Constant ^b	1.149	0.318	13.0222	<0.001	3.154	–	–
Postop 3 rd step ICU hospitalization (available) ^b	19.003	9879.74	0.001	0.998	17902297	0.001	–
Reason for ostomy opening ^b	1.308	0.681	3.694	0.055	3.699	0.974	14.042

^a: Univariate logictis regression model; ^b: Multivariate logistic regression model. SD: Standard deviation; OR: Odds ratio; CI: Confidence interval; ICU: Intensive care unit

In the colostomy group, malignancy showed a strong association with delayed closure in the univariate model; however, this effect was not maintained in multivariate analysis. The loss of significance may be due to the relatively small sample size, particularly within early and intermediate subgroups, and possible interactions between ICU admission and stoma indication. As a result, these findings should be interpreted with caution, and malignancy cannot be confirmed as an independent predictor in this cohort ($p>0.05$) (Table 2).

DISCUSSION

Ostomy creation is a critical surgical intervention performed to avert severe complications such as perforation and sepsis when intestinal integrity is compromised. It is often necessary in complex clinical scenarios including trauma, bowel obstruction, and malignancies.^[1,2] However, the optimal timing for stoma reversal remains a subject of debate and is influenced by factors such as the need for adjuvant therapy and the overall health status of the patient.

Advanced age and comorbid conditions have been shown to increase the risk of postoperative complications when ostomy closure is not properly timed.^[11,12] In the present study, we investigated the influence of timing on postoperative outcomes in patients undergoing enterostomy and colostomy closure. Our findings support patient-tailored surgical planning and provide clinically relevant insights, particularly for specific subgroups.

Among patients undergoing enterostomy closure, the majority were male (65.3%) with a mean age of 58.0 ± 14.6 years. These findings are consistent with the literature, indicating that enterostomies are more commonly required in older populations.^[13,14] Malignancy was the underlying cause in 79.0% of cases, underscoring the significant role of adjuvant treatment planning in determining closure timing. Previous reports have similarly indicated that adjuvant

chemotherapy and radiotherapy tend to delay ostomy reversal,^[15] a finding corroborated by the higher proportion of late closures in our malignancy cohort.

Notably, ICU admission following surgery was more common in the early closure group (17.8%). This suggests that early reversal may necessitate closer postoperative monitoring. However, the duration of ICU stay did not differ significantly between groups, implying that ICU admission was likely precautionary rather than indicative of increased complications. Although some studies have proposed that early reversal is associated with reduced complications, others report increased superficial surgical site infections due to transient immunosuppression from ongoing therapy.^[16,17]

The overall complication rate in the enterostomy group was 8.4%, with serosal injury (58.1%) and perforation (38.7%) being most frequent. Serosal injury was more prevalent in late closures ($p=0.045$), suggesting that prolonged stoma presence may lead to tissue fragility. This aligns with the literature indicating that long-term stomas can impair tissue integrity and necessitate advanced surgical techniques for safe reversal.^[14]

Although the mortality rate in our study was 3.1%, which is higher than that reported by Chow et al.^[18] (0.4%), our morbidity rate of 15.0% was comparable to their reported 17.3%. These findings emphasize the importance of multidisciplinary management and precise surgical scheduling to mitigate risk. The length of hospital stay was also longer in patients with delayed closure, consistent with findings by Hallböök et al.,^[19] who reported extended hospitalization in cases of postoperative complications.

Furthermore, the need for adjuvant therapy significantly delayed closure among patients with malignancies, consistent with previous research.^[15] These findings highlight the necessity of a multidisciplinary approach that balances oncologic priorities with surgical risk when determining closure timing.

Regarding colostomy closure, our data revealed a higher proportion of male patients (62.0%) with a mean age of 54.6 ± 15.8 years. Malignancy accounted for 58.2% of cases overall, and its frequency increased significantly in patients whose closure occurred after >20 weeks ($p < 0.001$), again underlining the impact of oncologic treatment planning on timing.

The complication rate was notably higher in colostomy closures (23.2%) compared to enterostomies, with serosal injury (48.2%) and perforation (40.7%) being the most frequent. These findings suggest that colostomy reversals may pose greater technical challenges and that prolonged intervals may further increase complication risk. In addition, ICU admission was most frequent in the 13–20 week group (23.1%), though ICU duration did not significantly differ. This supports prior literature suggesting that early closure may be technically difficult due to residual inflammation and edema.^[20]

Our observed anastomotic leakage rate of 5.6% falls within the 20–30% complication range reported in the literature for colostomy closure.^[21,22] This complication did not appear to be associated with timing. However, longer ostomy durations were associated with increased overall complication rates and extended hospital stays. Conversely, studies have demonstrated that early closure—especially in uncomplicated patients—can enhance quality of life and expedite social reintegration.^[21,23]

Collectively, our findings underscore the critical importance of individualized surgical timing in colostomy closure. Malignancy emerges as a major determinant of delayed reversal, and multidisciplinary coordination is essential to optimize outcomes. While early closure may be safe in carefully selected patients, meticulous preoperative planning remains essential for managing late closures and minimizing complications.

This study is subject to several inherent limitations. First, its retrospective nature and single-centre setting inherently limit the generalisability of the findings and introduce a risk of selection bias. As data were extracted from pre-existing medical records, inconsistencies or missing data entries may have influenced the accuracy and completeness of the dataset, thereby impacting the reliability of the results. Furthermore, the substantial imbalance in sample sizes between the early and late closure groups—particularly in the enterostomy cohort—reduced the statistical power of subgroup comparisons and limited the ability to detect significant differences between groups.

Another important limitation is the presence of potential confounding variables that were not accounted for or adjusted in the analysis. These include variations in surgical expertise, differences in perioperative management protocols, and surgeon-specific preferences, all of which may have influenced postoperative outcomes independent of closure timing. Additionally, patient-related factors such as nutritional status, performance status, and the presence of comorbidities—although partially recorded—were not systematically evaluated and thus may have introduced residual confounding.

Moreover, follow-up was limited to one year, and long-term outcomes such as quality of life, bowel function, and hernia development were not assessed. Future prospective multi-centre studies with standardised protocols and longer follow-up periods are warranted to validate these findings and provide more robust evidence on optimal stoma closure timing across diverse patient populations.

CONCLUSION

The study demonstrated that delayed ostomy closure was more common in patients with malignancy, largely due to the need for adjuvant therapy. Although a higher complication rate was observed in late closure, this difference was not statistically significant. Serosal injury and perforation were the most frequent complications. Preoperative rectoscopy and adjuvant treatments were found to be associated with late closure. Individualised surgical planning was shown to be effective in managing complication risk.

Disclosures

Ethics Committee Approval: The study was approved by the Umraniye Training and Research Hospital Scientific Research Ethics Committee (No: 364, Date: 17/10/2024).

Informed Consent: Informed consent was obtained from all participants.

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Appendix 1. Demographic and clinical characteristics of patients with enterostomy closure

	Enterostomy (n=366)			Enterostomy (n=366)	
	n	%		n	%
Sex			If anastomosis is with stapler type		
Male	239	65	Circular	13	3.8
Female	127	34	Linear	326	96
Age (years)			Presence of support strut?		
Mean±SD	58.1±14.5		None	108	29
Median (min-max)	60 (17-92)		Yes	258	70
Postoperative hospitalization period (days)			Existence of intraoperative complication?		
Mean±SD	11.7±8.2		None	335	91
Median (min-max)	9 (2-64)		Yes	31	8.4
ICU stay duration			Type of complication developed during ostomy closure		
None	326	89	Serosal injury	18	58
Yes	40	11	Perforation	12	38
ICU stay duration (days)			Obstruction	1	3.2
Mean±SD	2.7±1.9		Re-ostomy indicated during closure?		
Median (min-max)	2 (1-10)		None	356	97
Duration of ostomy closure			Yes	10	2.8
≤12 weeks	101	27	Preop rectoscopy anastomosis level (cm)		
>12 weeks	265	72	Mean±SD	7.38±6.04	
Reason for ostomy opening			Median (min-max)	6.0 (1-40)	
Benign	77	21	Preop rectoscopy featured condition		
Malignant	289	79	None	235	64
If benign, cause			Yes	98	26
Diverticular disease	1	1.3	Unknown	33	9.1
IBD	30	39	Conditions detected at rectoscopy		
Perforation	28	36	Polyp	32	32
Mesentery ischemia	9	11	Obstruction	23	23
Other	9	11	Diversion Colitis	10	10
If malignant, cause			Fistula	8	8.1
Colon	50	17	Nonspecific Colitis	7	7.1
Rectum	229	79	Other	18	19
Other	10	3	Neoadjuvant chemotherapy-radiotherapy		
Ostomy type			None	305	83
End	38	10	Yes	61	16
Loop	313	85	Adjuvant chemotherapy-radiotherapy		
Double barrel	15	4	None	249	68
Anastomosis type			Yes	117	32
Ileoileal	320	87	Mortality		
Ileocolic	32	8.8	None	355	96
Colorectal	2	0.5	Yes	11	3.1
Ileorectal	5	1.4	Morbidity		
Jejunocolic	2	0.5	None	311	85
Jejunojejunal	5	1.4	Yes	55	15
Anastomosis direction			Clavien dindo classification		
End to end	36	9.8	1	27	49
End to side	12	3.3	2	10	18
Side to side	318	87	3	1	1.9
Anastomosis technique			3a	1	1.9
Hand assisted	27	7.3	3b	6	11
Stapled	339	92	4b	2	3.6
			5	8	14

SD: Standard deviation; ICU: Intensive care unit; IBD: Inflammatory bowel disease

Appendix 2. Comparison of demographic and clinical parameters according to the timing of enterostomy closure

	≤12 weeks (n=101)		>12 weeks (n=265)		Test statistic	
	n	%	n	%	a;b	p
Sex						
Male	61	60	178	67	a=1.481	0.224
Female	40	39	87	32		
Age						
Mean±SD	60.29±15.90		57.22±14.05		b=2.110	0.035
Median (min-max)	62.0 (17-87)		59.0 (19-92)			
Duration of postoperative hospitalization (days)						
Mean±SD	12.56±9.54		11.49±7.70		b=0.208	0.835
Median (min-max)	8.0 (2-45)		9.0 (2-64)			
ICU stay duration						
None	83	82	243	91	a=6.808	0.009
Yes	18	17	22	8.3		
ICU stay duration (days)						
Mean±SD	2.72±1.64		2.68±2.21		b=0.891	0.411
Median (min-max)	2.0 (1-8)		2.0 (1-10)			
Reason for ostomy opening						
Benign	25	24	52	19	a=1.158	0.282
Malignant	76	75	213	80		
Cause if benign						
IBD	6	24	24	46	a=6.433	0.092
Perforation	12	48	16	30		
Mesentery ischemia	5	20	4	7.7		
Other	2	8	8	15		
Cause if malignant						
Colon	13	17	37	17	a=10.258	0.006
Rectum	56	73	173	81		
Other	7	9.2	3	1.4		
Ostomy type						
End	9	8.9	29	11	a=0.340	0.844
Loop	88	87	225	85		
Double barrel	4	4	11	4.2		
Anastomosis type						
Ileoileal	88	87	232	87	a=8.636	0.076
Ileocolic	8	7.9	24	9		
Colorectal	0	0	2	0.8		
Ileorectal	0	0	5	1.9		
Jejunocolic	2	2	0	0		
Jejunojejunal	3	3	2	0.8		
Anastomosis direction						
End to end	6	5.9	30	11	a=2.476	0.290
End to side	3	3	10	3.7		
Side to side	92	91	226	85		
Anastomosis technique						
Hand assisted	8	7.9	19	7.2	a=0.060	0.806
Stapled	93	92	246	93		
If anastomosis is with stapler type						
Circular	3	3.2	10	4.1	a=0.129	0.720
Linear	90	96	236	95		

Appendix 2. Cont.

	≤12 weeks (n=101)		>12 weeks (n=265)		Test statistic	
	n	%	n	%	a;b	p
Presence of support strut?						
None	24	24	84	32	a= 2.214	0.137
Yes	77	76	181	68		
Existence of intraoperative complication?						
None	93	92	242	91	a=0.054	0.816
Yes	8	7.9	23	8.7		
Type of complication during ostomy closure						
Serosal Injury	2	25	16	69	a=6.210	0.045
Perforation	6	75	6	26		
Obstruction	0	0	1	4.3		
Re-ostomy indicated during closure?						
None	98	97	258	97	–	0.553 (c)
Yes	3	3	7	2.6		
Anastomosis level						
Mean±SD	7.08±6.14		7.46 ± 6.05		b=0.858	0.391
Median (min-max)	5.0 (1–35)		6.0 (1–40)			
Preop						
None	71	70	164	61	a=8.256	0.016
Yes	17	16	81	30		
Unknown	13	13	20	7.5		
Conditions detected at rectoscopy						
Polyp	6	30	26	33	a=1.152	0.949
Obstruction	5	25	18	23		
Diversion colitis	2	10	8	10		
Fistula	1	5	7	8.9		
Nonspecific colitis	1	5	6	7.7		
Other	5	25	13	16		
Neoadjuvant chemotherapy-radiotherapy						
None	84	83	221	83	a=0.003	0.958
Yes	17	16	44	16		
Adjuvant chemotherapy-radiotherapy						
None	77	76	172	65	a=4.318	0.038
Yes	24	23	93	35		
Mortality						
None	97	96	258	97	–	0.504 (c)
Yes	4	4	7	2.7		
Morbidity						
None	80	79	231	87	–	0.071 (c)
Yes	21	20	34	13		
Clavien dindo classification						
1	10	64	17	29	a=9.931	0.128
2	3	9.6	7	29		
3	1	3.2	0	0		
3a	0	0	1	4.1		
3b	3	9.7	3	12		
4b	2	6.5	0	0		
5	2	6.5	6	25		

a: Chi-squared Test; b: Mann Whitney U Test; c: Fisher Exact test results are given. SD: Standard deviation; ICU: Intensive care unit; IBD: Inflammatory bowel disease

Appendix 3. Demographic and clinical characteristics of patients with colostomy closure

	Colostomy (n=108)			Colostomy (n=108)	
	n	%		n	%
Sex			Anastomosis direction		
Female	67	62	Side to side	26	24
Male	41	38	Anastomosis technique		
Age (year)			Hand assisted	21	19
Mean±SD	54.62±15.82		Stapled	87	80
Median (min-max)	56.0 (18–89)		If anastomosis is with stapler type		
Duration of postoperative hospitalization (days)			Circular	61	70
Mean±SD	12.76±7.58		Linear	26	30
Median (min-max)	11.0 (1–42)		Presence of support strut?		
ICU stay duration			None	47	43
None	92	85	Yes	61	56
Yes	16	15	Existence of intraoperative complication?		
ICU stay duration (days)			None	83	76
Mean±SD	4.59±6.04		Yes	25	24
Median (min-max)	2.0 (1–25)		Type of complication during ostomy closure		
Duration of ostomy closure			Haemorrhage	1	4
≤12 weeks	16	15	Serosal injury	13	52
13–20 weeks	26	24	Ischemia	1	4
>20 weeks	66	61	Perforation	10	40
Reason for ostomy opening			Re-ostomy indicated during closure?		
Benign	56	52	None	103	95
Malignant	52	48	Yes	5	4.7
If benign, cause			Preop rectoscopy anastomosis level (cm)		
Diverticular disease	16	28	Mean±SD	17.65±8.93	
IBD	3	5.3	Median (min-max)	19.0 (2–40)	
Perforation	18	32	Preop rectoscopy featured condition		
Mesentery ischemia	4	7.1	None	74	68
Other	15	27	Yes	22	20
If malignant, cause			Known	12	11
Colon	38	73	Neoadjuvant chemotherapy-radiotherapy		
Rectum	12	23	None	84	77
Other	2	4	Yes	24	23
Ostomy type			Adjuvant chemotherapy-radiotherapy		
End	86	79	None	63	58
Loop	19	17	Yes	45	42
Double barrel	3	2.7	Mortality		
Anastomosis type			None	104	96
Ileoileal	5	4.6	Yes	4	3.7
Ileocolic	10	9.2	Morbidity		
Colocolic	57	52	None	81	75
Colorectal	32	30	Yes	27	25
Ileorectal	4	3.8	Clavien dindo classification		
Anastomosis direction			1	18	66
End to end	79	73	3b	2	7.4
End to side	3	2.8	5	7	26

SD: Standard deviation; ICU: Intensive care unit; IBD: Inflammatory bowel disease

Appendix 4. Comparison of demographic and clinical characteristics of patients with colostomy closure according to the duration of ostomy closure

	Ostomy closure time							
	≤12 weeks (n=16)		13–20 weeks (n=26)		>20 weeks (n=66)		Test statistic	
	n	%	n	%	n	%	a,b,c	p
Sex								
Male	11	69	20	77	36	55	a=4.325	0.115
Female	5	31	6	23	30	45		
Age								
Mean±SD	58.88±16.45		49.35±16.65		55.26±15.26		b=3.631	0.163
Median (min-max)	56.5 (28–85)		49.5 (19–84)		56.0 (19–89)			
Duration of postoperative hospitalization (days)								
Mean±SD	12.88±5.69		11.92±7.69		13.20±8.05		b=1.060	0.589
Median (min-max)	13.0 (6–22)		9.0 (4–40)		12.0 (1–42)			
ICU stay duration								
None	16	100	20	77	56	85	a=6.374	0.041
Yes	0	0	6	23	10	15		
ICU stay duration (days)								
Mean±SD	–		–4.17±1.72		5.10±7.88		c=1.654	0.118
Median (min-max)	–		– 4.0 (2–7)		2.0 (1–25)			
Reason for ostomy opening								
Benign	13	81	20	77	23	34	a=19.728	<0.001
Malignant	3	19	6	23	43	66		
If benign, the reason is								
Diverticular disease	5	38	7	35	4	17	a=9.640	0.291
IBD	0	0	1	5	2	8.7		
Perforation	4	31	8	40	6	26		
Mesentery ischemia	2	15	1	5	1	4.3		
Other	2	16	3	15	10	43		
If malignant, the reason is								
Colon	2	67	5	83	31	72	a=1.105	0.893
Rectum	1	33	1	17	10	23		
Other	0	0	0	0	2	4.7		
Ostomy type								
End	12	76	19	73	55	83	a=6.707	0.152
Loop	2	12	7	27	10	15		
Double barrel	2	12	0	0	1	1.5		
Anastomosis type								
Ileioleal	0	0	3	11	2	3	a=8.621	0.375
Ileocolic	3	19	1	3.8	6	9.2		
Colocolic	8	50	16	61	33	50		
Colorectal	4	25	5	19	23	34		
Ileorectal	1	6.3	1	3.8	2	3		
Anastomosis direction								
End to end	11	68	22	84	46	69	a=3.151	0.533
End to side	1	6.3	0	0.0	2	3.1		
Side to side	4	25	4	16	18	27		

Appendix 4. Cont.

	Ostomy closure time							
	≤12 weeks (n=16)		13–20 weeks (n=26)		>20 weeks (n=66)		Test statistic	
	n	%	n	%	n	%	a,b,c	p
Anastomosis technique								
Hand assisted	4	25	7	27	10	15	a=2.020	0.364
Stapled	12	75	19	73	56	85		
Type if anastomosis with stapler								
Circular	8	67	15	79	38	68	a=0.912	0.634
Linear	4	33	4	21	18	32		
Presence of support strut?								
None	5	31	10	38	32	48	a=1.913	0.384
Yes	11	69	16	62	34	52		
Existence of intraoperative complication?								
None	14	88	18	69	51	77	a=1.875	0.392
Yes	2	12	8	31	15	23		
Type of complications during ostomy closure								
Serosal injury	1	50	5	63	7	47	a=2.348	0.672
Perforation	1	50	3	37	6	40		
Other	0	0	0	0.0	2	13		
Re-ostomy indicated during closure?								
None	15	94	25	96	63	95	a=0.125	0.939
Yes	1	6	1	3.8	3	4.5		
Preop rectoscopy anastomosis level (cm)								
Mean±SD	17.50±9.12		18.00±7.57		17.87±9.65		b=0.053	0.974
Median (min-max)	19.0 (2–30)		20.0 (2–30)		18.0 (3–40)			
Preop rectoscopy featured condition								
None	11	69	18	69	45	69	a=8.364	0.079
Yes	3	19	8	31	11	16		
Unknown	2	12	0	0.0	10	15		
Neoadjuvant chemotherapy-radiotherapy								
None	12	75	16	62	56	85	a=5.948	0.051
Yes	4	25	10	38	10	15		
Adjuvant chemotherapy-radiotherapy								
None	9	56	12	46	42	64	a=2.379	0.304
Yes	7	44	14	54	24	36		
Mortality								
None	16	100	26	100	62	94	a= 2.643	0.267
Yes	0	0	0	0	4	6		
Morbidity								
None	13	81	18	69	50	76	a= 0.815	0.665
Yes	3	19	8	31	16	24		
Clavien dindo classification								
1	3	100	4	50	11	68	a= 2.571	0.632
3b	0	0	1	12	1	6.2		
5	0	0	3	38	4	25		

a: Chi-squared Test; b: Kruskal Wallis Test; c: Mann Whitney U Test

Retrospective Analysis of Cardiac CT Angiography Applications in Pediatric Cardiology Clinic: Single Center Experience

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ABSTRACT

Objective: Congenital heart disease (CHD) is one of the most common congenital anomalies worldwide, necessitating detailed imaging for accurate diagnosis and surgical planning. While transthoracic echocardiography (TTE) serves as the first-line imaging modality, it may be insufficient in evaluating complex intracardiac and extracardiac structures. Cardiac computed tomography angiography (CTA) has emerged as a valuable complementary technique in pediatric patients, offering high-resolution anatomical visualization with relatively low radiation exposure. This study aims to retrospectively assess the role of cardiac CTA in the anatomical evaluation and clinical management of pediatric patients diagnosed with CHD at a tertiary care center.

Materials and Methods: Pediatric patients who underwent cardiac CTA between January 1, 2021, and September 1, 2025, were retrospectively analyzed. Demographic data, clinical findings, radiation dose, and contrast volume were evaluated. Both intracardiac and extracardiac anomalies were examined in detail.

Results: A total of 1,337 pediatric patients (mean age: 3.89 years; 56% male) were evaluated using cardiac CTA. The most common diagnoses were coarctation of the aorta (7.87%), Tetralogy of Fallot (7.5%), and double outlet right ventricle (6.38%). CTA demonstrated high diagnostic accuracy in assessing critical anatomical features such as the spatial relationships of the great vessels, coronary anomalies, and abnormal venous connections.

Conclusion: Cardiac CTA facilitates detailed anatomical assessment in pediatric CHD patients, supporting surgical planning and improving clinical outcomes.

Keywords: Cardiac computed tomography angiography (CTA), congenital heart disease (CHD), pediatric cardiology

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INTRODUCTION

Congenital heart defects (CHDs) are among the most common birth defects, affecting approximately 0.8% to 1.2% of live births worldwide.^[1,2] These malformations originate from the intracardiac structures, the great vessels, and extracardiac vascular abnormalities. The wide range of anatomical variations and differences in clinical course require a multi-disciplinary imaging approach to the diagnosis and management of CHD.^[3] The clinical spectrum of CHD is wide, ranging

from newborn to adult and usually requires postoperative and long-term follow-up. Diagnostic accuracy varies depending on patient age, anatomic complexity, cardiac function, and history of preoperative treatment or surgery.^[4]

Cardiovascular imaging is critical for primary diagnosis, followed by preoperative evaluation and surgical planning, and long-term postoperative patient follow-up. Transthoracic echocardiography (TTE) remains the primary noninvasive imaging method for congenital heart disease (CHD) and is



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used routinely for all cases.^[5] It provides high-resolution visualization of intracardiac anatomy, particularly valvular function and myocardial contractility. However, in postoperative patients or those with complex anatomy, TTE can be limited due to suboptimal acoustic windows related to patient-specific characteristics. The diagnostic quality of TTE is also highly dependent on the experience of the operator. In addition, TTE is not highly sensitive for evaluating extracardiac structures, such as the distal aorta, the aortic arch and its branches, the pulmonary artery and its associated branches, the pulmonary veins, and the tracheobronchial tree.^[6]

In the preoperative evaluation of patients undergoing surgery for CHD, additional imaging modalities are often required to provide anatomic information in addition to TTE. Conventional invasive cardiac catheterization (ICA) has historically been the gold standard for cardiac imaging, providing both hemodynamic and anatomic assessment.^[7] However, ICA is now considered for selected cases due to its invasive nature, prolonged procedure time, risk of complications, and prolonged hospital stay. The use of ICA is also limited by its inability to assess airway pathology or extracardiac vascular structures.^[8]

Technological advances in imaging have recently enabled the development of cardiac computed tomography angiography (CTA). CTA can now provide detailed anatomical visualization with significantly lower radiation doses and contrast volumes. CTA has been increasingly used in the diagnostic algorithm for CHD.^[9] Multi-detector, ECG-gated CT, multiplanar, and 3D reconstructions have provided images with high spatial and temporal resolution. Advanced software applications provide high-quality imaging at reduced radiation doses, which is especially important in pediatric populations.^[10] Surgical advances in cyanotic CHD have led to a significant increase in survival rates, hence the need for periodic evaluation of these patients and early detection of late postoperative complications. The comprehensive assessment of complex anatomical and functional changes following corrective or palliative surgery requires advanced imaging strategies.^[11]

CTA facilitates rapid and detailed evaluation of postoperative anatomy, aiding in clinical decision-making. It provides essential information regarding recurrence, residual lesions, vascular stenosis, and extracardiac anomalies. In contrast to MRI, which often requires sedation, CT is frequently performed in pediatric patients without sedation, resulting in shorter hospitalization times and greater procedural safety, especially for infants and young children.

Although echocardiography retains its role as the primary imaging modality, in cases where it is insufficient, CTA

provides critical and often decisive complementary data in both the pre- and post-operative periods.^[12]

Accordingly, cardiac CT is increasingly being used in the evaluation of CHD. Modern CT systems provide higher image quality, lower radiation doses, and shorter scan times—establishing CTA as an indispensable component of contemporary CHD diagnostic algorithms, with high diagnostic value that directly influences clinical decision-making.^[13]

The evaluation of CHD involves more than just the cardiac system. These patients often present with associated abnormalities involving the airways, peripheral vasculature, and lung parenchyma. Cardiac CTA allows accurate visualization of these structures. Airway compression can occur both preoperatively and postoperatively and is a significant contributor to morbidity and mortality. Conditions such as tracheal or bronchial compression due to abnormal vasculature, congenital tracheoesophageal anomalies, and dynamic airway collapse require accurate imaging.^[14] In addition, lymphatic abnormalities are common in single-ventricle physiology, particularly after Glenn or Fontan procedures, and CTA plays an essential role in their diagnosis and follow-up.^[15,16]

This study aimed to evaluate our patient population who underwent cardiac CTA in the preoperative and postoperative periods at our pediatric cardiac center, focusing on detailed anatomical characterization and the diagnostic value of CTA in the management of CHD.

MATERIALS and METHODS

Our study was a single-center, retrospective study. This study included patients who were evaluated with cardiac CT angiography at our pediatric cardiology clinic between January 1, 2021, and September 1, 2025. The study was designed in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of Health Sciences University, Basaksehir Cam and Sakura City Hospital (protocol code 2025-151, approved on June 25, 2025).

We included patients between the ages of 0 and 18 who underwent cardiac CT angiography. All participants initially underwent transthoracic echocardiography (TTE) as part of both diagnostic evaluation and routine follow-up. Complementary imaging techniques, such as computed tomography angiography (CTA), were also employed to achieve a more comprehensive anatomical analysis. Demographic information—including age, sex, height, weight, and body surface area (BSA)—was recorded, with BSA calculated using the Du Bois formula:

$$BSA = 0.007184 \times \text{height}^{0.725} \times \text{weight}^{0.425}$$

Cardiac CT imaging was conducted using a 640-slice single-source CT scanner (Aquilion ONE, GENESIS Edition; Canon Medical Systems, Otawara, Tochigi, Japan) featuring a wide 16 cm detector and employing the Adaptive Iterative Dose Reduction 3D Enhanced (AIDR 3D Enhanced) algorithm. A prospective ECG-gated approach was applied during a single cardiac cycle for all subjects. Images were obtained in Volume Axial mode (rotation time: 0.35 seconds; scan length: 80–120 mm), with tube current managed via automatic exposure modulation. To enhance iodine contrast-to-noise efficiency in pediatric imaging, tube current was modulated using automatic exposure control, and a reduced tube voltage of 80 kV was applied.

All patients received an intravenous bolus of iodinated contrast agent (Kopaq 300 mgI/mL; Onko&Kocsel Pharmaceuticals, Kocaeli, Turkey) at 1.5 mL/kg, followed by a 10–20 mL saline flush using a dual-head power injector (MEDRAD, Bayer HealthCare, Beek, Netherlands). The injection rate ranged from 0.7 to 0.9 mL/kg, adjusted according to catheter caliber and patient size. Undiluted contrast was used throughout. Scans were performed without breath-holding or sedation, and an experienced cardiac radiologist supervised all examinations. Imaging acquisition targeted the initial contrast passage through the cardiovascular structures, centering the acquisition window at 45% of the R–R interval in patients with heart rates exceeding 90 bpm. Scanning was paused during phases deemed non-essential. For each individual, the most motion-free cardiac phase closest to the predefined target was retrospectively selected by the radiologist.

Data were reconstructed at 0.5 mm slice thickness using a standard kernel and the AIDR 3D Enhanced algorithm. Post-processing included multiplanar reconstruction (MPR), maximum intensity projection (MIP), and 3D volume rendering (VR). Radiation dose metrics—including dose-length product (DLP), volumetric CT dose index (CTDIvol), and scanned anatomical area—were documented for every examination. The CTDI and DLP values referenced a 32 cm phantom, while effective dose (ED) was calculated by multiplying the DLP by a factor of 2 to adapt to a 16 cm phantom model. Conversion coefficients specific to neonates and infants (0.039 mSv/(mGy·cm)) were applied based on age group for accurate dose estimation. All CCTA procedures were performed by a pediatric cardiovascular radiologist with over 15 years of experience in congenital heart disease imaging.

CT angiographic evaluation was performed with a comprehensive and systematic approach in patients with CHD. The analysis included the assessment of major vascular anom-

alies, such as aortic disorders (vascular rings, coarctation, aortic arch anomalies, and patent ductus arteriosus), pulmonary artery anomalies (pulmonary sling), conotruncal anomalies, transposition of the great arteries, tetralogy of Fallot, and single-ventricle palliation. The systemic and pulmonary venous structures were evaluated in detail, including persistent left superior vena cava, interrupted inferior vena cava, and anomalous pulmonary venous return.

Coronary arteries were assessed for origin, course, and anomalies according to the Leiden Convention and modified Leiden Convention. Cardiac structures, including valves, pericardium (with emphasis on effusion and congenital absence), and outflow tracts (LVOT and RVOT), were carefully analyzed. The morphology and function of the aortic and pulmonary valves were included in the evaluation. Thoracic and extracardiac structures, such as the esophagus, trachea, and bronchi, were examined for compression, along with mediastinal masses, hematomas, and thymic morphology. Pulmonary findings, including hypoplasia, peribronchial thickening, bronchiectasis, atelectasis, emphysema, mosaic pattern, infiltration, pulmonary edema, and sequestration, were recorded. Pleural findings, such as effusion, thickening, and pneumothorax, were also documented.

Abdominal and systemic organ evaluations included hepatosplenomegaly, asplenia, polysplenia, hepatic hemangiomas, liver congestion, portal and hepatic vein thrombosis, and portal venous gas. Renal and renal collecting system pathologies were assessed. Skeletal findings, such as thoracic wall deformities, rib fractures, and vertebral anomalies, were included.

The aortic assessment included the following areas: ascending aorta, proximal and distal arch, isthmus, descending aorta, aortic annulus, sinotubular junction, and aortic root. Additional parameters, such as radiation dose, scan coverage, dose length product (DLP), and effective dose (ED), were documented. Demographic data, including date of birth, age, sex, height, weight, intubation status, and clinical condition, were documented for all patients. This comprehensive CT angiographic evaluation provided crucial anatomical and functional information to support accurate diagnosis and surgical planning in congenital heart disease.

Ventriculoarterial connection was defined as DORV if more than 50% of the aorta originated from the right ventricle. Great artery relationship was assessed as normal, D malposition, L malposition, side-by-side, or anterior-posterior. Ventricular septal defects (VSD) were evaluated as subaortic, subpulmonic, doubly committed, or remote. Outflow tract

stenosis, atrioventricular valve abnormalities, and coronary artery abnormalities were considered present or absent.

In this study, the classification of coronary arteries was conducted according to the Leiden Convention and modified Leiden Convention. In the surgical classification, the sinus that does not face the pulmonary valve was designated as the "non-facing sinus." Based on this reference point, the sinus on the right side was labeled as "Sinus 1," and the sinus on the left side as "Sinus 2." This classification can be applied independently of the relative positions of the great arteries or the anatomical location of the aortic valve within the body. The surgical classification of coronary arteries begins with positioning in the non-facing sinus and orienting towards the pulmonary valve. Starting from Sinus 1, a counterclockwise order is followed, and the coronary arteries are coded as "L" for the left anterior descending artery (LAD), "Cx" for the left circumflex artery (LCx), and "R" for the right coronary artery (RCA). Detailed documentation was made for coronary arteries originating from different sinuses or from separate orifices within the same sinus.

In imaging modalities (CT, MRI, and TTE), the fundamental principles of the surgical classification were preserved, but adjustments were made to accommodate imaging perspectives. In this context, the physician was positioned in the non-facing sinus, with their back towards the pulmonary valve, observing the aorta from a cranial-to-caudal viewpoint. In this orientation, the right sinus was designated as "Sinus 1," and the left sinus as "Sinus 2." The naming of coronary arteries was adapted to a clockwise order to align with the imaging perspective.

Statistical Analysis

The statistical analysis of the data obtained in this study was performed using the Statistical Package for the Social Sciences (SPSS) software. Descriptive statistics were used to summarize demographic and clinical variables. Continuous variables were expressed as mean, standard deviation (SD), minimum, and maximum values, while categorical variables were presented as frequencies and percentages. The basic demographic and clinical data of the patients, such as age, gender, height, weight, body surface area (BSA), radiation dose, and contrast volume, were reported as mean, SD, minimum, maximum, and percentage distributions. The normality of all variables was assessed using the Shapiro-Wilk test. Additionally, the normal distribution of continuous variables was confirmed through histograms, skewness and kurtosis coefficients, and Q-Q (quantile-quantile) plots. For data that did not meet normality assumptions, the median, interquar-

tile range (IQR), and minimum-maximum values were reported. All data were summarized using descriptive statistics after confirming appropriate normality assumptions, and the results were presented in tables. Additionally, the diagnostic accuracy of specific anatomical findings was evaluated using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC).

RESULTS

This retrospective study analyzed the demographic and clinical characteristics of patients who underwent cardiac computed tomography angiography (CTA) in the Department of Pediatric Cardiology. A total of 1,337 patients who underwent CTA between January 1, 2021, and September 1, 2025, were included in the study.

Of the patients, 56% were male (n=754) and 44% were female (n=566). The mean age was 3.89 years (range: 0.1–13.9 years). The age group distribution was as follows: 0–2 years (n=774, 57.46%), 2–7 years (n=166, 12.32%), 7–12 years (n=146, 10.84%), and 12–18 years (n=261, 19.38%). The mean weight was 15.89 kg (range: 3.12–49.78 kg), with a mean weight percentile of 35.97% (range: 23.92–44.17). The weight standard deviation (SDS) was –0.36 (range: –0.52 to 0.87). The mean height was 102.8 cm (range: 55.24–160.9 cm), with a mean height percentile of 42.74% (range: 26.87–41.7%). The height SDS was –0.17 (range: –0.92 to 0.69). The mean BMI was 14.95 kg/m² (range: 9.87–21.94 kg/m²), with a BMI percentile of 30.34% (range: 21.32–68.7%) and a BMI SDS of –0.52 (range: –1.28 to 0.89). During CTA acquisition, the radiation dose was 1.32 mSv (range: 0.88–2.32), and the mean contrast volume was 15.28 mL (range: 5.12–23.4). General patient characteristics are summarized in Table 1.

The most common congenital heart defects observed in patients undergoing CTA were aortic hypoplasia/coarctation of the aorta (7.87%, n=106), tetralogy of Fallot (TOF) (7.5%, n=101), Fontan/Glenn stage evaluation (6.46%, n=87), double outlet right ventricle (DORV) (6.38%, n=86), ventricular septal defect (VSD) (6.98%, n=94), and transposition of the great arteries (TGA) (5.27%, n=71).

Other commonly detected anomalies included atrial septal defect (ASD) (4.16%, n=56), atrioventricular septal defect (AVSD) (4.53%, n=61), and pulmonary valve anomalies (3.49%, n=47). Rare anomalies included Ebstein's anomaly (1.04%, n=14), tricuspid atresia (3.12%, n=42), pulmonary atresia (1.78–2.08%, n=24–28), and truncus arteriosus (1.11%, n=15). The distribution of patients who underwent CTA is shown in Table 2.

Table 1. The baseline clinical characteristics

	n	%
Sex (male)	754	56
Age (years)	3.89 (0.1–13.9)	
0–2 years	774	57.46
2–7 years	166	12.32
7–12 years	146	10.84
12–18 years	261	19.38
Weight (kg)	15.89 (3.12–49.78)	
Weight (percentile)	35.97 (23.92–44.17)	
Weight (SDS)	-0.36 (-0.52–0.87)	
Height (cm)	102.8 (55.24–160.9)	
Height (percentile)	42.74 (26.87–41.7)	
Height (SDS)	-0.17 (-0.92–0.69)	
BMI kg/m ²	14.95 (9.87–21.94)	
BMI (percentil)	30.34 (21.32–68.7)	
BMI (SDS)	-0.52 (-1.28–0.89)	
Contrast volume (cc)	15.28 (5.12–23.4)	
Radiation dose (mSv)	1.32 (0.88–2.32)	

SDS: Standard deviation score; BMI: Body mass index

The relationship between the great vessels and the presence of coronary anomalies is especially important when planning surgery for patients with DORV and TGA. The great vessel relationships in TGA and DORV patients were as follows: D malposition in TGA (87.3%, n=62) and DORV (33.7%, n=29); side-by-side great vessel arrangement in TGA (5.63%, n=4) and DORV (39.53%, n = 34); L malposition in TGA (2.81%, n=2) and DORV (12.79%, n=11); normal great vessel relationship in TGA (2.81%, n=2) and DORV (10.46%, n=9); and inversus arrangement in TGA (1.40%, n=1) and DORV (3.48%, n=3). Coronary anomalies were present in 45% of TGA patients and 33% of DORV patients. The most common coronary anomaly in both disease groups was the origin of the Cx from the RCA. Additionally, in DORV patients, arch hypoplasia (24.41%, n=21), interrupted aortic arch (9.30%, n=8), anomalous pulmonary venous return (16.27%, n=14), and persistent left superior vena cava (PLSVC) (12.79%, n=11) were observed. Ventricular septal defect (<1.5 mm) was detected in 22.09% (n=19) of cases. Coronary anomalies in both DORV and TGA patients were identified with high sensitivity and specificity using CTA. The main anatomical structures evaluated by CTA in DORV and TGA patients are shown in Table 3.

Coronary artery anomalies were identified in 20.79% (n=21) of TOF patients. In addition, APCA (<2 mm) was observed in 16.83% (n=17) and MAPCA (>2 mm) in 15.84% (n=16) of cases. The mean Nakata index was 315.72±139.43, McGoon ratio

1.79 ± 0.19. Mean pulmonary valve diameter was 8.51±1.59 mm, MPA was 9.31±2.12 mm, RPA 7.39±1.37 mm, and LPA diameter was 7.75±1.58 mm. Cardiac CTA demonstrated high sensitivity and specificity in detecting critical anatomical features such as coronary anomalies, MAPCA presence, and dimensions of pulmonary arteries and their branches, which are essential for TOF surgery. Detailed evaluation of great vessel relationships and coronary artery anatomy was performed in patients with TGA and DORV, as shown in Table 4.

DISCUSSION

Congenital heart defects are considered one of the most prevalent birth anomalies. Recent advances in both surgical techniques and medical management have markedly extended the survival of individuals with these conditions. Yet, this prolonged life expectancy has also brought about a higher incidence of related complications and a greater demand for follow-up surgical treatments over time.

Transthoracic echocardiography remains the most widely used and gold standard method for the diagnosis and follow-up of congenital heart disease. Although it provides high-resolution imaging, transthoracic echocardiography has several important limitations. It is often inadequate for evaluating extracardiac structures, which can complicate surgical planning. In addition, the quality of the images obtained can vary significantly with patient age, body habitus, and operator experience, which can lead to diagnostic problems. Conventional invasive angiography has long been considered the gold standard for both hemodynamic and anatomic assessment. However, its use has declined in recent years due to several disadvantages, including high radiation exposure, the need for contrast agents, invasive nature, and prolonged hospital stay. Due to advances in technology, CTA has become a valuable alternative, offering lower radiation doses, reduced contrast requirements, and the ability to acquire high-resolution images in a single cardiac cycle.

In recent years, the widespread adoption of electrocardiogram (ECG)-gated and low-dose computed tomography angiography has further increased the utility of this imaging modality. These techniques allow high-quality imaging even in pediatric patients with higher heart rates, significantly reducing the radiation dose. In our study, computed tomography angiography was performed using electrocardiogram-gated techniques, 80 kilovolts to lower radiation exposure, and low-volume contrast agents calculated based on body weight (cc/kg). This approach significantly reduced the need for sedation in our patients and shortened hospital stays, reflecting the benefits of modern imaging protocols.^[17]

Table 2. Pediatric congenital heart defects in computed tomography angiography patients

Disease	n	%
Ventricular septal defect (VSD)	94	6.98
Atrial septal defect (ASD)	56	4.16
Patent ductus arteriosus (PDA)	32	2.38
Fallot tetralogy (TOF)	101	7.5
Transposition of the great arteries (TGA)	71	5.27
Coarctation of the aorta (CoA) / arcus hypoplasia	106	7.87
Pulmonary valve anomalies (including pulmonary stenosis)	47	3.49
Mitral valve defects (including mitral atresia)	44	3.27
Aortic valve anomalies (including aortic stenosis)	71	5.27
Double inlet left / right ventricle (DILV)(DIRV)	32	2.38
Double outlet right ventricle (DORV)	86	6.38
Tricuspid atresia	42	3.12
Hypoplastic left heart syndrome (HLHS)	32	2.38
Pulmonary atresia with intact ventricular septum (IVS PA)	24	1.78
Pulmonary atresia with VSD (VSD PA)	28	2.08
Truncus arteriosus (All types: Type I-IV, A4 vs.)	15	1.11
Interrupted aortic arch (IAA)	21	1.56
Total anomalous pulmonary venous return (TAPVR/TAPVD)	39	2.9
Partial anomalous pulmonary venous return (PAPVR)	41	3.04
Congenitally corrected TGA (ccTGA)	26	1.93
Aortic arch anomalies	26	1.93
Ebstein anomaly	14	1.04
Atrioventricular septal defect (AVSD)	61	4.53
Fontan / Glenn stages evaluation	87	6.46
Aortic arch anomalies	35	2.6
Coronary evaluation	47	3.49
Other	69	5.12

In this study, we evaluated the results of cardiac computed tomography angiography, which is increasingly used in our clinic for detailed anatomical assessment and surgical planning in complex congenital heart disease. Our findings support the use of computed tomography angiography as an essential modality for accurate anatomical definition and development of an effective surgical strategy in this complex patient population.

Transposition of the great arteries is among the most frequent cyanotic congenital heart conditions observed in the neonatal period. In such cases, identifying coronary artery anomalies is crucial for the safe planning and execution of arterial switch operations.^[18] Coronary artery anomalies are significant factors that can significantly increase postoperative mortality and morbidity.^[19] Therefore, accurate preoperative identification of the coronary anatomy is essential for

surgical success. While transthoracic echocardiography is generally sufficient to assess the origin of coronary arteries, it has limitations in evaluating the distal course of these arteries and their relationship to perivascular tissue. As shown in our previous study, computed tomography angiography provides statistically significantly better detection of coronary artery anomalies in patients with transposition of the great arteries compared with transthoracic echocardiography. In this study, we also found that computed tomography angiography provided high specificity and sensitivity in evaluating the coronary arteries, which is consistent with similar findings reported in the literature. In addition, the spatial relationship between the great arteries is a critical factor in the surgical success of the Le-Compte maneuver and arterial transfer during the arterial switch operation. In our study,

Table 3. Essential CT angiography findings in DORV / TOF

Anatomy		n	%	SNS (%)	SPS (%)	PPV (%)	NPV (%)	AUC (%)
DORV	Coronary anomalies	29	33.72	89	98	95	95	0.96
	Arcus hypoplasia	21	24.41	96	98	94	98	0.96
	Interrupted aortic arch	8	9.30	100	100	100	100	1.00
	APCA	15	17.44	95	98	93	98	0.95
	APVC	14	16.27	100	100	99	98	0.95
	PLSVC	11	12.79	100	100	100	100	1.00
	VSD (<1,5mm)	19	22.09	58	82	48	92	0.81
TOF	Coronary anomalies	21	20.79	85	98	89	95	96
	APCA (<2mm)	17	16.83	79	97	85	99	94
	MAPCA (>2mm)	16	15.84	91	99	92	99	97
	Nakata index (mm ² /m ²)	315.72±139.43						
	McGoon ratio	1.79±0.19						
	Pulmonary annulus diameter (mm)	8.51±1.59						
	Pulmonary annulus Z score	-1.15±1.58						
	Main pulmonary artery (MPA) diameter (mm)	9.31±2.12						
	Main pulmonary artery Z score	1.51±0.69						
	Right pulmonary artery (RCA) diameter (mm)	7.39±1.37						
	Right pulmonary artery (RCA) Z score	0.61±1.41						
	Left pulmonary artery (LPA) diameter (mm)	7.75±1.58						
	Left pulmonary artery (LPA) Z-score	1.09±1.12						

CT: Computed tomography; DORV: Double outlet right ventricle; TOF: Fallot tetralogy; SNS: Sensitivity; SPS: Specificity; PPV: Positive predicative value; NPV: Negative predicative values; AUC: Area under the curve; APCA: Aberrant pulmonary collateral artery; APVC: Anomalous pulmonary venous connection; PLSVC: Persistent left superior vena cava; VSD: Ventricular septal defect; MAPCA: Major aortopulmonary collateral arteries

the most common aortic malposition was D malposition, as reported in the literature. This was followed by L malposition and anterior-posterior positioning. These findings highlight the importance of accurately assessing the spatial relationships of the aorta during surgical planning.

Double outlet right ventricle is a complex congenital heart defect with surgical planning and timing highly dependent on its specific subtype.^[20] In these patients, an optimal surgical strategy requires a thorough understanding of the relationship between the ventricular septal defect and the great arteries, as well as the 3D orientation of the great vessels and the presence of coronary artery anomalies.^[21] In our study, coronary artery anomalies were identified in 32 (45%) of the patients with a double outlet right ventricle, a rate consistent with previous studies in the literature. The most common coronary artery anomaly in our series was the origin of the left circumflex artery from the right coronary artery, a finding frequently reported in other studies.^[22] In addition, 21 (24%) of our patients with double outlet right ventricle had aortic

arch hypoplasia, while 8 (9%) had an interrupted aortic arch. These findings underscore the importance of evaluating aortic arch morphology carefully during surgical planning. Accurate identification of these extracardiac pathologies may help surgeons anticipate potential perioperative complications and ultimately may improve patient outcomes.^[23]

Tetralogy of Fallot is the most common cyanotic congenital heart disease and typically requires complete corrective surgery within the first year of life.^[24] In these patients, the structure of the pulmonary arteries and their branches, the anatomical course of the coronary arteries, the presence of major aortopulmonary collateral arteries, and the presence of additional ventricular septal defects are critical for surgical planning.^[25] Conventional angiography has traditionally been used to evaluate patients with Tetralogy of Fallot before surgery. This technique has long been the gold standard for hemodynamic and anatomical assessment. However, it has several significant disadvantages, including its invasive nature, the risk of catheter-related complications, high radiation

Table 4. Great vessel relationship/coronary artery origins TGA and DORV

	n	%
Relationship of the great vessels		
D-malpose		
TGA	62	87.3
DORV	29	33.7
Side-by-side		
TGA	4	5.63
DORV	34	39.53
L-malpose		
TGA	2	2.81
DORV	11	12.79
Normal		
TGA	2	2.81
DORV	9	10.46
Inversus		
TGA	1	1.40
DORV	3	3.48
Coronary artery origins		
Usual coronary artery (1LCx-2R)		
TGA	39	55
DORV	57	66.27
Unusual coronary artery		
TGA	32	45
DORV	29	33.72
1L-2RCx		
TGA	18	23.91
DORV	16	18.60
2LCxR		
TGA	7	9.85
DORV	8	9.30
1R- 2LCx		
TGA	5	7.04
DORV	2	2.32
1LR-2Cx		
TGA	2	2.8
DORV	1	1.16
1RCxL		
TGA	1	1.4
DORV	2	2.32

TGA: Transposition of the great arteries; DORV: Double outlet right ventricle;
Cx: Circumflex coronary artery; L: Left anterior descending coronary artery;
R: Right coronary artery

exposure, the need for large amounts of contrast media, and prolonged hospital stay. As a result, conventional angiography has been largely replaced in recent years by computed

tomography angiography, which provides detailed anatomical information with less invasiveness, lower radiation doses, and reduced contrast requirements.^[26] However, in certain special cases, such as when major aortopulmonary collateral arteries (MAPCAs) need to be embolized in the preoperative period, conventional invasive angiography may still be preferred. Outside of these special situations, computed tomography angiography is now widely used because of its lower risk of complications, shorter procedure time, and reduced contrast requirements. Both the literature and our study have shown that the results of conventional angiography and computed tomography angiography are comparable in patients with Tetralogy of Fallot.^[27] Computed tomography angiography provides high sensitivity and specificity for evaluation of the pulmonary arteries and their branches, detection of coronary artery anomalies, and identification of major aortopulmonary collateral arteries. In addition, it provides detailed information on pulmonary artery diameters, branch angles, and lung parenchyma, which are critical for surgical planning.^[28] In our study, 21 (21%) patients had coronary anomalies, 17 (16.83%) had anomalous pulmonary collateral arteries smaller than 2 mm (APCA), and 16 (15.84%) had main aortopulmonary collateral arteries larger than 2 mm (MAPCA). A conal coronary branch crossing the right ventricular outflow tract (RVOT) was the most common coronary anomaly. Similar findings have been reported in the literature, where conal coronary branches crossing the RVOT are the most commonly observed coronary anomalies in patients with Tetralogy of Fallot.^[29] However, one of the major limitations of computed tomography angiography is its reduced sensitivity and specificity for detecting small ventricular septal defects, as it typically acquires images in a single cardiac cycle. Therefore, in cases where additional ventricular septal defects are suspected, it may be necessary to use complementary imaging modalities such as transthoracic echocardiography.

Prolonged mechanical ventilation and extended stays in the intensive care unit are not limited to patients with Tetralogy of Fallot; they are also seen in other cases of congenital heart surgery, often in association with aortopulmonary collateral arteries. In these patients, surgical intervention to close these collateral arteries may be necessary to enable successful ventilator weaning.^[30] Computed tomography angiography is widely used to accurately identify extensive aortopulmonary collateral arteries in various congenital heart diseases, providing high sensitivity and resolution.

In addition, because the imaging field in computed tomography angiography includes the lung parenchyma, pulmonary abnormalities can also be accurately identified. In our

study, the most common lung lesion detected was partial atelectasis, which was observed in 11% of patients. Similar findings have been documented in the literature, indicating that atelectasis is the most common extracardiac anomaly in patients with congenital heart disease.

An atrial septal defect is the most commonly identified congenital heart defect in adults, and it is often associated with partial anomalous pulmonary venous return. In adult patients, transthoracic echocardiography often provides suboptimal image quality, making computed tomographic angiography a preferred method for evaluating partial anomalous pulmonary venous return.^[31] In our study, 43 patients had partial anomalous pulmonary venous return, 28 of whom also had large atrial septal defects, consistent with previous reports in the literature.^[32]

Patients with single ventricle physiology often undergo multiple surgeries, and evaluating the pulmonary vasculature is essential before Glenn or Fontan procedures.^[33] In our clinic, this evaluation is usually performed by computed tomography angiography because of its low radiation dose and reduced contrast requirements. In our study, 87 (6.5%) of the patients evaluated by cardiac computed tomography angiography were in this group. Similar findings have been reported in the literature, where computed tomography angiography is commonly used to evaluate single ventricle anatomy.^[34]

Coronary artery anomalies may present with symptoms in the neonatal period or remain silent until adolescence, thus reflecting a broad clinical spectrum. For patients with potential coronary anomalies, computed tomography angiography is a highly sensitive evaluation method.^[35] In our study, 47 (3.49%) of the patients underwent computed tomography angiography specifically to evaluate the origin and course of the coronary arteries. In addition, patients with myocarditis who have widespread myocardial infarction findings on physical examination or electrocardiogram are increasingly being evaluated with computed tomography angiography. Approximately half (22) of the patients in our study who underwent coronary evaluation had a history of myocarditis. Similar findings have been reported in the literature, where cardiac computed tomography angiography is frequently used for coronary evaluation in pediatric populations.^[36]

In conclusion, computed tomography angiography is an essential adjunct to transthoracic echocardiography for the comprehensive evaluation of cardiac anatomy. While transthoracic echocardiography provides a highly accurate assessment of intracardiac structures, valves, and blood flow, computed tomography angiography provides superior visualization of

extracardiac structures. The combined use of these two modalities is critical for optimal surgical planning and long-term clinical management of patients with congenital heart disease.

CONCLUSION

Cardiac computed tomography angiography (CTA) has proven to be an invaluable imaging modality for the detailed anatomical evaluation of pediatric patients with congenital heart disease (CHD). This study highlights the critical role of CTA in identifying complex cardiac and extracardiac anomalies, which are essential for accurate surgical planning and long-term patient management. With its ability to provide high-resolution, three-dimensional anatomical detail at relatively low radiation doses, CTA effectively complements transthoracic echocardiography, particularly in cases where conventional imaging methods may be insufficient. As the complexity of CHD varies widely, a personalized imaging approach that includes CTA can significantly improve surgical outcomes and enhance the quality of life for pediatric patients. Future research should continue to focus on optimizing radiation doses and contrast protocols to further expand the clinical applications of this powerful diagnostic tool.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences, Basaksehir Cam and Sakura City Hospital Clinical Scientific Ethics Committee (No: 151, Date: 25/06/2025).

Informed Consent: Informed consent was obtained from all participants.

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Maternal Obesity and Postpartum Hemorrhage in Women Undergoing Cesarean Delivery: A Retrospective Cohort Study

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ABSTRACT

Objective: Postpartum hemorrhage (PPH) is one of the most common causes of maternal death. Our objective was to determine whether an association exists between maternal obesity and increased risk of PPH.

Materials and Methods: Women who underwent cesarean delivery between July 2022 and June 2023 were evaluated retrospectively. The patients were divided into two groups according to their body mass index (BMI): Group 1 had a BMI ≥ 30 kg/m² (n=82), and Group 2 had a BMI < 30 kg/m² (n=109). Demographic features, duration and mode of placental separation, and amount of PPH were recorded. To measure blood loss, the weight of surgical gauze sponges used during the procedure and the volume of blood aspirated via surgical suction were recorded.

Results: Postpartum blood loss was compared between the groups, but the difference was not statistically significant. Obesity is often considered a risk factor for PPH. Our study did not provide supporting data regarding the increased risk of obesity. Risk assessment scores for PPH have been proposed, but many women who experience severe hemorrhage have scores indicating a low risk.

Conclusion: Obesity is a risk factor for many obstetric complications; therefore, clinicians should be more alert. Nevertheless, obstetricians should be prepared for PPH regardless of the BMI of the pregnant individual.

Keywords: Cesarean delivery, obesity, postpartum hemorrhage, pregnancy

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INTRODUCTION

Approximately 3–5% of all deliveries are complicated by postpartum hemorrhage (PPH).^[1,2] Approximately 15% of maternal deaths worldwide are due to obstetric hemorrhage.^[3] Recently, the incidence of PPH has increased in developed countries.^[2] Kramer et al.^[4] partly explained this increase by the induction and augmentation of labor and cesarean section. Multi-

ple pregnancies, chorioamnionitis, and operative delivery are known risk factors for PPH.^[5] Previous studies have suggested that maternal obesity is a risk factor. According to a population-based cohort study in Sweden, maternal obesity is associated with a slightly increased risk of PPH.^[6] Another study from the United Kingdom also suggested that the increased risk of PPH can be attributed to maternal obesity.^[7]



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Studies have suggested that more than half of pregnant women in the United States are overweight or obese.^[8] Obesity is associated with adverse pregnancy outcomes. Maternal death, gestational diabetes, preeclampsia, and an increased rate of cesarean sections are among them.^[9] Because the incidence of PPH is increasing, researchers have hypothesized an association between obesity and an increased risk of PPH. Population-based studies from Sweden and the United Kingdom have confirmed the existence of an association.^[6,7] However, one study suggested that maternal obesity decreases the risk of PPH and has a protective effect.^[10] Other studies have reported no association between maternal obesity and PPH.^[11] An inconsistency in this subject is apparent.

The risk of PPH is not the same for each delivery mode.^[2] Surgical morbidity and tissue injury are more probable in obese women than in those with a lower body mass index (BMI).^[12] Therefore, it would not be wrong to expect a greater risk for PPH in obese women undergoing cesarean section than in women with similar BMI undergoing vaginal delivery. This finding alone does not indicate an increased risk of PPH in obese women. An association exists between obesity and increased rates of cesarean section, preeclampsia, and magnesium sulfate use.^[13] This association may explain the increased risk of hemorrhage in obese women. Obesity is a known risk factor for thrombosis.^[14] A BMI greater than 30 kg/m² was associated with higher serum concentrations of fibrinogen,^[15] and Charbit et al.^[16] found that fibrinogen levels can be used to differentiate between severe and non-severe PPH. Paglia et al.^[10] argued that the increased fibrinogen level and accompanying hypercoagulability might modify the risk of severe PPH.

PPH is a potentially life-threatening complication; therefore, it is important to establish the risk factors with precautions. To investigate obesity as a potential risk factor for PPH, we aimed to compare postpartum blood loss in obese and non-obese women who underwent term delivery with cesarean section.

MATERIALS and METHODS

This retrospective cohort study was conducted at a tertiary referral hospital in Istanbul, Türkiye. The study was approved by the institution's ethics committee (No: 4070/29.08.2023), and patients had signed informed consent forms at admission, permitting the use of their data for research provided their identity was concealed. Informed consent was part of the standard admission procedure because the institution was a teaching hospital. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Data were obtained from the institution's patient database. A total of 191 patients were included in the study. Patients who underwent cesarean delivery between July 2022 and June 2023 were included. Exclusion criteria were previous diagnosis of placental invasion anomalies and placenta previa. The demographic features, duration and mode of placental separation, amount of PPH, and complications were recorded. To measure blood loss during PPH, the quantity and weight (in grams) of surgical gauze sponges that were used, and the volume of blood aspirated with surgical suction were recorded. Patients with incomplete records in the database were excluded from the study.

Patients were divided into two groups. Group 1 consisted of women with a BMI ≥ 30 kg/m² (n=82), and Group 2 included women with a BMI <30 kg/m² (n=109). The BMI of the patient was calculated according to anthropometric measurements made at the time of pregnancy diagnosis, which was no later than the eighth week of gestation.

A power analysis was conducted using G*Power version 3.1.9.7,^[17] and a minimum sample size of n=185 was calculated ($\alpha=0.05$ and Power=0.80). Age, gestational age at delivery, gravidity, parity, abortion, preoperative hematocrit level, duration of surgery, change in hematocrit after surgery, volume of blood aspirated with surgical suction, weight of gauze sponges, and duration of placental separation were recorded and compared for each group.

Statistical Analysis

Data analysis was performed with SPSS (Version 20.0; SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov normality test was used to assess the distribution. Normally distributed parameters were compared using the independent samples t-test, whereas non-normally distributed parameters were compared using the Mann–Whitney U test. The mode of placental separation was expressed as percentages for spontaneous and manual separation; the comparison of the groups was performed using the χ^2 test. A value of $p < 0.05$ was considered statistically significant.

We used ChatGPT-4 (OpenAI, USA) for language revision and grammatical editing to improve the clarity and readability of the manuscript.

RESULTS

The clinical characteristics and BMIs of the patients were examined. The gestational age at delivery, gravidity, parity, abortion, and preoperative hematocrit levels were similar. The mean age of the higher BMI group was significantly higher than that of the other group ($p=0.04$). The parameters are listed in Table 1.

Table 1. Comparison of clinical characteristics and BMI

Maternal measures	Group 1 BMI ≥30 (n=82)	Group 2 BMI <30 (n=109)	p
Age (mean±SD)	30.3±5.4	28.6±5.9	0.040^
Gestational age at delivery (mean±SD)	37.7±1.9	37.7±2.4	0.170^^
Gravidity (mean±SD)	3.1±1.6	2.9±1.5	0.305^^
Parity (mean±SD)	1.7±1.3	1.6±1.2	0.685^^
Abortions (mean±SD)	0.4±0.7	0.3±0.5	0.299^^
Preoperative hematocrit value (percent) (mean±SD)	34.1±3.0	33.9±3.5	0.769^

^: Independent samples t test; ^^: Mann Whitney U test; p<0.05. BMI: Body mass index; SD: Standard deviation

Table 2. Comparison of delivery measures and BMI

Delivery measures	Group 1 BMI ≥30 (n=82)	Group 2 BMI <30 (n=109)	p
Duration of surgery (mean±SD)	37.8±12.2	36.5±12.9	0.375
Change in hematocrit value (mean±SD)	4.0±2.5	4.1±2.7	0.635
Volume of blood aspirated with surgical suction (mL) (mean±SD)	118.8±106.9	101.4±76.8	0.623
Weight of blood in gauze sponges (grams) (mean±SD)	776.7±402.6	770.2±343.1	0.795
Duration of placental separation (seconds) (mean±SD)	17.2±6.8	19.0±8.0	0.187

Mann Whitney U test; p<0.05. BMI: Body mass index; SD: Standard deviation

The duration of surgery (37.8±12.2 vs. 36.5±12.9, p=0.375), change in hematocrit (postoperative sample taken 4 hours after surgery) (4.0±2.5 vs. 4.1±2.7, p=0.635), aspirated blood volume (mL) with surgical suction (118.8±106.9 vs. 101.4±76.8, p=0.623), weight (g) of gauze sponges used in surgery (776.7±402.6 vs. 770.2±343.1, p=0.795), and duration (s) of placental separation (17.2±6.8 vs. 19.0±8.0, p=0.187) were compared. No statistically significant differences in these parameters were found between the groups (Table 2).

Finally, we assessed the potential effect of obesity on placental separation. In the high BMI group, placental separation was spontaneous in 39% of the patients, whereas manual intervention was required in 69% of the patients. In the other group, the percentages were 37.6% for spontaneous and 62.4% for manual. These differences were not statistically significant (Table 3).

DISCUSSION

Obesity is one of the most common public health concerns worldwide. The frequency of obesity is increasing; therefore, its associated diseases are becoming more common. From an obstetrician's perspective, obesity raises concerns owing to its association with various pregnancy complications, such as preeclampsia and gestational diabetes.^[18] However, there isn't a consensus on whether obesity is a risk factor for PPH. Although some studies have reported an association,^[6]

Table 3. Comparison of the mode of placental separation between the study groups

	Mode of placental separation (Spontaneous)		Mode of placental separation (Manual)		p
	n	%	n	%	
Group 1 BMI ≥30	32	39	50	61	0.843
Group 2 BMI <30	41	37.6	68	62.4	

χ² test; p<0.05. BMI: Body mass index

in this study, we did not observe any significant differences in terms of blood loss between the high and low BMI groups. There are conflicting findings in the literature regarding the association between obesity and PPH. Our study design aimed at testing this association, and we expected greater blood loss and longer duration of surgery in the high BMI group than in the lower BMI group. However, our findings suggested otherwise. Our data were in parallel with those studies that did not attribute a higher risk of PPH to obese patients.^[10] The volume of blood aspirated with surgical suction and the weight of

gauze sponges were used to assess blood loss during surgery, and the differences between groups were not statistically significant, although a minimal increase was seen in both parameters in the high BMI group. This finding supports the idea that obesity alone is not a risk factor for PPH when delivery mode is controlled.^[10] According to a review by Holly et al.,^[19] obesity alone showed no association with atonic PPH, and they argued that underlying conditions, such as hypertension and diabetes mellitus, constitute the real risk. Additionally, although statistically insignificant, the change in hematocrit was lower in the high BMI group. This may be due to hypercoagulability in obese patients, as suggested by Paglia et al.^[10]

Conner et al.^[20] investigated the effect of obesity on the “incision-to-delivery” interval and demonstrated an association between increased BMI and increased skin incision-to-delivery time. In our study, the duration of surgery was slightly longer in the high BMI group; however, the difference was not statistically significant. Furthermore, the duration of placental separation was also assessed in our study. However, again the difference was insignificant between the high and low BMI groups.

Placental adherence abnormalities and invasion of the villous tissue into the myometrium prevent spontaneous separation of the placenta from the uterine wall at delivery. When not diagnosed during prenatal examinations, manual removal of the placenta can cause heavy hemorrhage from the uteroplacental vascular structures during delivery.^[21] Vieira et al.^[22] studied the placenta accreta spectrum (PAS) regarding its potential association with maternal obesity, and a database study reported that obesity was neither an independent risk factor for PAS nor associated with the severity of PAS. Apart from the duration of placental separation, we did not report a significant difference between the groups due to the mode of placental separation (spontaneous or manual).

Our study has several limitations. First, the patients were operated on by different surgical teams because the institution is one of the largest teaching hospitals in the region. Therefore, surgical teams with different levels of experience may have affected our findings. For example, lean patients may be perceived as technically easier to operate on, potentially leading to the inclusion of a relatively inexperienced obstetric resident in the surgical team. This may have lengthened the duration of surgery and therefore affected the blood loss parameters in the low BMI group. Although each surgical team was required to include at least one specialist and experienced attending surgeon, we could not completely rule out this confounding factor.

Second, the retrospective nature and sample size of the study also pose limitations. However, since this was a single-cen-

ter study, all recorded data for each patient, including the surgical reports on surgical gauze weight and aspirated fluid, were standardized, which allowed a healthy comparison. Additionally, only a limited number of studies have investigated the effect of maternal obesity on the risk of PPH while accounting for the mode of delivery. Our study specifically focused on cesarean deliveries, which is one of its strengths.

The findings of this study may make obesity seem innocent regarding pregnancy-related complications. However, this is certainly not the case. Obesity can complicate pregnancy and delivery in multiple ways. Opøien et al.^[23] found that BMI >30 kg/m² was an independent risk factor for post-cesarean surgical site infections. The risks of gestational diabetes and preeclampsia are also associated with obesity.^[18] The risk of stillbirth, which is one of the most serious complications of pregnancy, has also been reported to be associated with maternal obesity.^[24]

CONCLUSION

In conclusion, the lack of an association between obesity and PPH should not lead obstetricians to undermine obesity as a risk factor in prenatal care. Our results contribute to the literature by reinforcing the notion that obesity alone is not an independent risk factor for PPH. However, extra care should still be given to obese patients both prenatally and during delivery.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences, İstanbul Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (No: 4070, Date: 29/08/2023).

Informed Consent: Informed consent was part of the standard admission procedure because the institution was a teaching hospital.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Clinical Characteristics and Treatment Patterns in Pediatric Localized Scleroderma: A Referral-center Experience

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ABSTRACT

Objective: Localized scleroderma is a rare disease that can cause significant morbidity. Due to its rarity, data are limited, and no standardized treatment exists for patients resistant to first-line therapies. This study aims to evaluate clinical and treatment features based on a referral pediatric rheumatology center's experience.

Materials and Methods: The medical files of 36 included pediatric localized scleroderma patients were retrospectively reviewed, and demographic, clinical, laboratory, treatment, and outcome data were recorded.

Results: Of the patients, 30 (83.3%) were female, the median age at diagnosis was 6.37 years (IQR: 4.04), and the median follow-up duration was 25.5 months (IQR: 56). The most common subtype was linear scleroderma (n=15, 41.67%), followed by circumscribed morphea (n=14, 38.89%). Among patients with linear scleroderma, 6 had craniofacial involvement. ANA positivity was observed in 38.9% of patients. Extracutaneous findings in the form of joint contractures were present in three patients. Systemic treatment was administered to 94% of patients, with methotrexate (MTX) used in 33 (91.67%) and corticosteroids in 26 (72.22%). MTX was effective in 58%, though some patients required additional or alternative therapies such as mycophenolate mofetil (n=14, 38.89%), intravenous immunoglobulin (n=9, 25.0%), or tocilizumab (n=2, 5.56%). Relapses occurred in 19%, and complete clinical response was achieved in 61%. Side effects were mostly mild and mainly related to MTX.

Conclusion: Pediatric localized scleroderma shows diverse clinical presentations and often requires systemic treatment, primarily MTX. While most patients respond well, a subset needs additional therapies. Early diagnosis and tailored treatment are essential to improve outcomes and reduce morbidity.

Keywords: Antirheumatic drugs, autoimmune diseases, localized scleroderma, rheumatology

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INTRODUCTION

Scleroderma comprises a group of chronic autoimmune connective tissue diseases characterized by sclerotic skin changes due to excessive collagen deposition and fibrosis.^[1] It is generally divided into two main forms: systemic sclerosis (SSc), which affects internal organs along with skin involvement, and localized scleroderma (LS), also known as morphea, which is confined to the skin and sometimes underlying tissues. Among children, LS is the more frequently observed form and represents the vast majority of pediatric scleroderma cases.^[2,3]

Localized scleroderma is considered a rare condition, though its true incidence may be underestimated. According to population-based data from the United States, its incidence is estimated to be around 0.4–2.7 per 100,000 individuals. It follows a bimodal distribution, with incidence peaks occurring between ages 2–14 and again in mid-adulthood. It is reported to be more common in females and among Caucasians.^[4] In the pediatric population, linear morphea is the most prevalent subtype, whereas adults more commonly present with the plaque-type form.



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Although the precise pathogenesis of morphea is not fully understood, it is believed to involve an aberrant immune response triggered by environmental factors—such as trauma, infections, or certain medications—in individuals with a genetic predisposition. This dysregulation leads to T-cell activation and subsequent release of interferon- γ -associated cytokines, which initiate inflammatory and profibrotic cascades, ultimately causing excessive collagen deposition. Depending on the subtype, the disease may extend beyond the dermis to involve deeper tissues, including subcutaneous fat, fascia, muscle, and even bone.^[4] Diagnosis is primarily based on characteristic cutaneous features, but in atypical cases or when differential diagnosis is needed, skin biopsy can offer valuable diagnostic information.^[5]

Despite its rarity, morphea can result in significant morbidity, particularly when deeper tissues or functionally important areas are involved. The scarcity of large, multicenter studies—largely due to the low incidence of the disease—limits the development of standardized diagnostic and treatment approaches.^[6] Although treatment options beyond first-line therapies have been described in the literature, especially for refractory cases, there is still no universally accepted therapeutic algorithm.^[7] Therefore, real-life experiences remain valuable to better understand the clinical spectrum and management of this uncommon disease.

In this study, we aim to present the clinical characteristics, diagnostic approaches, and treatment patterns of pediatric localized scleroderma patients from a single center, contributing to the limited but growing body of evidence in the field.

MATERIALS and METHODS

This retrospective study included pediatric patients aged 0–18 years diagnosed with localized scleroderma who were followed up at the Pediatric Rheumatology Clinic of Istanbul University Faculty of Medicine. A total of 45 patient records were initially reviewed. Patients with clinical features suggestive of systemic sclerosis or with diagnoses such as lichen sclerosis, as well as those with incomplete data or lost to follow-up, were excluded. Consequently, 36 patients were included in the final analysis.

Demographic data (age at symptom onset, age at diagnosis, sex), family history, clinical features (localized scleroderma subtype, involved regions, extracutaneous findings), laboratory parameters including autoantibodies, and treatment-related information (first-line therapies, subsequent treatments if applicable, and treatment responses) were retrospectively collected from patient records. Antinuclear antibody (ANA) positivity was defined as a titer of 1:80 or higher.

Disease activity assessment was based on clinical examination, including evaluation of erythema, induration, and lesion size. Clinical improvement was defined as a reduction in erythema and induration, stabilization or regression in lesion size, and absence of new lesion formation, as documented in follow-up records.^[8] Complete clinical response was defined as the absence of erythema and induration, no new lesion formation, and no progression of existing lesions. Relapse was defined as the re-appearance of disease activity after a period of clinical improvement, characterized by new or expanding lesions, or recurrence of erythema and induration in previously inactive areas.

Statistical Analysis

Data were collected and organized using Microsoft Excel (Microsoft Corporation, Redmond, WA) and analyzed with SPSS version 17.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the data. Categorical variables are presented as counts and percentages, while continuous variables are expressed as means with standard deviations or medians with interquartile ranges, as appropriate. The normality of continuous variables was assessed using the Shapiro-Wilk test.

Ethics

Ethical approval was granted by the Istanbul University Faculty of Medicine Clinical Research Ethics Committee (Approval number: 2025-3429010). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients and/or their legal guardians.

RESULTS

A total of 36 patients with localized scleroderma were included in the study. The median time from symptom onset to diagnosis was 5 months (IQR: 30.5). The median follow-up duration of the cohort was 25.5 months (IQR: 56). The demographic features, disease subtypes, and laboratory findings of the patients at diagnosis are summarized in Table 1.

Patients were referred to pediatric rheumatology primarily by dermatology ($n=25$, 69.44%), followed by general pediatrics ($n=10$, 27.78%) and neurology ($n=1$, 2.78%), which were also the specialties of initial presentation. Skin biopsy was performed at diagnosis in 17 (47.22%) patients.

Comorbidities were identified in three patients: type 1 diabetes mellitus in one, recurrent lower respiratory tract infections in another, and both congenital heart disease and hepatic hemangioma in a third patient. No patients had a family history of localized scleroderma. However, four patients (11.11%) reported a family history of rheumatic diseases—two with rheumatoid arthritis and two with psoriasis.

Table 1. Demographic, clinical, and laboratory characteristics of the cohort at the time of diagnosis

Demographic data	
Female, n (%)	30 (83.33)
Age at diagnosis (years), median (IQR)	6.37 (4.04)
Time from symptom onset to diagnosis (months), median (IQR)	5 (30.5)
Follow-up duration (months), median (IQR)	25.5 (56)
Subtypes, n (%)	
Linear (total)	15 (41.67)
Craniofacial	6 (16.67)
Trunk and extremities	9 (25)
Circumscribed	14 (38.89)
Generalized	1 (2.78)
Mixed	6 (16.67)
Laboratory evaluation at diagnosis	
White blood cell count (/ μ L), median (IQR)	7650 (2540)
Hemoglobin (g/dL), median (IQR)	12.2 (1.4)
Platelet count ($\times 10^3/\mu$ L)	325 (74)
CRP (mg/L), median (IQR)	0.7 (2.45)
ESR (mm/h), median (IQR)	6 (13)
ANA positivity, n (%)	14 (38.9)
Other autoantibodies (anti-Scl70), n (%)	1 (2.78)

IQR: Interquartile range; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; ANA: Antinuclear antibodies

The most common subtype was linear scleroderma (n=15, 41.67%), followed by circumscribed morphea (n=14, 38.89%), mixed-type (n=6, 16.67%), and generalized morphea (n=1, 2.78%). Among the 15 patients with linear scleroderma, 6 presented with craniofacial involvement, including 3 with *en coup de sabre* and 3 with Parry-Romberg syndrome (PRS). All 6 patients classified as mixed-type exhibited features of both linear and circumscribed morphea. Notably, one patient within the mixed-type group had PRS accompanied by circumscribed morphea on the trunk. Representative images of different subtypes of localized scleroderma are presented in Figure 1, and the distribution of lesions by different localized scleroderma subtypes is summarized in Table 2.

At the time of diagnosis, autoantibody positivity was evaluated, and ANA were found to be positive in 14 patients (38.9%). One patient with linear scleroderma tested positive for anti-Scl-70 antibodies; however, during 73 months of follow-up, this patient did not develop systemic sclerosis or systemic organ involvement.

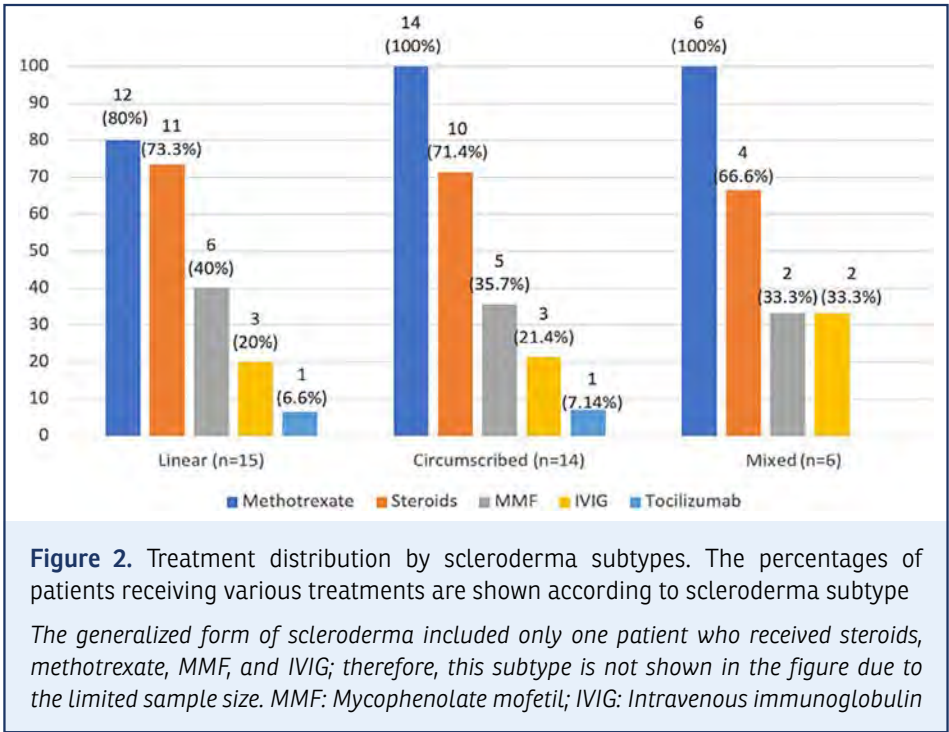
Extracutaneous involvement in the form of joint contractures was documented in 3 patients (8.33%). In two of these, joint limitation occurred in the same anatomical region as the skin lesion, while in one, the affected joint was unrelated to the lesion site. Among the three patients with extracutaneous involvement, age at diagnosis was 5.9, 7.2, and 7.3 years. Time from symptom onset to diagnosis varied considerably,



Figure 1. Examples of different subtypes of localized scleroderma. **(a)** Linear scleroderma on the forearm. **(b)** Circumscribed morphea on the dorsum of the foot

Table 2. Localization of the lesions according to scleroderma subtypes

	n	%	Head and neck	Trunk	Upper extremity	Lower extremity	Gluteal region
Circumscribed	14	38.89	5	1	4	7	1
Linear scleroderma (trunk and extremities)	9	25.0	–	4	6	5	0
Linear scleroderma (craniofacial)	6	16.67	6	–	–	–	–
Mixed	6	16.67	1	2	4	5	1
Generalized	1	2.78	–	–	–	–	–



with two patients diagnosed within 5 months of symptom onset, while one patient experienced a longer interval of 62 months, reflecting a delayed recognition of disease.

All patients with craniofacial scleroderma underwent at least one cranial MRI scan. No neurological or ocular involvement was detected, although mild signal increase in the right internal capsule suggestive of gliotic changes was observed in one patient on neuroimaging.

Systemic treatment was initiated in 34 out of 36 patients (94.44%). Treatment regimens included methotrexate (MTX) in 33 patients (91.67%), corticosteroids in 26 (72.22%), mycophenolate mofetil (MMF) in 14 (38.89%), intravenous immunoglobulin (IVIG) in 9 (25.00%), and tocilizumab in 2 (5.56%). MTX was administered to all patients at a dose of 10–15 mg/m² per week, with a median treatment duration of 12 months (IQR: 18 months) among patients who completed therapy or were still on

treatment. MMF was given to all patients at 500–1000 mg/m² per day, with a median duration of 25 months (IQR: 36 months). IVIG was administered at 1 g/kg per dose, given once monthly; among the 9 patients receiving IVIG, 6 received 6 doses, 1 received 9 doses, 1 received 11 doses, and 1 patient discontinued after 4 doses due to an adverse event. Tocilizumab was administered subcutaneously at 162 mg every 2 weeks in 2 patients, with treatment durations of 3 years in one patient and 4 years in the other. Most patients were followed by dermatology and had received topical treatment prior to referral; however, detailed information on the specific agents used was not available.

As initial disease-modifying antirheumatic drugs therapy, MTX was started in 33 patients; MMF was used as the first-line agent in one patient. Among the 33 patients who received MTX, sufficient improvement was observed in 19 (57.58%). In five patients (15.15%), MTX was discontinued due to adverse

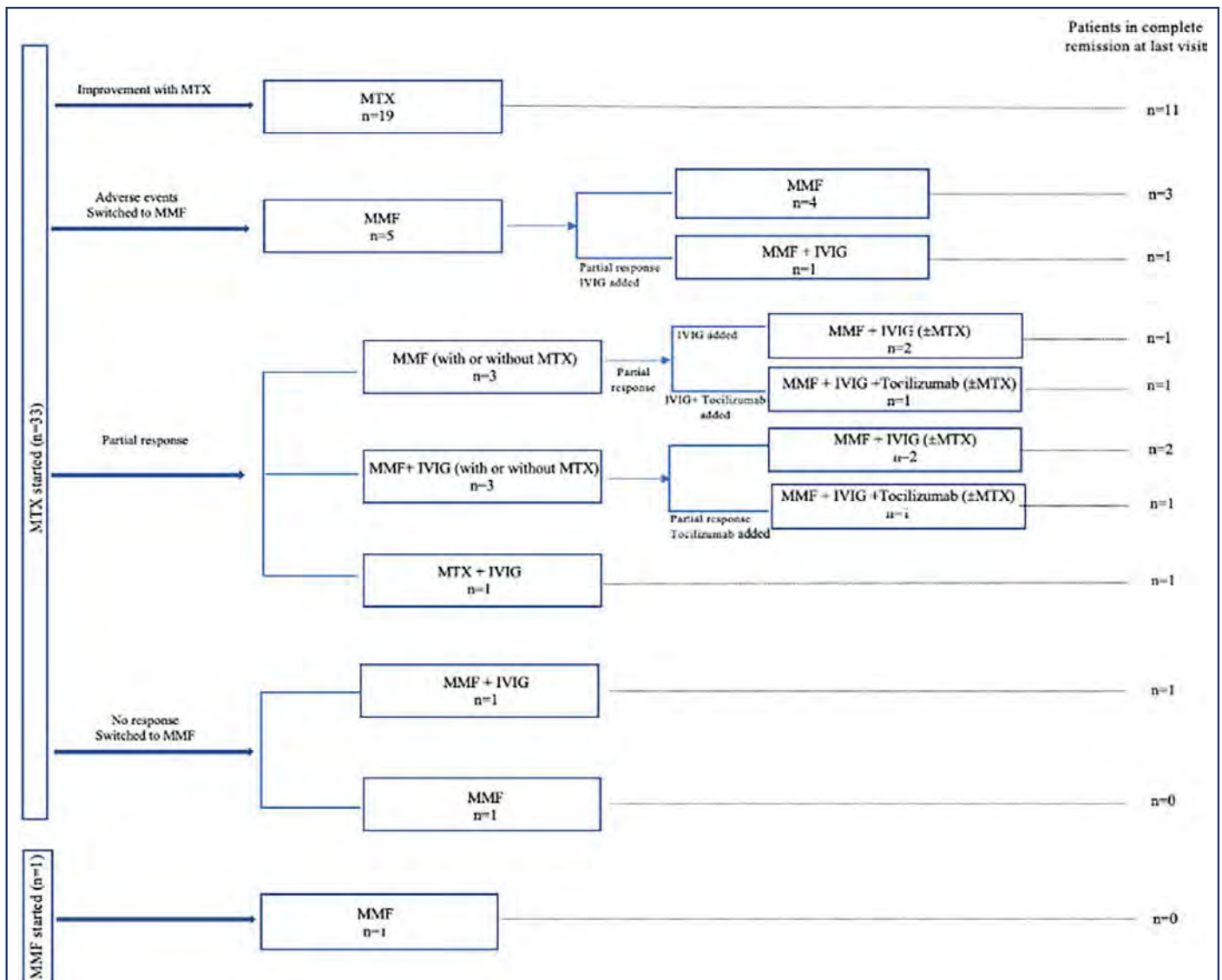


Figure 3. Systemic treatments in pediatric localized scleroderma patients

The figure illustrates the types of systemic therapies used, treatment switches, reasons for switching or discontinuation, and the number of patients achieving remission at the last follow-up for each therapy. MMF: Mycophenolate mofetil; MTX: Methotrexate; IVIG: Intravenous immunoglobulin

effects and switched to MMF. In six patients (18.18%), although MTX led to partial reduction in disease activity, MMF was either added or used as a replacement due to inadequate improvement. In two patients (6.06%), no response to MTX was observed, and treatment was switched to MMF. In one patient, MTX resulted in partial improvement, but due to extensive lesion distribution, IVIG was added to the treatment regimen.

Among the 14 patients who received MMF, four (28.57%) were started on IVIG simultaneously. In an additional four patients (28.57%), IVIG was added after an inadequate

response to MMF alone. Sufficient response to MMF was achieved in the other six patients.

In two patients who showed insufficient response to corticosteroids, MTX, MMF, and IVIG, tocilizumab was used and resulted in clinical improvement.

Treatment distribution according to different localized scleroderma subtypes is illustrated in Figure 2. Treatments of patients receiving systemic therapy, treatment switches and their reasons, as well as the number of patients in remission at the last visit, are shown in Figure 3.

Relapses occurred in seven patients (19.44%), accounting for a total of nine episodes. Five occurred during MTX therapy, two during MMF, and one after cessation of all treatment. Complete clinical response, defined as complete resolution of disease activity, was observed in 22 patients (61.11%).

MTX-related side effects were reported in 7 patients (21.21%), primarily gastrointestinal symptoms such as vomiting. In five cases, treatment modification was required due to adverse effects. IVIG-related headache was reported in one patient. No significant side effects were associated with MMF or tocilizumab in this cohort.

DISCUSSION

This study presents data from a single tertiary referral center for pediatric rheumatology in Türkiye, focusing on patients with localized scleroderma. Given the rarity of this condition, cohort studies such as ours provide valuable insights into the clinical characteristics and subtype distribution in different populations.

In our cohort, skin biopsy was performed in 47.22% of patients. These observations align with the view that biopsy is not mandatory for diagnosis and is generally considered in selected cases.^[5,7] The most frequently observed subtype was linear scleroderma, which is consistent with previous literature. However, the proportions of linear scleroderma and circumscribed morphea were relatively close. This is in contrast to many previously published cohorts, where linear scleroderma has been reported as more clearly predominant.^[9-12] This discrepancy may reflect differences in patient populations, geographic and genetic factors, or referral patterns specific to different centers. It also highlights the heterogeneity in subtype distribution across different cohorts and underlines the importance of local data in understanding the full spectrum of the disease. In addition, we acknowledge the wide interquartile range for time to diagnosis in our cohort. This variability may reflect referral delays and initial misdiagnoses, which are common challenges in clinical practice and contribute to the observed heterogeneity.

Another notable difference observed in our study compared to the literature was the relatively low frequency of extracutaneous manifestations in our cohort. While the reported rates of extracutaneous involvement in localized scleroderma vary across studies, the U.S.-based National Registry for Childhood-Onset Scleroderma has reported such findings in up to 70% of patients.^[10] In our cohort, musculoskeletal involvement was the most frequently observed extracutaneous manifestation, which is consistent with the literature.^[11,13,14]

Neurological involvement is a well-recognized extracutaneous feature, particularly in patients with craniofacial scleroderma. It is recommended that all patients with *en coup de sabre* (ECDS) or PRS undergo neuroimaging, regardless of neurological symptoms.^[7] In our study, all patients with ECDS or PRS underwent cranial imaging, but abnormalities were detected in only one case. This contrasts with findings from a previous study evaluating cranial involvement in juvenile localized scleroderma, where neuroimaging abnormalities were reported in 7 out of 14 patients with craniofacial involvement.^[15] One possible explanation for the lower detection rate in our cohort could be the relatively short interval between symptom onset and diagnosis, allowing for earlier intervention. The abnormality observed in our patient was reported as gliotic changes. Although neurological involvement is known to occur more frequently in patients with facial involvement, no disease-specific pattern of neurological symptoms or imaging findings has yet been established in localized scleroderma.^[16]

According to the SHARE (Single Hub and Access point for pediatric Rheumatology in Europe) recommendations, the first-line treatment for juvenile localized scleroderma consists of corticosteroids and MTX. In refractory cases, switching to or adding MMF may be considered.^[7] For patients unresponsive to these therapies, alternative treatment options exist, but there are no standardized recommendations for this subgroup, leading to variability in therapeutic approaches reported in the literature.

In our cohort, systemic treatment was used in the majority of patients. This proportion appears higher than those reported in previous studies.^[10,13,17] However, it is important to highlight that our center is a referral institution, where patients with more severe disease or those unresponsive to topical therapies are more likely to be evaluated. In our cohort, the most frequently used systemic treatments were corticosteroids and MTX, in line with existing studies.^[11-14,18] The efficacy of MTX in localized scleroderma has been demonstrated in previous studies, and in our cohort, the majority of patients showed clinical improvement with MTX treatment.^[19,20] Other agents used included tocilizumab and IVIG. A notable finding in our study was the relatively high use of IVIG, administered in approximately 25% of patients. Importantly, favorable responses to IVIG were observed in these cases. IVIG is commonly used in connective tissue diseases when first-line therapies fail and has also been employed in localized scleroderma, although data supporting its use in this condition remain limited.^[21-24] Our findings contribute to the growing body of evidence suggesting a potential role for IVIG in selected patients with resistant disease.

CONCLUSION

This study provides valuable insight into the clinical features, subtype distribution, extracutaneous manifestations, and treatment patterns of juvenile localized scleroderma in a single-center cohort from Türkiye. As a rare disease, localized scleroderma remains understudied, and regional cohort data such as ours help fill important gaps in the literature. However, several limitations should be acknowledged, including the retrospective design, the relatively small sample size, and the wide variation in follow-up time, which may influence interpretation of outcomes and relapse rates. Despite these limitations, our results are largely consistent with existing literature and also offer new observations, such as the relatively high frequency of circumscribed morphea and the prominent use of IVIG. Further prospective, multicenter studies are needed to better define the natural history of the disease and to guide treatment strategies, particularly in patients with refractory or atypical presentations.

Disclosures

Ethics Committee Approval: The study was approved by the Istanbul University Faculty of Medicine Clinical Research Ethics Committee (No: 2025-3429010, Date: 26/06/2025).

Informed Consent: Written informed consent was obtained from all patients and/or their legal guardians.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Evaluation of Clinical, Radiological, and Pathological Efficacy Regarding Neoadjuvant Chemotherapy in Breast Cancer

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ABSTRACT

Objective: The aim of this study was to evaluate the radiological, clinical, and pathological responses before and after neoadjuvant chemotherapy (NAC) in patients with breast cancer, to examine the reliability of imaging modalities, and to compare treatment responses according to pathological subtypes.

Materials and Methods: Forty breast cancer patients who underwent neoadjuvant chemotherapy followed by surgery between June 2020 and 2025 were retrospectively analyzed. Tumor diameters before and after treatment were measured using positron emission tomography-computed tomography (PET-CT). Axillary lymph node metastases were compared clinically, radiologically, and pathologically. In addition, treatment responses were analyzed according to pathological subtypes.

Results: A significant reduction in tumor size was observed following NAC ($p<0.001$). Among the 20 patients who demonstrated a complete response on PET-CT, only 8 had a complete pathological response. The sensitivity, specificity, positive predictive value, and negative predictive value of PET-CT in detecting complete response were 100%, 62.5%, 40%, and 100%, respectively. A statistically significant downstaging after NAC was observed ($p<0.001$). Higher response rates were found in human epidermal growth factor receptor 2 (HER2)-positive and triple-negative subtypes.

Conclusion: Neoadjuvant chemotherapy significantly reduces tumor size and axillary involvement, enabling more conservative surgical approaches. Although PET-CT has high sensitivity in detecting complete response, its low positive predictive value highlights the need for complementary evaluation methods. Pathological subtypes are predictive of treatment response and should be taken into account during treatment planning.

Keywords: Breast cancer, HER2, neoadjuvant therapy, positron emission tomography-computed tomography

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INTRODUCTION

Breast cancer is one of the most commonly encountered cancers worldwide. Early-stage breast cancer can be treated curatively by surgery. In locally advanced and inoperable breast cancer cases, neoadjuvant chemotherapy (NAC) has significant clinical value, as shown by many trials.^[1] NAC is effective in locally advanced or metastatic breast cancer cases by either downstaging or causing shrinkage of the tumor, allowing breast-conserving surgery (BCS) instead of mastectomy.^[2,3] Moreover, NAC is effective in cases with axillary lymph node involvement by downstaging, making it possible to avoid axillary dissection and its complications.^[4-6]

Pathological complete response (pCR) after NAC is an important prognostic factor. Therefore, early evaluation of post-NAC response is important for verifying treatment efficacy as well as identifying non-responders to plan alternative treatment options.^[7,8] For these reasons, evaluation after NAC is performed using mammography and ultrasonography, generally combined with magnetic resonance imaging (MRI) and/or positron emission tomography (PET-CT).

Some studies have reported that patients, especially those with triple-negative and HER2-positive tumors, who achieve a complete pathological response to NAC have longer overall and disease-free survival.^[9-11] In earlier periods, NAC had a



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limited role; however, its use in early breast cancer has recently been debated.^[12] Moreover, some studies suggest avoiding surgical treatment in patients with pCR.^[13,14] Therefore, it is important to identify patients expected to have the best response and understand the long-term advantages of NAC.

In this study, we evaluated the radiological, clinical, and pathological responses to NAC in 40 breast cancer patients retrospectively.

MATERIALS and METHODS

In this retrospective study, data of 129 patients operated for breast cancer between June 2020 and June 2025 in Istanbul Aydın University Medical Faculty, Department of General Surgery, were evaluated. Forty patients subject to NAC were included in the study. Treatment strategy was decided by the Oncology Council, consisting of doctors from the general surgery, medical oncology, radiation oncology, nuclear medicine, and radiology departments. The NAC decision was taken regarding clinical and radiological staging in light of PET-CT. All of the tumors were marked by metallic clips before NAC. After NAC, the surgical technique was decided based on the latest clinical and radiological findings. All of the surgical operations were performed by the same surgical team. The surgical technique was either breast-conserving surgery or mastectomy.

Sentinel lymph node biopsy (SLNB) was performed with methylene blue and evaluated with frozen section in the operating room. In patients with metastasis and failed dye sampling in SLNB, axillary dissection was performed. Pathological diagnosis was performed by the same pathology team both in frozen section and postoperative evaluation.

Complete response was accepted in cases with complete remission in breast tumor, axillary metastatic lymph node, or distant metastasis with radiologic evaluation and PET-CT after NAC. Tumor shrinkage by 25% in diameter and/or decrease in metastatic lymph node involvement or disappearance was accepted as partial response. No change in tumor size or lymph node involvement, less than 25% shrinkage in tumor diameter, or less than 20% increase in tumor size was accepted as stable disease. More than 20% increase in tumor size and/or increased axillary lymph node involvement was accepted as progressive disease.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics version 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics, including mean, standard deviation (SD), and percentages, were calculated. Continuous variables are presented as

mean±standard error of the mean (SEM) with ranges, unless otherwise specified. For categorical variables, comparisons were made using the Chi-square test or Fisher's exact test, as appropriate. The distribution of continuous data was assessed using the Kolmogorov–Smirnov test. Normally distributed variables were analyzed with the Student's t-test, while non-normally distributed variables were analyzed with the Mann–Whitney U test. A p-value of <0.05 was considered statistically significant.

AI-Assisted Figure Generation

Graphical visualizations illustrating the distribution of clinical and pathological responses according to molecular subtypes in patients receiving neoadjuvant chemotherapy for breast cancer were generated using the artificial intelligence tool ChatGPT (GPT-5, OpenAI, August 2025 version). Aggregated, anonymized study data were provided to the AI system without any patient-identifiable information. The prompts included detailed instructions specifying the type of figure (e.g., bar chart, pie chart), axis labeling, color coding for molecular subtypes, and legend formatting. The generated figures were reviewed and finalized by the authors to ensure accuracy and consistency with the study results.

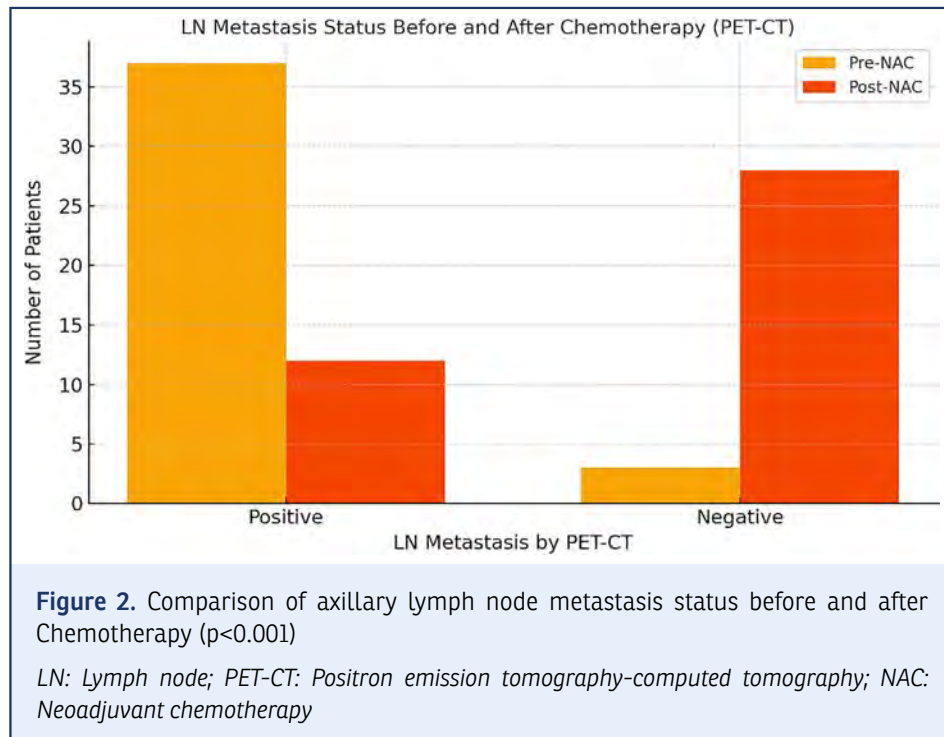
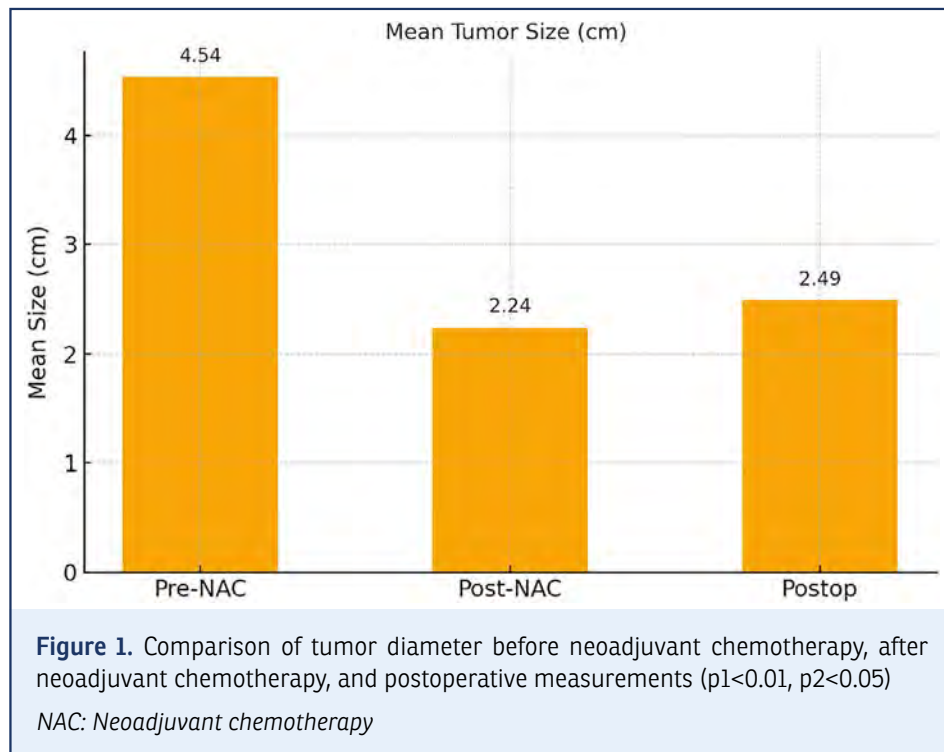
Ethics Committee Approval

This study was approved by the Ethics Committee of Istanbul Aydın University (approval number: 165/2025). It was conducted in accordance with the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki and its later amendments. Due to the retrospective nature of the study, the requirement for individual informed consent was waived by the ethics committee. No intervention or modification was made in patient care within the scope of this research.

RESULTS

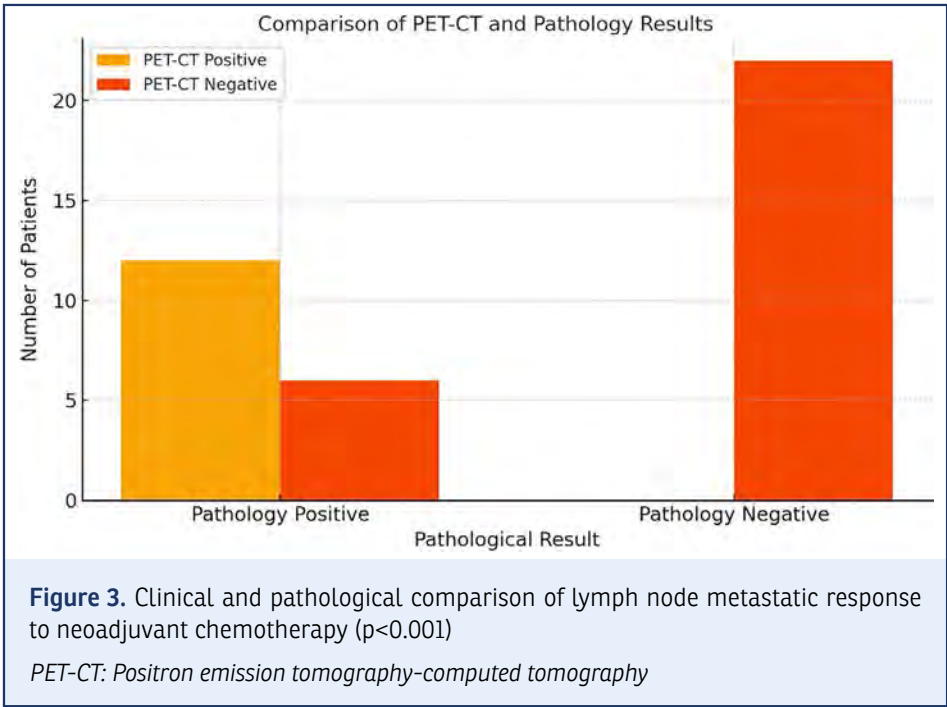
The mean age of the patients at the time of NAC was 59.2±11.0 years (31–70). Regarding the core biopsy results, 35 (87.5%) had invasive ductal carcinoma, 2 (5%) had invasive lobular carcinoma, 1 (2.5%) had inflammatory carcinoma, 1 (2.5%) had metaplastic carcinoma, and 1 (2.5%) had mucinous carcinoma.

Postoperative pathological examinations revealed complete regression in 8 (20%) patients. Remaining patients had pathological results similar to the pre-NAC results. Mean tumor size with PET-CT evaluation before NAC was 4.54±0.72 cm (mean ± SEM; range: 1–26 cm), whereas mean tumor size after NAC was 2.24±0.77 cm (mean±SEM; range: 0–25 cm).



There was a statistically significant regression in the tumor size ($p<0.001$). However, mean tumor size after NAC within the surgical specimens was 2.49 ± 0.71 cm (mean $\pm$ SEM; range: 0–25 cm), which was statistically significantly higher than the PET-CT results ($p<0.05$) (Fig. 1).

In 37 (92.5%) patients, clinical and radiological lymph node involvement was present, with 3 (7.5%) free of axillary involvement. After NAC, 12 (30%) patients had persistent axillary lymph node involvement ($p<0.001$) (Fig. 2). After NAC, 25 of 37 patients had radiological regression in lymph node involve-



ment. There was a statistically significant difference between pre-NAC and post-NAC involvement radiologically ($p<0.001$). Twelve patients with both pre-NAC and post-NAC axillary lymph node positivity had axillary dissection, and all of these patients were proven to be metastatic in the pathological examination. The remaining 28 patients had SLNB, in which 3 of them had additional axillary dissection due to positivity of SLNB, and pathological examination also confirmed metastasis. In another 3 patients, SLNB failed to stain the lymph nodes; therefore, additional axillary dissection was performed, and no metastatic lymph node was detected in the dissection specimen. In 3 of the SLNB-negative patients, micrometastasis was revealed perioperatively in the paraffin section, but no additional operation was performed. As a result, post-NAC radiological examination revealed 12 positive cases, whereas in post-surgical specimens, 18 patients had metastasis (3 of them with micrometastasis) (Fig. 3). There was a statistically significant difference regarding these results ($p<0.001$).

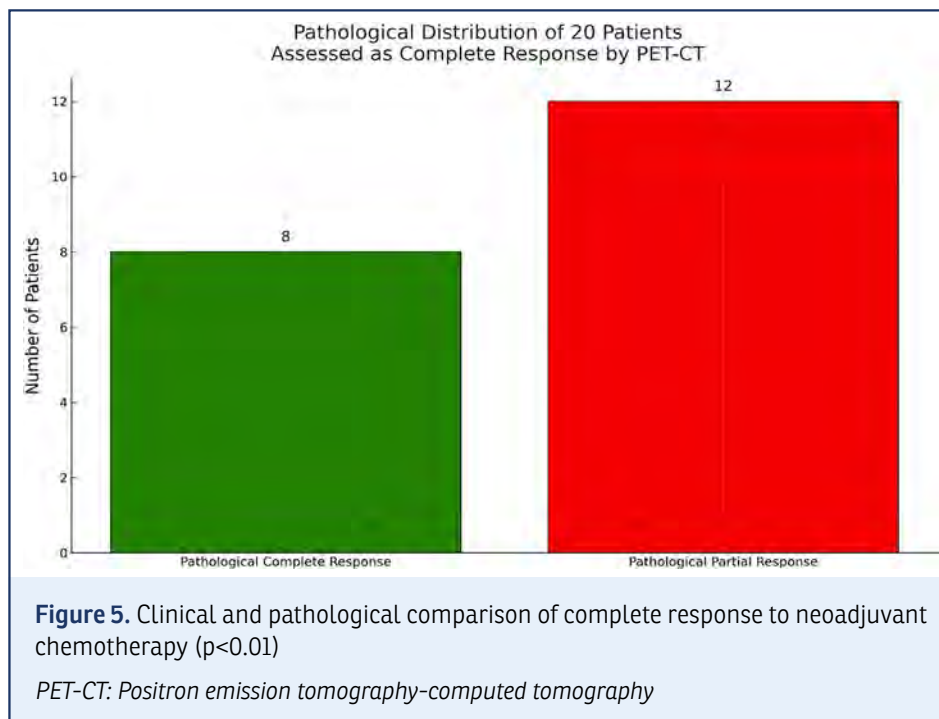
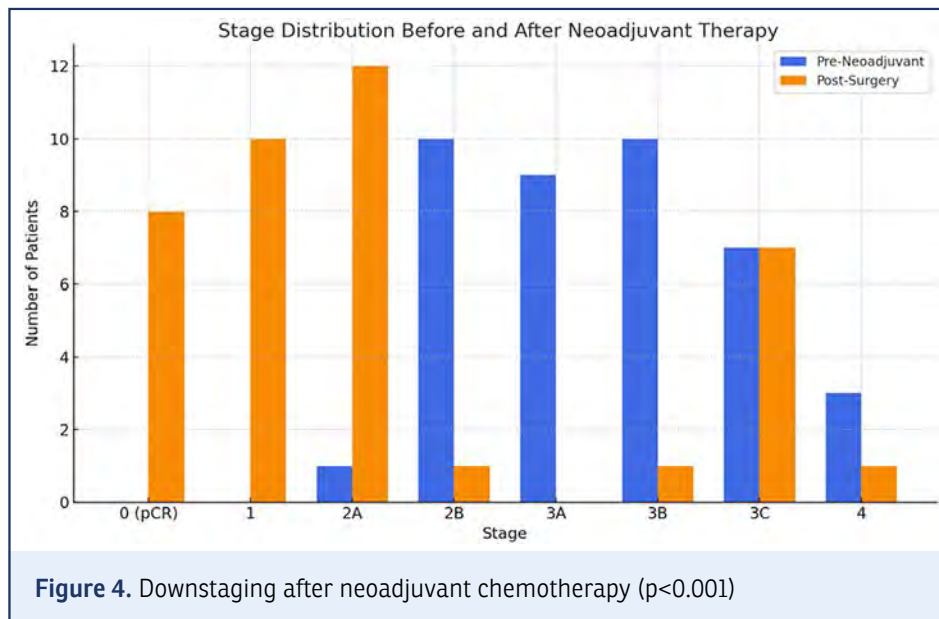
During surgery, 20 patients had mastectomy (50%) and 20 (50%) had BCS. In the mastectomy group, 3 patients were suitable for BCS after NAC but preferred mastectomy.

Clinical and radiological examinations regarding TNM classification revealed that 1 patient (2.5%) had Stage 2A, 10 (25%) had Stage 2B, 9 (22.5%) had Stage 3A, 10 (25%) had Stage 3B, 7 (17.5%) had Stage 3C, and 3 (7.5%) had Stage 4 disease. None of the NAC patients had Stage 1 disease. Post-surgical pathological examination revealed that 10 patients (25%) had

Stage 1, 12 (30%) had Stage 2A, 1 (2.5%) had Stage 2B, 1 (2.5%) had Stage 3B, 7 (17.5%) had Stage 3C, and 1 (2.5%) had Stage 4. In 8 patients (20%), pathological complete response was achieved. These results showed that NAC significantly ensured downstaging. Stages of our patients statistically significantly decreased clinically and radiologically ($p<0.001$) (Fig. 4).

Evaluation of NAC effects regarding PET-CT scans revealed complete response in 20 (50%) patients, partial response in 10 (25%) patients, and stable disease in 10 (25%) patients. Comparison of these results with pathological results showed that complete response was obtained only in 8 (20%) patients, whereas partial response was obtained in 22 (55%) patients, with stable disease in the remaining 10 (25%) patients. According to these findings, specificity and sensitivity of PET-CT in assessment of complete response were 62.5% and 100%, respectively. Positive predictive ratio was 40% and negative predictive ratio was 100%. This suggests that PET-CT does not miss patients with complete response; however, as the tumor diameter and axillary lymph node involvement decrease, patients with partial response are misdiagnosed as complete response, and this was statistically significant ($p<0.01$) (Fig. 5).

According to luminal staging, 5 patients were Luminal A, 14 were Luminal B, 17 were HER2-positive, and 4 were triple-negative. Regarding this classification, response to NAC was 82% in HER2-positive patients, 100% in triple-negative patients, 80% in Luminal A patients, and 57% in Luminal B patients (Fig. 6).

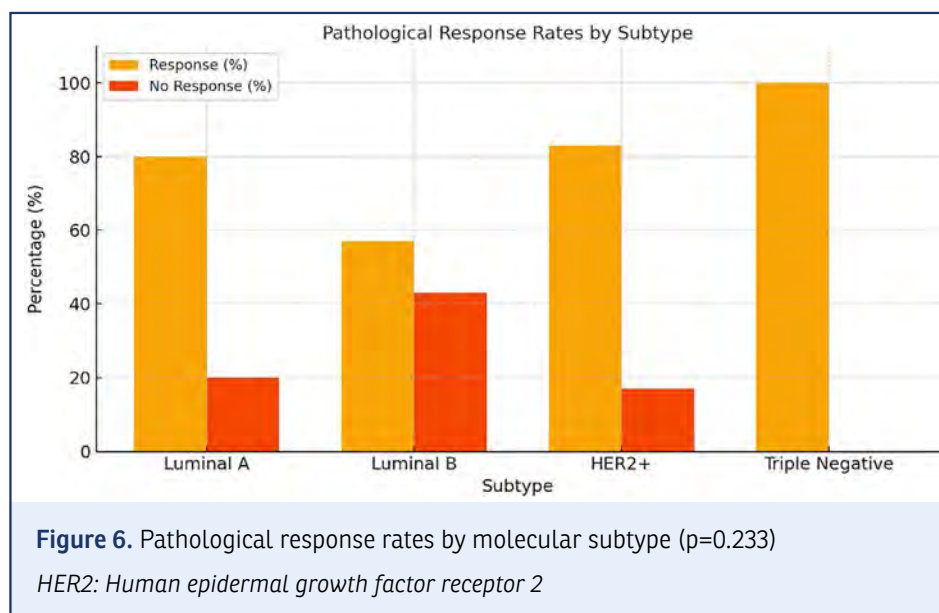


DISCUSSION

Neoadjuvant chemotherapy (NAC) was developed for the treatment of locally advanced breast cancer and is now part of the routine management of biologically aggressive disease, especially for ER-negative and/or HER2-positive cancers. NAC provides survival rates similar to adjuvant chemotherapy.^[7] Moreover, NAC gives an opportunity to perform breast-conserving surgery in patients planned to have mastectomy before NAC, either by disappearance of disease or decreasing tumor

size.^[15] Many studies suggest the possibility of sentinel lymph node biopsy (SLNB) in both node-negative and node-positive patients, thus avoiding unnecessary axillary dissections.^[16–18]

In our study, less aggressive surgical options were possible due to the downstaging effect of NAC. Moreover, 92.5% node positivity before NAC decreased to 30%, allowing avoidance of axillary dissection and its complications in most of them after chemotherapy. However, although PET-CT detected 12 lymph node metastases after NAC, patho-



logical examination revealed macrometastases in 15 patients and micrometastases in 3 patients ($p<0.05$).

Also, mean tumor size was higher in the postoperative pathological evaluation compared to the tumor size measured before NAC ($p<0.05$). These two statistically significant findings suggest to us that as the tumor size and lymph node involvement decrease, detection of tumoral activity in PET-CT decreases. Therefore, SLNB should always be performed in patients with axillary lymph nodal metastasis regression.

Response to NAC is strongly related to the tumor biology, as especially triple-negative and HER2-positive breast cancers have a better response to NAC, with even subtypes of such tumors differing significantly.^[19]

In our study, of 30 patients with complete or partial response, 14 were HER2-positive and 4 were triple-negative. Although this was not statistically significantly different ($P = 0.233$), our results about outcomes after NAC were compatible with the literature suggesting that NAC is more beneficial in such patients.^[20,21]

In studies investigating the malignant disease response following NAC, certain evaluation criteria previously applied^[22–25] were adapted into a more practical format, and patient responses were assessed using PET-CT. All patients who were found to have a complete pathological response were also evaluated as having a complete response on PET-CT. However, the detection of micrometastases or low-volume metastases in some patients deemed negative on PET-CT has raised concerns regarding the reliability of this imaging modality.

In some previous studies, patients with complete response were not operated on; however, local recurrence rates were

higher in this group. The reason for these recurrences was thought to be due to neglect of local therapies.^[13,14] In another meta-analysis, NAC was shown to be as effective as adjuvant therapy in decreasing distant recurrence and mortality but was associated with a higher incidence of local recurrence than adjuvant chemotherapy.^[12] This may partially explain the higher use of BCS after NAC compared to adjuvant chemotherapy. From our point of view, in patients with complete response, if tumor marking is not performed before NAC, providing safe tumor-free margins in such non-palpable tumors may be the cause of inadequate local control. Therefore, in order to reduce the incidence of local recurrence in patients with complete and partial response after NAC therapy, strategies like precise tumor localization, detailed pathological examination, and appropriate radiotherapy treatment should be taken into consideration.^[12]

The appropriate imaging study after NAC to assess response is still under discussion. There are studies supporting the use of PET-CT, which is currently popular but not considered the primary diagnostic test, as well as studies favoring classical dynamic contrast-enhanced MRI. Some studies suggest PET-CT as the first-line imaging modality, while others recommend MRI, leading to confusion.^[26,27] Some studies report that the sensitivity of MRI for detecting lymph node metastasis is moderate.^[28] To resolve these debates, improvements in MRI or the development of new imaging techniques are necessary.^[29] Recent studies integrating PET-CT with MRI have shown promising results.^[30]

In our study, evaluation of NAC with PET-CT revealed a positive predictive value of 40% and a negative predictive value of 100%,

which is consistent with some reports in the literature, although the limited number of patients may be a study limitation.

CONCLUSION

NAC provides BCS by shrinkage of tumor and improvement of axillary involvement in locally advanced breast cancer cases. In our study, PET-CT is shown to have high sensitivity but limited specificity and low positive predictive value in detection of complete response after NAC. These results suggest that to assess the response to NAC, PET-CT may be supported by conventional imaging studies like MRI to obtain adequate oncological and functional results while planning further treatment modalities like surgery and radiotherapy.

Disclosures

Ethics Committee Approval: The study was approved by the Istanbul Aydın University Non-interventional Clinical Research Ethics Committee (No: 165/2025, Date: 06/08/2025).

Informed Consent: Written informed consent was obtained from all patients.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Use of AI for Writing Assistance: Artificial intelligence was used to generate the figures. Graphical visualizations illustrating the distribution of clinical and pathological responses according to molecular subtypes in patients receiving neoadjuvant chemotherapy for breast cancer were generated using the artificial intelligence tool ChatGPT (GPT-5, OpenAI, August 2025 version). Aggregated, anonymized study data were provided to the AI system without any patient-identifiable information. The prompts included detailed instructions specifying the type of figure (e.g., bar chart, pie chart), axis labeling, color coding for molecular subtypes, and legend formatting. The generated figures were reviewed and finalized by the authors to ensure accuracy and consistency with the study results.

Author Contributions: Concept – S.B., S.K.; Design – S.B., Y.E.A., S.K.; Supervision – S.B., B.K., S.K.; Materials – S.B., C.E.; Data collection and/or processing – S.B., C.E., S.K.; Data analysis and/or interpretation – S.B., Y.E.A., B.K.; Literature search – S.B., Y.E.A., B.K., C.E.; Writing – S.B., C.E., S.K.; Critical review – S.K., Y.E.A., B.K., C.E., S.K.

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Retrospective Analysis of Emergency Laparotomy and Laparoscopy Outcomes: A Single-center Experience Comparing Etiologies and Early Postoperative Results in Geriatric and Adult Patients

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ABSTRACT

Objective: Emergency gastrointestinal surgery carries high postoperative complication and mortality rates, particularly in geriatric patients. Unlike elective procedures, limited preoperative optimization and frequent intraoperative contamination contribute to poorer outcomes. With the global increase in the geriatric population, understanding age-related risks is essential. This study aimed to compare early postoperative outcomes and etiological factors between adult and geriatric patients undergoing emergency laparotomy or laparoscopy.

Materials and Methods: We retrospectively reviewed adult patients undergoing emergency general surgery between November 2021 and May 2025. Trauma cases, acute appendicitis, cholecystitis, and negative explorations were excluded. Demographics, comorbidities, preoperative laboratory values, surgical indications, techniques, ICU needs, complications, length of stay, and 30-day mortality were recorded. Patients were divided into adults (18–64 years) and geriatrics (≥65 years). Postoperative complications were evaluated using Clavien–Dindo and Comprehensive Complication Index (CCI) scores. Multivariate logistic regression was used to identify predictors of 30-day mortality.

Results: Sixty patients were included (39 geriatric). Geriatric patients had higher ASA scores, more comorbidities, and lower preoperative albumin levels. Surgical indications, techniques, complication rates, and length of stay were similar between groups. Thirty-day mortality occurred in nine geriatric patients (15%), with low albumin identified as the only independent predictor.

Conclusion: Advanced age alone did not independently influence postoperative outcomes, while low serum albumin significantly affected 30-day mortality. Emergency surgical care should focus on individualized management considering patient comorbidities, nutritional status, and etiology rather than age. Future multicenter studies are needed to refine risk stratification and optimize postoperative care.

Keywords: Emergency surgery, geriatrics, laparoscopy, laparotomy

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INTRODUCTION

In emergency surgical interventions for gastrointestinal pathologies, the primary concerns are the high postoperative complication rates and elevated mortality. Early complication rates can exceed 50%, while mortality rates have been reported between 15% and 21%.^[1,2] Unlike elective surgery, the inability to optimize metabolic, pulmonary, and cardiac

comorbidities preoperatively, frequent intraoperative contamination due to gastrointestinal flora, and recent nutritional deficiencies before admission contribute to higher complication and mortality rates.

The proportion of the geriatric population—defined as individuals aged 65 years and older, accounting for approximately 15% of the global population—is steadily increas-



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ing.^[3] Analyses show that 46–63% of emergency surgeries in major centers are performed in geriatric patients.^[2,4] With advancing age, the prevalence of comorbidities, malignancies, and prior surgeries increases, leading to higher risks of complications in both open and laparoscopic procedures. Careful postoperative monitoring, along with early detection and prevention of complications, is therefore essential.

Several risk stratification systems have been developed. The Portsmouth–Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (P-POSSUM) was initially used for patients undergoing emergency laparotomy.^[5] Later, the United Kingdom's National Emergency Laparotomy Audit (NELA) calculator was developed to estimate preoperative mortality risk.^[6] Subsequently, other scoring systems were introduced, with the aim of improving postoperative outcomes after emergency laparotomy or laparoscopy.^[7–9]

This retrospective study aimed to compare outcomes between geriatric and adult patient groups by analyzing etiological factors and early postoperative results in patients who underwent open or laparoscopic emergency general surgical procedures.

MATERIALS and METHODS

Between November 20, 2021, and May 30, 2025, adult patients who presented to the emergency room (ER) and underwent emergency surgery performed by the general surgery team—either laparoscopic or open—were retrospectively reviewed. Patients requiring re-laparotomy or re-laparoscopy during the same hospitalization, trauma patients, and those undergoing emergency surgery for acute appendicitis or acute cholecystitis were excluded to maintain data homogeneity. Negative laparotomy/laparoscopy cases were also excluded. Patients newly diagnosed at emergency admission with perforation, hemorrhage, or intestinal obstruction were included.

Patient demographics (age, sex), American Society of Anesthesiologists (ASA) scores, comorbidities (diabetes mellitus [DM], chronic obstructive pulmonary disease [COPD], coronary artery disease [CAD], arrhythmia, cerebrovascular disease [CVD]), and acetylsalicylic acid use were recorded. Cancer diagnoses prior to admission, organ system involved, and previous surgery history were documented.

This study was approved by the Baškent University Institutional Review Board (Project no: KA25/282-24.07.2025). Informed consent was obtained from the patients or their first-degree relatives before surgery, after providing detailed information regarding the procedures and associated risks.

This study was conducted in accordance with the principles of the Declaration of Helsinki.

Preoperative laboratory values included white blood cell (WBC) count, neutrophil count, lymphocyte count, platelet count, serum albumin, C-reactive protein (CRP), and creatinine. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing neutrophil count by lymphocyte count, and the CRP-to-albumin ratio (CAR) was calculated by dividing CRP by albumin.

Surgical indications, surgical techniques (open/laparoscopic), ICU admission and length of stay, and postoperative complications were recorded. Complications were assessed using the Clavien–Dindo classification and the Comprehensive Complication Index (CCI).^[10,11] Hospital length of stay (LOS) and 30-day mortality rates were compared. Patients were divided into adults (18–64 years) and geriatrics (≥65 years).

This study was approved by the Institutional Review Board (project no. KA25/282, July 24, 2025). Informed consent was obtained from patients or first-degree relatives before surgery. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis was performed using SPSS software (Version 25.0, SPSS Inc., Chicago, IL, USA). Normally distributed continuous variables were described as mean ± standard deviation ($p > 0.05$ in Kolmogorov–Smirnov or Shapiro–Wilk tests, $n < 30$). Non-normally distributed continuous variables were described as median values. Continuous variables were compared using the Student t-test or Mann–Whitney U test, depending on distribution. Categorical variables were analyzed with chi-square or Fisher's exact test. Multivariate logistic regression was performed to control for confounders and identify independent predictors of 30-day mortality. Variables significant in univariate analysis ($p < 0.10$) were included in the multivariate model. Statistical significance was set at $p < 0.05$.

RESULTS

During the study period, a total of 60 patients who required emergency general surgical intervention following admission to the emergency department were included. Of these, 34 patients (56%) were female and 26 (44%) were male. Twenty-one patients (35%) aged 18–64 years were classified as Group 1, and 39 patients (65%) aged 65 years or older were classified as Group 2.

In Group 2 (≥65 years), the ASA score was significantly higher ($p = 0.009$). Analysis of comorbidities revealed that the prevalence of DM, CAD, and acetylsalicylic acid use was

Table 1. Preoperative data

Variable	Total (n=60)		Group 1 (<65, n=21)		Group 2 (≥65, n=39)		p
	n	%	n	%	n	%	
Sex							1
Female	34	56	12	57.1	22	56.4	
Male	26	43.3	9	42.9	17	43.6	
ASA score							0.001*
I-II	13	21.7	13	61.9	0	0	
III-IV	47	78.3	8	38.1	39	100	
Diabetes mellitus	49	81.7	14	66.7	35	89.7	0.039*
COPD	24	40	5	23.8	19	48.7	0.097
Coronary artery disease	46	76.7	10	47.6	36	92.3	0.001*
Disrythmia	25	41.7	6	28.6	19	48.7	0.174
Acetyl salicylic acid usage	45	75	11	52.4	34	87.2	0.005*
Cerebrovascular disease	3	5	2	9.5	1	2.6	0.278
Previous malingnancy							0.872
None	40	66.7	13	61.9	27	69.2	
Gastrointestinal tract	14	23.3	5	23.8	9	23.1	
Urinary tract	2	3.3	1	4.8	1	2.6	
Gynecologic	4	6.7	2	9.5	2	5.1	
Previous surgical intervention							0.688
None	31	51.7	12	57.1	19	48.7	
Gastrointestinal tract	15	25	3	14.3	12	30.8	
Urinary tract	3	5	1	4.8	2	5.1	
Gynecologic	7	11.7	3	14.3	4	10.3	
Hernia repair	4	6.7	2	9.5	2	5.1	
WBC counts (n/mm ³)	10350 (2260–35500)		10400 (5000–23200)		10300 (2260–35500)		0.940
Neutrophil counts (n/mm ³)	8255 (1450–33300)		7700 (2800–20600)		8400 (1450–33300)		0.871
Lymphocyte counts (n/mm ³)	1075 (300–4100)		1200 (600–3000)		900 (300–4100)		0.099
Neutrophil/lymphocyte ratio	6.8 (1.3–74)		5.9 (1.6–30.5)		8.9 (1.3–74)		0.227
CRP/albumin ratio	34.6 (0.4–198.8)		24.8 (0.4–95.9)		45.7 (0.6–198.8)		0.127
Hemoglobin (g/dL)	12.3 (±2.6)		12.5 (±2.5)		12.2 (±2.7)		0.556
Platelet (×1000/mm ³)	244 (68–544)		233 (155–544)		248 (68–483)		0.889
Creatinin (mg/dL)	1.1 (0.4–8.1)		0.9 (0.5–7)		1.1 (0.4–8.1)		0.136
CRP (mg/L)	110 (2–517)		82 (2–327)		128 (2–517)		0.288
Albumin (g/dL)	3.3 (±0.8)		3.7 (±0.7)		3.1 (±0.7)		0.002*

*: Statistically significant. ASA: American society of anesthesiologists; COPD: Chronic obstructive pulmonary disease; WBC: White blood cell; CRP: C-reactive protein

significantly higher in this group. The mean creatinine level was higher in Group 2; however, this difference was not statistically significant ($p>0.05$). A notable finding in the preop-

erative laboratory evaluation was that the albumin level was significantly lower in Group 2. Other laboratory parameters were statistically similar between the groups (Table 1).

Table 2. Operative data and outcomes

Variable	Total (n=60)		Group 1 (<65, n=21)		Group 2 (≥65, n=39)		p
	n	%	n	%	n	%	
Surgical indications							1
Intestinal obstructions	51	85	18	85.7	33	84.6	
Perforation	9	15	3	14.3	6	15.4	
Etiology							0.432
Brid	12	20	3	14.3	9	23.1	
Inflammatory	8	13.3	4	19	4	10.3	
Hernia	17	28.3	4	19	13	33.3	
Iatrogenic injury	6	10	3	14.3	3	7.7	
Malignancies	15	25	7	33.3	8	20.5	
Others	2	3.3	0	0	2	5.1	
Surgical technique							1
Open	43	71.7	15	71.4	28	71.8	
Laparoscopic	17	28.3	6	28.6	11	28.2	
Conversion to open	6	10	1	4.8	5	12.8	
ICU requirement	36	60	7	33.3	29	74.4	0.003*
ICU duration (day)	1 (0–15)		0 (0–7)		2 (0–15)		0.007*
Postoperative complication	33	55	12	57.1	21	53.8	1
CCI (%)	20.9 (0–100)		0 (0–51.7)		20.9 (0–100)		0.212
LOS (day)	6 (0–28)		7 (2–22)		6 (0–28)		0.679
30-day mortality	9	15	0	0	9	23.1	0.021*

ICU: Intensive care unit; CCI: Comprehensive complication index; LOS: Length of stay

No statistically significant differences were observed between the groups in terms of surgical indications, etiological causes, or surgical techniques. Thirty-six patients (60%) required postoperative intensive care unit (ICU) monitoring. The median ICU length of stay was 1 day (range, 0–15 days). Twenty-four patients were admitted to the surgical ward postoperatively, and none required subsequent ICU admission. Both ICU requirements and ICU duration were significantly higher in Group 2 (Table 2).

Postoperative complications (POCs) occurred in 35 patients (55%). The cumulative assessment of POCs using the Comprehensive Complication Index (CCI) yielded a mean score of 20.9 (range, 0–100). The mean length of hospital stay (LOS) was 6 days (range, 0–28 days). No statistically significant differences were observed between the groups in terms of postoperative complications, CCI scores, or LOS (Table 2).

Postoperative 30-day mortality occurred in nine patients (15%), all of whom were in Group 2, and this difference was statistically significant ($p=0.021$). Two patients, aged 66 and 87 years, died on postoperative days 2 and 4, respectively,

due to myocardial infarction. The remaining patients died as a result of abdominal septic shock.

In multivariate regression analysis, age group was not found to have a statistically significant impact on 30-day mortality. In contrast, serum albumin level was identified as the only factor significantly associated with mortality. The mean albumin level in the nine patients who died was 2.6 ± 0.8 g/dL, compared with 3.4 ± 0.7 g/dL in surviving patients ($p=0.005$). Multivariate analysis revealed that low albumin was the only independent risk factor for 30-day mortality (OR: 4.5; 95% CI: 1.4–14.4; $p=0.011$) (Table 3). The post-hoc power calculated based on serum albumin level results was found to be 72.4%.

DISCUSSION

The results of this single-center, retrospective analysis indicate that advanced age is not an independent factor affecting outcomes in patients requiring emergency general surgical interventions, whereas low preoperative serum albumin levels may influence early postoperative mortality.

Table 3. Analysis of the factors affecting 30-day mortality

Univariate analysis		Multivariate analysis		
Variable	p	OR	95% CI	p
Albumin	0.005	4.5	(1.4–14.4)	0.011

OR: Odds ratio; CI: Confidence interval

Among the patients included in our study, 52% had no history of previous abdominal surgery. Fifteen patients (25%) had a history of gastrointestinal surgery, seven patients (12%) had undergone gynecologic surgery, four patients (7%) had abdominal wall hernia repair, and three patients (5%) had a history of urologic surgery. No statistically significant differences were observed between the groups. In the study by Cihoric et al.,^[8] the rate of previous abdominal surgery was 20%, whereas Tengberg et al.^[12] reported 57%. Although considerable variation exists across centers, Jeppessen et al.^[13] reported one of the highest rates, with 64% of patients having a history of prior surgery. This heterogeneous distribution may impact intraoperative and postoperative outcomes.

A diagnosis of malignancy was present preoperatively in 20 patients (34%). Fourteen patients (23%) had gastrointestinal, four (7%) had gynecologic, and two (3%) had urologic malignancies. The groups were statistically similar in this regard. Considering the metabolic burden and adjuvant treatments, malignancy may negatively influence postoperative outcomes and is also an important factor in determining surgical strategy in emergency settings. Differentiating between palliative and definitive surgical approaches can influence both intraoperative and postoperative outcomes.^[14] In a 2023 study, Tolstrup et al.^[15] recommended intraoperatively developed, multidisciplinary strategies as the standard of care for emergency surgical interventions. They emphasized that within 30 minutes of surgery, decisions should be made to proceed with definitive, palliative, or damage control surgery, based on the patient's physiological status, to optimize outcomes.

The Clavien–Dindo (CD) classification is commonly used to grade postoperative complications (POCs).^[10] Complications are graded from I to V, with grade V representing patient death. Classification is based on the highest-grade complication. The Comprehensive Complication Index (CCI), in contrast, incorporates all complications into a single score ranging from 0 to 100, providing a more comprehensive assessment of the postoperative course.^[11] In our study, the overall incidence of complications was similar between groups (57% vs. 55%, $p=1$). Although not statistically signif-

icant, higher CCI values in the geriatric group may suggest more severe complications (0% vs. 20.9%, $p=0.212$).

In our study population, nine patients (15%) died within 30 days postoperatively. This rate aligns with literature reporting outcomes of major abdominal surgeries. Studies including less complex procedures (e.g., appendectomy, cholecystectomy) report much lower rates,^[16] whereas case series focusing on major procedures report mortality rates of 15–21%.^[17]

Low albumin levels have been repeatedly linked to adverse postoperative outcomes across general surgery. Several studies highlight the prognostic importance of albumin in emergency surgery. Hacim et al.^[17] reported significantly lower albumin in patients who died after emergency laparotomy compared with survivors (2.35 vs. 4.15 g/dL, $p<0.001$). Similarly, in a multicenter study by Cihoric et al.,^[8] analyzing 1,084 patients, low preoperative albumin was an independent risk factor for mortality. By contrast, Chua et al.,^[3] in 170 emergency laparotomy cases, found that although albumin was lower in elderly patients, it did not significantly influence survival. Variability in indications, patient populations, and functional capacity may explain these differences.

Risk stratification systems aim to predict survival following emergency laparotomy/laparoscopy. More than 20 models exist, with long-term evidence showing reductions in mortality when applied.^[8,18] Properly designed stratification contributes to standardized care, timely complication management, and improved outcomes.^[19]

Another factor reported in emergency GI surgery is subspecialist expertise. In 2019, Brown et al.^[20] demonstrated that upper and lower GI surgeons had lower complication and mortality rates than non-specialists in emergency cases. They also reported higher use of laparoscopic techniques among GI subspecialists.

Being a tertiary university hospital affiliated with the Ministry of Health provides advantages for our center. Emergency surgeries are routinely performed by two senior academic surgeons, helping standardize procedures. Additionally, extensive experience in colorectal surgery and solid-organ transplantation (liver, kidney, heart) contributes to expertise in intensive care management.

This study has limitations. As a retrospective, single-center analysis with a small sample size, its evidence level is limited and generalizability is low. Prospective studies incorporating preoperative risk stratification are expected to yield more objective findings. Larger multicenter studies, including functional assessments, are necessary for more reliable conclusions.

CONCLUSION

In conclusion, in emergency intra-abdominal general surgery, advanced age was not identified as an independent risk factor for 30-day mortality. Outcomes cannot be stratified by age alone; individualized management should consider comorbidities, nutritional status, and etiology. Low serum albumin levels may be an important determinant of outcomes. Multicenter and randomized studies are crucial for improving care and complication management.

Disclosures

Ethics Committee Approval: The study was approved by the Başkent University Medical and Health Sciences Research Board Ethics Committee (No: KA25/282, Date: 24/07/2025).

Informed Consent: Informed consent was obtained from the patients or their first-degree relatives before surgery, after providing detailed information regarding the procedures and associated risks.

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Clinical and Treatment Characteristics of Pediatric Cranial/Extracranial Germ Cell Tumors and Literature Review

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ABSTRACT

Objective: Germ cell tumors (GCTs) arise from primordial germ cells and vary greatly in clinical behavior, histology, and location. This study reviews the clinical and prognostic features of cranial/extracranial GCTs in the pediatric population through our clinical trial study and literature review.

Materials and Methods: This study is a retrospective analysis of hospital system data on children ages 0–17 with germ cell tumors. A total of 26 patients who were diagnosed and treated for germ cell tumors in the pediatric hematology and oncology department of our university hospital between 2019 and 2023 were included in this study. Patients diagnosed with both intracranial and extracranial germ cell tumors were included. Within the scope of the study, 30 studies were scanned from PubMed and the National Cancer Institute (NCI) data system, and 7 of these were found to be related to the subject and summarized in a table.

Results: The mean age of the 26 patients with GCT was 10.3 years (range: 5 months–17 years). Fifteen patients were girls (58%) and eleven were boys (42%). Three GCTs were located intracranially (3/26, 11%) and 23 extracranially (23/26, 89%). Nineteen patients (73%) received chemotherapy, and 7 patients (26%) had surgery-based treatment with no additional chemotherapy. All 3 patients with intracranial GCTs had chemotherapy plus radiotherapy (11%). In total, 2 patients (7%) died because of chemotherapy-refractory disease.

Conclusion: GCTs are highly responsive to treatment, including surgery and chemotherapy. With new studies, treatment options will be defined with a flow chart, allowing the selection of the best surgery, radiotherapy, and chemotherapy for optimal prognosis.

Keywords: Childhood, clinic, germ cell tumors, treatment, literature

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INTRODUCTION

The majority of GCTs occur in the gonads or along the mid-line structures of the body.^[1] Pediatric GCTs are rare, with an incidence of approximately 11.7 per million for boys and 6.7 per million for girls.^[2] Although rare, GCTs account for about 3% of tumors in children under the age of 15 and 14% of tumors in children and young adults between the ages of 15 and 19. Benign mature teratomas (MT) are the most common histology.^[3,4]

Although GCTs are histologically similar, classification depends on their location of origin. A germinoma in the brain

is histologically identical to a seminoma in the testicle or a dysgerminoma in the ovary.^[5] A non-germinomatous germ cell tumor (NGGCT) is typically the same as a non-seminomatous extracranial GCT and includes yolk sac tumor, embryonal carcinoma, choriocarcinoma, or mixed tumors.^[2,6]

Another classification depends on the tumor markers they secrete. Elevated alpha-fetoprotein (AFP) is markedly related to yolk sac tumor, dysgerminoma or seminoma, embryonal carcinoma, and immature teratoma.^[7] Similarly, elevated human chorionic gonadotropin (β -hCG) is related to tumors such as choriocarcinoma or embryonal carcinoma. Generally, CNS



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GCTs cannot be biopsied, and the diagnosis is based on elevated tumor markers.^[8] In the definition of germinoma, serum β -hCG is less than 50 mIU/mL, although germinomas have been reported with β -hCG levels in the range of 50–100 mIU/mL. Alpha-fetoprotein greater than 10 ng/mL is considered above normal and may suggest yolk sac tumor, immature teratoma, or NGGCT.^[9,10] In contrast, in extracranial GCTs, immature teratoma is defined as having AFP less than 1000 ng/mL.^[11]

GCT survival rates improved dramatically after the introduction of platinum-based chemotherapy in the 1980s. Five-year survival rates of 90% have been reported.^[11,12] This study aims to determine the incidence rates, treatment protocols, and outcomes of GCTs in children aged 0–17 years registered in our clinical database system and to review the limited literature.

MATERIALS and METHODS

Patient Selection and Registration

Demographic data, gender, tumor localization, treatment protocol, operation type, AFP, β -hCG, and lactate dehydrogenase (LDH) levels, tumor histology, evidence and localization of metastasis, grade, and prognosis data of patients who were followed up in our pediatric hematology clinic with a diagnosis of GCT between 2019–2023 were evaluated retrospectively. Patients with GCT between 0–17 years old were included in the study. Patients over 18 years and with diagnoses other than GCT were excluded. All data were recorded in patient charts. Verbal and written consent of the patients was obtained during the recording of all data, and the study was designed in accordance with the Helsinki Declaration. Ethical Committee approval was obtained from the Basaksehir Cam and Sakura City University Ethical Committee (KAEK 24.11.2022/2022.10.345).

Review Data

A comprehensive literature search was performed in PubMed using combinations of the keywords: childhood, germ cell tumors, clinic, treatment, literature. The search proceeded by selecting keywords, date range, and all studies related to pediatric germ cell tumors in accordance with the PRISMA guideline. In addition, references of selected papers were retrieved to find relevant studies. After primary selection, 7 of 30 studies were determined to be most relevant to pediatric germ cell tumors.

Statistical Analysis

Data were evaluated using IBM SPSS 21.0 (SPSS Statistics 21.0, Armonk, New York: IBM Corp.). The distribution of variables was examined with the Kolmogorov test. Comparisons

between groups with normal distribution were evaluated with the t-test, while groups with non-normal distribution were evaluated with the Mann–Whitney U test. Mean, standard deviation, median, value range, and ratio distribution analysis of variables, K-S Lilliefors test, variance analysis according to distribution (ANOVA/Kruskal–Wallis), chi-square, and Fisher’s exact tests for ratios were the methods used in statistical analysis.

RESULTS

The mean age of the 26 patients with GCT was 10.3 years (range: 5 months–17 years). Fifteen patients were girls (58%) and eleven were boys (42%). Three GCTs were located intracranially (3/26, 11%) and 23 extracranially (23/26, 89%). Nineteen patients (73%) received chemotherapy, and 7 patients (27%) had surgery-based treatment with no additional chemotherapy. All 3 patients with intracranial GCTs had chemotherapy plus radiotherapy (11%). In total, 2 patients (7%) died because of chemotherapy-refractory disease. Gonadal and extragonadal distribution according to age groups and gender is displayed in Table 1.

The mean AFP value was 9204 ng/mL (range: 1–121,000 ng/mL). Eight patients had germinomatous histology and nine had non-germinomatous histology. Four patients had teratoma histology, of which 2 were mature and 2 immature. Three patients had mixed histology, all boys with testicular involvement.

Table 1. Gonadal, extragonadal distribution according to age groups and gender

	Gender			
	Boy		Girl	
	n	%	n	%
Age of diagnosis				
0–5 years				
Gonadol	3	11.5	2	7
Extragonadol	0	0	3	11.5
5–10 years				
Gonadol	0	0	1	3.8
Extragonadol	0	0	0	0
10–17 years				
Gonadol	3	11.5	8	30.7
Extragonadol	5	20.2	1	3.8
Total	11	43.2	15	56.8

n: Number of patients

Table 2. Tumors according to location and histology in children aged 0 to 17 years diagnosed with GCTs

Histological type	CNS	Pelvis	Mediastinum	Retroperitoneum	Gonads (overian/testicular)	Other
Yolk sac tumor	-	2	1	-	3(2/1)	
Teratoma	-	-	2	-	2(1/1)	
^a Germinoma/ ^b Dysgerminoma/ ^c Seminoma	3(a)	-	-	-	10 (7/3) (2 cases a, 7 case b, 1 case c)	Vaginaa:1 case b
Mixed tumor	-	-	-	-	3(b)	
Choriocarcinoma	-	-	-	-	-	None
Embryonal carcinoma	-	-	-	-	-	None
Total	3	2	3		18	26

GCTs: Germ cell tumors; CNS: Serebral nervous system; ^a: Germinoma; ^b: Dysgerminoma; ^c: Seminoma.

Human chorionic gonadotropin elevation is seen in tumors such as choriocarcinoma or embryonal carcinoma. Germinoma is defined as having serum β -hCG less than 50 mIU/ml, although germinomas have been reported with β -hCG levels in the 50–100 mIU/ml range. Among extracranial NG-GCT patients, 3 had β -hCG over 50 mIU/ml (mean: 8629 mIU/ml, range: 69.9–18,965 mIU/ml). In laboratory analysis, the mean LDH level was 362 IU/L (range: 151–2000 IU/L).

All GCT patients underwent diagnostic mass biopsy and initial positron emission tomography to confirm the diagnosis, grade, and risk group of the illness. Tumors according to location and histology in children aged 0–17 years diagnosed with GCTs are displayed in Table 2.

Nineteen patients (73%) received chemotherapy, and 7 patients (27%) had surgery-based treatment with no additional chemotherapy. All 3 patients with intracranial GCTs had chemotherapy plus radiotherapy (11%). In total, 2 patients (7%) died because of chemotherapy-refractory disease.

The standard chemotherapy regimen of three drugs—bleomycin, etoposide, and cisplatin (BEP)—was the initial option in 16 extracranial GCT patients (61%). Two patients relapsed and were treated with paclitaxel, ifosfamide, and cisplatin (TIP), commonly used as salvage for pediatric malignant germ cell tumors.

All 3 patients with intracranial GCTs were germinomas and received chemotherapeutic agents including carboplatin, etoposide, and ifosfamide, or cisplatin, vincristine, and cyclophosphamide, combined with reduced-volume or local radiotherapy. One patient had treatment-refractory disease and was switched to an ifosfamide, carboplatin, and etoposide (ICE) salvage regimen.

According to risk classification, the numbers of low-, medium-, and high-risk extracranial GCT patients were 12, 3, and 8, respectively. Additionally, regarding the grading system, the total counts of Grade 1, 2, 3, and 4 extracranial GCT patients were 6, 4, 8, and 5, respectively.

DISCUSSION

Germ cell tumors account for 3% of pediatric cancers. There is a bimodal age distribution, with the first peak at ages 1–3 and the second peak during adolescence. The Turkish Pediatric Oncology Group (TPOG) and Turkish Pediatric Hematology Association (TPHA) established the pediatric cancer registry in 2002. Childhood cancer cases registered between 2002–2024, and the results of this analysis, were presented at the 2025 ASCO (American Society of Clinical Oncology) Annual Meeting. The GCT count was 5.7% of all cancer cases (3042/52,907), with a median age of 9.0 years, and male/female distribution of 1119/1916, along with 4 hermaphrodite and 3 unknown gender cases.^[13] The age distribution of our study patients was similar to these data, as the mean age of the 26 patients with GCT was 10.3 years (range: 5 months–17 years). There were 2 patients under 1 year of age (5 and 7 months), 1 patient aged 9 years, 8 patients aged 1–3 years, and 15 adolescent patients (10–19 years).

An extragonadal site of origin is more common in pediatric GCT, with yolk sac tumor being the most common histopathological finding. Origin from pluripotent cells accounts for the wide variety of tumors encountered and their multiple anatomic sites, including gonadal, sacrococcygeal, mediastinal, retroperitoneal, and other para-axial locations. Different histologic types—including endodermal sinus tumor (yolk sac tumor), germinoma (dysgerminoma, germinoma, and sem-

Table 3. Overview of the entities in the new GCT classification (WHO classification of pediatric germ cell tumors)

Non-invasive germ cell neoplasia	Intratubular germ cell neoplasia (male gonad)
Germinoma-family tumours	Gonadoblastoma (mostly in dysgenetic gonad)
Non-germinomatous germ cell tumours	Germinoma/dysgerminoma/seminoma (GDS)
	Teratoma family
	Mature cystic teratoma
	Extragenital teratoma
	Fetus in fetu
	Teratomas of the female gonad
	Monodermal teratomas
	Immature teratoma
	Pre-pubertal-type testicular teratoma
	Post-pubertal-type teratoma
	Embryonal carcinoma
	Yolk sac tumor (pre- and post-pubertal type)
	Choriocarcinoma (non-gestational)
	Malignant mixed germ cell tumor

GCTs: Germ cell tumors. Poynter et al.^[2]

inoma), embryonal carcinoma, and choriocarcinoma—may coexist in a single tumor, accounting for 25% of GCTs. The 2022 edition of the WHO (World Health Organization) classification of pediatric tumors, introduced in Virchows Archiv, is based on the first organ-independent classification of germ cell tumors, reflecting advances in molecular biology, histopathology, and clinical practice, and is displayed in Table 3.^[14]

In our study, the results for GCTs according to location and histology in children aged 0–17 years are displayed in Table 1. In Table 2, the histological diagnoses of our study patients were as follows: 15% cystic teratoma (4/26 cases), 23% yolk sac tumor (6/26 cases), 12% germinoma (3/26 cases), 11% mixed GCT (3/26 cases), 26% dysgerminoma (7/26 cases), and 12% seminoma (3/26 cases).

Figures 1 and 2 show pelvic magnetic resonance images of a patient who presented with a large sacrococcygeal mass in sagittal and axial planes. A trucut biopsy was performed from the patient, who had an 8×6×5 cm mass lesion and a serum AFP level of 49,190 ng/ml at admission. Before pathology results were obtained, the patient developed urinary and stool retention, and the mass had a history of extremely rapid growth. Since the patient’s preliminary diagnosis was germ cell tumor, the BEP chemotherapy protocol was started. After the first cycle, the patient’s AFP level decreased to 23,100 ng/ml, and after the second cycle it decreased to 2500 ng/ml. The obstructive symptoms caused by the mass disappeared, and the size of the lesion decreased by nearly 80% after 2 cycles of BEP chemotherapy (Figs. 3, 4).

Although literature data indicate dysgerminomas as the most common histological feature, our study was compatible with other histopathological studies, including those by



Figure 1. Magnetic resonance imaging of sacrum/coccyx at moment of diagnosis. (Sagittal section). A hyperintense mass on T2 sequence, measuring 85×62 mm in axial sections with heterogeneous contrast after vena cava inferior, continuing towards the perirectal region and anal canal level in the distal sacral region. Additionally, 3 lymphadenopathy (LAP) were observed in the left parailiac region, the largest of which measured 23×30 mm. An another LAP measuring 21×15 mm was observed in the left inguinal region

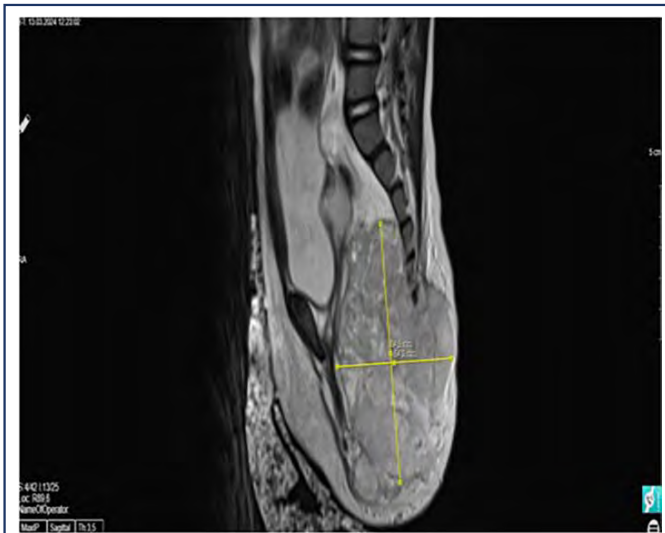


Figure 2. Magnetic resonance imaging of sacrum/coccyx at moment of diagnosis (axial section)



Figure 4. After 2 cycles of BEP chemotherapy, a 24×15mm sized residual lesion with heterogeneous enhancement is observed in the ischiorectal region of the left side of the coccyx (axial section)



Figure 3. After 2 cycles of BEP chemotherapy, an 80% remarkable rate of involution which means good response to treatment was detected in the lesion (sagittal section)

BEP: Bleomycin, etoposide, and cisplatin

Evers et al.^[15] and Schneider et al.^[16]. No cases of pure embryonal carcinoma or choriocarcinoma were encountered in our study; these histopathological types were observed only as components of mixed GCTs (5/38 cases).

When the locations of the cases are evaluated, ovarian tumors accounted for 10 cases (38%) and testicular tumors for 8 cases (30%). In total, 18 cases (69%) were gonadal and 8 (31%) were extragonadal. These findings are similar to those of Evers et al.^[15] and Malogolowkin et al.^[17].

In extracranial GCTs, AFP elevation is associated with yolk sac tumor, dysgerminoma or seminoma, embryonal carcinoma, and immature teratoma. AFP is secreted by yolk sac tumors, while β -hCG is secreted by choriocarcinoma. In our study, the mean AFP level was 9204 ng/ml (range: 1–121,000 ng/ml), which is markedly high. Additionally, among extracranial NGGCT patients, 6 had β -hCG levels over 50 mIU/ml (mean: 8629 mIU/ml, range: 69.9–18,965 mIU/ml). Tumor markers are useful both for diagnosis and for monitoring treatment response.

In our study, elevated AFP was found in 46% of patients (12/26), while elevated β -hCG was present in 11% (3/26). In contrast, in the Evers et al.^[15] study, only 13% had AFP elevation and 3% had β -hCG elevation. In testicular GCTs in our study, AFP elevation was found in 37% (3/8) and β -hCG elevation in 12% (1/8). In the study by Kutluk et al.,^[18] AFP elevation was 88% and β -hCG elevation was 48%. In our gonadal GCT group, AFP elevation was 38% (7/18) and β -hCG elevation was 5.5% (1/18), while in Bartlett et al.^[19]'s study, AFP elevation was 22% and β -hCG elevation 3%. Elevated AFP is particularly indicative of yolk sac tumor and embryonal carcinoma, while elevated β -hCG is associated with choriocarcinoma and germinomas.^[20,21]

A comprehensive literature search identified 7 of 30 studies as most relevant to the aims of this study. General clinical features of childhood GCTs based on the literature review are displayed in Table 4. In our study, elevated AFP in yolk sac

Table 4. General clinical features of childhood GCTs based on literature review

Study/(reference)	Patient count/age distribution	Gender		Histopathology	Location of GCT	Overall survival (5 years)
		Girl	Boy			
Evers et al. (Denmark) (1984–2013)/ ^[15]	57 (0–18 years)	71 (%)	29 (%)	1. Yolk Sak Tm (33%) 2. Immature Teratoma (20%) 3. Embryonal Carcinoma (18%)	1. Over (37%) 2. Sacrococcygeal (22%) 3. Testis (18%)	<2 years: 28% >2 years: 48%
Pauniah et al. (Finland) (1969–2008) (Malignant GCT)/ ^[22]	403 (0–18 years)	37 (%)	63 (%)	1. Mature Cystic Teratoma (69%) 2. Yolk Sak Tm (12%) 3. Immature Teratoma (10%) one	1. Over (46%) 2. Sacrococcygeal (16%) 3. Testis (15%)	97%
Poynter et al. (America) (1975–2006)/ ^[2]	2110 (0–19 years)	54 (%)	36 (%)	- Infant and small child: Teratoma, Yolk Sak tumor - >10 years of age Boys: Teratoma, Embryonal carcinoma, Mixed germ hc tm - >10 years of age Girls: Teratoma, Germinoma	- <4 years of age Boys: Gonadal = Extragonadal - <4 years of age K: Almost all extragonadal - >10 years of age Boys: Testicles come first - >10 years of age Girls: Ovary comes first	94%
Schneider et al. (Germany) (1981–2000)/ ^[16]	1442 (0–18 years)	56 (%)	44 (%)	1. Teratoma (37%) 2. Yolk Sak Tm (27%) 3. Germinoma (18%)	1. Ovarian (29%) 2. CNS (21%) 3. Sacrococcygeal (19%)	Undeclared
Kaatsch et al. (Germany) (1987–2011)/ ^[8]	1366 (0–14 years)	55 (%)	45 (%)	1. Yolk Sak Tm (32%) 2. Teratoma (28%) 3. Germinoma (20%)	- <4 years of age: Pelvis, testicles - 4–14 years of age: CNS, ovarian 85%, lowest	92% (gonadal: 96–98%; highest) (Intracranial: 81% (Benign teratomas: 96%, Malignant GCT: 46% Undeclared
Malogolowkin et al. (America) (1941–1986)/ ^[17]	188 (0–18 years)	69 (%)	31 (%)	1. Benign Teratoma (56%) 2. Malignant Teratoma (26%) 3. Germinoma (20%)	1. Ovary (39%) 2. Sacrococcygeal (36%) 3. Testis (7%)	81% (Benign teratomas: 96%, Malignant GCT: 46% Undeclared
Miao et al. (China) (2005–2015)/ ^[32]	127 (0–14 years)	58 (%)	32 (%)	- Girls: 1. Mature Cystic Teratoma (86%) 2. Immature Teratoma (7%) 3. Dysgerminoma (3%), Yolk Sak Tm (3%) - Boys: 1. Mature Cystic Teratoma (58%) 2. Yolk Sak Tm (36%) 3. Immature Teratoma (4%)	- Girls: 55% right 45% left - Boys: 53% right 47% left	OS rate of our study (2019–2023) is 87%. The EFS rate was found to be 84.5%.
Our study	26 (0–17 years)	61 (%)	39 (%)	1. Dysgerminoma (26%) 2. Yolk sac tumor (23%) 3. Cystic teratoma (15%)	1. Ovarian (38%) 2. Testicular (30%) 3. Other (CNS, Sacrococcygeal mediastinal, other extragonadal) (32%)	

CNS: Serebral nervous system; OS: Overall survival; EFS: Event free survival

Table 5. The chemotherapy regimens and recommended risk categorization in pediatric extracranial germ cell tumors NHI (National Health Institute) Childhood Extracranial Germ Cell Tumors Treatment (PDQ®) 2024

Risk category	Site of tumor			Surgery and chemotherapy
	Testicular	Ovarian	Extragonadal	
Low-risk	Stage I*	None	None	Surgery alone
Intermediate-risk	Stage II-IV	Stage I-III	Stage I-II	Surgery+PEBx3
High-risk	None	Stage IV	Stage III-IV	Surgery+PEBx4

*: Stage I testicular tumors that do not show fall of α FP as expected or show a rise of α FP after initial decline should be put in intermediate-risk category and receive adjuvant chemotherapy PEB Cisplatin, etoposide, and bleomycin. Evers et al.,^[15] NHI (National Health Institute) Childhood Extracranial Germ Cell Tumors Treatment (PDQ®) 2024.^[28,29]

tumors and elevated β -hCG in mixed GCTs were consistent findings, with β -hCG elevations related to choriocarcinoma or germinoma components.

According to the Children's Oncology Group (COG) risk classification, the numbers of low-, medium-, and high-risk extracranial GCT patients were 12, 3, and 8, respectively. By grading system, the total numbers of Grade 1, 2, 3, and 4 extracranial GCT patients were 6, 4, 8, and 5, respectively.

In the study by Pauniah et al.,^[22] stage 1 cases were the majority, whereas in our study stage 3 cases predominated. However, low-grade, low-risk testicular tumors were still the majority in our study, similar to Pauniah's findings. Likewise, in the study by Kutluk et al.^[18] on testicular GCTs, stage 1 cases were most common, while in Terenziani et al.^[23]'s study on ovarian GCTs, stage 3 cases predominated. Both studies showed outcomes similar to ours.

GCTs most commonly spread via hematogenous and lymphatic pathways, with distant metastases typically occurring in the lungs, liver, and bone. In our study, distant metastases occurred in 3 patients (11.5%, 3/26), all with high-risk Grade 4 yolk sac tumors. Two were ovarian and one was mediastinal.

The first approach in GCT treatment is surgical excision. In our study, surgery was performed in all cases: 12/26 (46%) underwent total excision with oophorectomy (malignant cases), 8/26 (30%) total excision with orchiectomy (malignant cases), and 6/26 (23%) biopsy. Malogolowkin et al.^[17] reported 89% total excision and 11% subtotal excision or biopsy. Suita et al.^[24] reported 76% total excision and 24% subtotal excision or biopsy. Both studies showed similar rates to ours. For mature cystic teratomas, total surgical excision alone is considered sufficient treatment,^[25,26] consistent with our 5 cases, all excised successfully.

Of the 6 non-excisable cases, 3 were intracranial germinomas and 3 mediastinal yolk sac tumors. These tumor types present greater surgical challenges due to their locations, which likely explains their lower excision rates compared with other histopathological types.

Treatment of GCTs typically includes chemotherapy (CT) and/or radiotherapy (RT) after surgical excision. The overall recommendation is 4 cycles of BEP (cisplatin, etoposide, and bleomycin per cycle) for standard-risk patients. An alternative strategy to reduce toxicity in standard-risk patients is carboplatin, a cisplatin analogue with fewer long-term effects. Chemotherapy regimens and recommended risk categories in pediatric extracranial GCTs from the NHI Childhood Extracranial Germ Cell Tumors Treatment (PDQ®) are displayed in Table 5.^[27]

In our series, 19 patients (73%) received chemotherapy and 7 (27%) had surgery only. All 3 intracranial GCT patients received chemotherapy plus RT. BEP was the first-line regimen for extracranial GCTs, while 2 relapsed cases were treated with TIP (paclitaxel, ifosfamide, cisplatin). Intracranial germinoma patients received carboplatin+etoposide protocols with RT.^[28]

Of the intracranial GCT patients, all received combinations of chemotherapy and RT, with only 1 experiencing refractory disease and requiring TI-ICE. In total, 5 patients died due to chemotherapy-refractory disease.

In our study of 26 pediatric GCT cases, 2 patients (7%) died, 3 (11%) relapsed, and 21 (80%) were cured. The overall survival rate (OS) was 93%. However, this must be interpreted cautiously due to short-term follow-up in the Kaplan-Meier analysis. In Terenziani et al.^[23]'s study on ovarian GCTs, the 5-year OS was 98.5% and event-free survival (EFS) was 84.5%.^[22] Our OS rates are close, but our EFS rates are lower.

In our intracranial GCT subgroup, the OS was 100% and EFS 83.3%, compared with Voirin et al.,^[29] who reported both 100%, and Akyüz et al.,^[30] who reported OS of 62.5% and EFS of 37.5%. These discrepancies may be explained by short follow-up duration, small sample size, and differences in chemotherapy protocols, particularly before platinum-based regimens.

Long-term adverse effects in pediatric GCT survivors remain insufficiently studied due to a lack of robust longitudinal data. The Platinum Study, reported in the COG blueprint 2023, has been instrumental in defining late effects in adults with testicular GCTs.^[31] Known complications include ototoxicity, peripheral neuropathy, secondary malignancies, and cardiovascular disease. Since children and adolescents receive comparable chemotherapy regimens, it is plausible they experience similar late effects, emphasizing the importance of systematic long-term follow-up.

Limitations

This study has several limitations. The age range (0–17 years) excludes older adolescents and young adults (up to 25 years), which may limit generalizability. In our country, the national health insurance system does not support patients aged 18–25 as pediatric cases, so they cannot be treated by pediatric oncologists. Future studies should include this group to provide more representative data.

Another limitation is the short follow-up, which affects OS and EFS rates in the Kaplan–Meier analysis. A larger, multicenter design would help overcome sample size limitations and provide stronger evidence for pediatric GCT outcomes.

CONCLUSION

Proper surgical resection and staging techniques are critical to achieving the best outcomes and ensuring that patients receive appropriate treatment without unnecessary overtreatment or inadequate therapy. Collaborations with international centers and new studies will help reduce treatment-related toxicities and late effects while improving outcomes for high-risk patients. Future multicenter trials and international collaborations to standardize treatment protocols are strongly needed.

Disclosures

Ethics Committee Approval: The study was approved by the Basaksehir Cam and Sakura City University Clinical Research Ethics Committee (No: 2022.10.345, Date: 24/11/2022).

Informed Consent: Obtained from patients' parents. Written informed consent was provided for publication of clinical details and identifying images.

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Ultrasound-guided Dextrose Prolotherapy for Refractory Piriformis Syndrome: A Retrospective Study

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ABSTRACT

Objective: Piriformis syndrome is a neuromuscular condition characterized by sciatic nerve compression by the piriformis muscle, resulting in buttock pain radiating to the posterior thigh. While physical therapy and corticosteroid injections are commonly used, treatment-refractory cases remain challenging. Dextrose prolotherapy is a regenerative technique gaining interest, but its efficacy in piriformis syndrome is not well established.

Materials and Methods: This retrospective study included 43 patients diagnosed with piriformis syndrome based on clinical criteria, including a positive FAIR test and at least one additional provocative maneuver. Patients received three sessions of ultrasound-guided injections of 5% dextrose (1 mL per site, 5 mL total) targeting the piriformis musculotendinous junction at 3-week intervals. Pain and functional status were assessed at baseline, 1-month, and 3-month follow-ups using the visual analog scale (VAS) and Oswestry disability index (ODI). Patient satisfaction and adverse events were also recorded.

Results: Mean VAS scores decreased from 7.6 to 2.3 ($p < 0.001$), and median ODI scores improved from 48 to 20 over three months ($p < 0.001$). Eighty-eight percent of patients reported satisfaction with the treatment. No major complications were observed; minor adverse events were mild and self-limiting.

Conclusion: Ultrasound-guided dextrose prolotherapy significantly reduced pain and improved function in patients with refractory piriformis syndrome. These findings support its role as a minimally invasive treatment option, warranting further prospective studies.

Keywords: Dextrose, piriformis syndrome, prolotherapy, ultrasound-guided injections, sciatic pain

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INTRODUCTION

Piriformis syndrome is a neuromuscular disorder caused by compression or irritation of the sciatic nerve by the piriformis muscle, leading to buttock pain radiating to the posterior thigh, often mimicking sciatica. While the exact mechanisms are still unclear, inflammation, muscle spasm, and hypertrophy of the piriformis muscle are thought to contribute to sciatic nerve entrapment.^[1,2] The piriformis muscle originates from the anterior sacrum (S2–S4) near the sacroiliac joint and inserts on the greater trochanter of the femur.^[1]

Essentials for the diagnosis are tenderness over the muscle, positive provocative tests like Lasègue's and FAIR (flex-

ion, adduction, internal rotation) tests, and buttock pain extending along the sciatic nerve route that worsens with hip flexion. The FAIR test, which reproduces pain through hip positioning, is highly sensitive for detecting sciatic nerve irritation by the piriformis muscle.^[3] Advanced cases may present with gluteal muscle atrophy.^[4,5]

Standard treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), physical therapy, and corticosteroid injections. However, regenerative and proliferative injection therapies, such as dextrose prolotherapy, are gaining attention. Prolotherapy involves injecting proliferant agents, like dextrose, to stimulate controlled inflammation and promote repair of damaged connective tissues.^[6,7]



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Prolotherapy has shown efficacy in musculoskeletal conditions like tendinopathies and various spinal conditions—sacroiliac joint dysfunction and instability in particular—where a satisfactory proportion of the patients achieved clinically meaningful functional gains.^[6,8] Despite these findings, the efficacy of prolotherapy in piriformis syndrome is underexplored. Prolotherapy may offer a cost-effective, minimally invasive option for chronic pain management targeting the piriformis musculotendinous junction, which has limited vascular supply.^[9] This study evaluates the efficacy of dextrose prolotherapy in patients with piriformis syndrome refractory to conservative treatments.

MATERIALS and METHODS

Study Design

This retrospective study analyzed hospital records of patients treated between April 1, 2022, and April 1, 2025, at a single tertiary physical medicine and rehabilitation center. University of Health Sciences, Istanbul Kanuni Sultan Suleyman Training and Research Hospital Ethic Commitment approved the protocol (ID: 2022.03.78) on 28/03/2022, and informed consent was waived due to the retrospective design, with all data de-identified to protect patient confidentiality. The study was conducted in accordance with the Declaration of Helsinki.

Participants

Forty-three patients with chronic piriformis syndrome were included, based on prior studies of injection therapies, to achieve sufficient statistical power to detect meaningful changes in pain and function (3). Inclusion criteria were: (1) age 18–65 years; (2) physiatrist-diagnosed piriformis syndrome via clinical findings, including a positive FAIR test, tenderness at the piriformis muscle, and at least one additional provocative test (one of Lasègue's, Freiberg's, Beatty's, or Pace's maneuver);^[10,11] (3) symptoms persisting for more than 3 months despite conservative treatments; and (4) complete records for ultrasound-guided dextrose prolotherapy with pre-treatment, 1-month, and 3-month follow-up evaluations.

Baseline data included age, sex, body mass index (BMI), symptom duration, and functional status. To minimize selection bias, patients were systematically selected by sorting records chronologically by treatment date and including every third eligible patient. Exclusion criteria included lumbar disc herniation (confirmed by magnetic resonance imaging), prior lower back or hip surgery, trauma to the lumbar/gluteal region, recent injection therapy applied to the piriformis region (within 6 months), cognitive impairment, lumbosacral radiculopathy, or significant systemic

metabolic diseases (uncontrolled diabetes, hypertension, cardiac failure, active inflammatory conditions).

Intervention

Patients received ultrasound-guided dextrose prolotherapy targeting the piriformis musculotendinous junction and enthesis, using a low-frequency curvilinear transducer (1–7 MHz) operated by a physiatrist trained in musculoskeletal ultrasound. The treatment solution consisted of 5% dextrose, with 1 mL injected per point across 5 sites (total 5 mL per session), targeting areas of maximum tenderness around the musculotendinous junction. Injections were administered at 3-week intervals for three sessions (9 weeks total). Patients continued standard exercises (piriformis stretching, core stabilization) post-injection to support recovery.

Outcome Measures

Pain levels were measured using the Visual Analog Scale (VAS), a widely recognized tool for quantifying pain intensity.^[12] This scale ranges from 0 to 10, where 0 represents no pain and 10 signifies the worst imaginable pain. Patients were asked to rate their pain based on their subjective experience, providing a straightforward and reliable metric for assessing pain severity.

Functional disability was assessed using the Oswestry Disability Index (ODI), a validated questionnaire designed to evaluate the impact of pain on daily functioning.^[13] The ODI consists of 10 domains—pain intensity, lifting, self-care, walking, sitting, sexual function, standing, social life, sleep quality, and travel—each scored on a 0–5 scale. The total score is expressed as a percentage (0–100%), with higher scores indicating greater disability. This comprehensive tool captures the multidimensional impact of pain on patients' lives.

Assessments occurred at baseline, 1-month, and 3-month follow-ups. Patient satisfaction was recorded once at the 3-month follow-up as a secondary outcome, rated as "satisfied" or "not satisfied" based on self-reported symptom relief.

Data Collection and Analysis

Data were extracted by the principal investigator, blinded to outcomes during extraction to reduce bias. Descriptive statistics included means±standard deviations for normally distributed variables and medians (interquartile range) for non-normal variables, assessed via the Shapiro–Wilk test. Repeated measures ANOVA with post-hoc Bonferroni tests analyzed normally distributed data, while the Friedman test with Wilcoxon signed-rank tests evaluated non-parametric data. Missing data were addressed using listwise deletion, with sen-

Table 1. Baseline characteristics of participants

Characteristic	Value
Age (years, mean±SD)	47.6±9.2
Sex (female/male, n)	28/15
BMI (kg/m², mean±SD)	26.3±3.4
Symptom duration (months, median [IQR])	6 [4–12]
Baseline VAS (mean±SD)	7.6±1.1
Baseline ODI (% , median [IQR])	48 [44–54]

SD: Standard deviation; BMI: Body mass index; IQR: Interquartile range; VAS: Visual analog scale; ODI: Oswestry disability index

sitivity analyses to assess impact. Statistical significance was set at $p<0.05$, and analyses were conducted using IBM SPSS Statistics version 25.0 (Armonk, New York, IBM Corp.).

RESULTS

Of the 67 patients initially screened for eligibility, 43 patients met the inclusion criteria and were included in the final analysis. The participants included 28 females (65%) and 15 males (35%), with a mean age of 47.6 ± 9.2 years (range: 28–62 years). The mean body mass index was 26.3 ± 3.4 kg/m², with 49% classified as overweight and 14% as obese. The right side was more commonly affected than the left (58% vs. 42%). The median symptom duration before prolotherapy treatment was 6 months (IQR: 4–12 months, range: 3–24 months). At baseline, participants reported severe pain with a mean VAS score of 7.6 ± 1.1 (range: 5–10) and significant functional disability with a median ODI score of 48% (IQR: 44–54%, range: 38–62%). Complete baseline characteristics are presented in Table 1.

Pain severity demonstrated statistically significant improvement over the study period ($p<0.001$). Mean VAS scores decreased from 7.6 ± 1.1 at baseline to 2.5 ± 1.0 at the 1-month follow-up, representing a mean reduction of 5.1 points (67% improvement). This improvement was sustained at the 3-month follow-up, with mean VAS scores of 2.3 ± 0.9 , corresponding to a total mean reduction of 5.3 points (70% improvement) from baseline. Pain reduction was statistically sig-

nificant from baseline to both 1-month ($p<0.001$) and 3-month ($p<0.001$) follow-up points. No statistically significant change was observed between the 1-month and 3-month assessments ($p=0.12$), indicating sustained therapeutic benefit.

Functional status showed parallel improvements to pain scores. ODI scores improved significantly over time ($p<0.001$), decreasing from a median of 48 (IQR: 44–54) at baseline to 22 (IQR: 18–26) at the 1-month follow-up, representing a median improvement of 26 points (54%). At the 3-month follow-up, the median ODI score was 20 (IQR: 16–24), corresponding to a total median improvement of 28 points (58%) from baseline. Similar to pain outcomes, post-hoc analyses revealed significant functional improvements from baseline to both 1-month ($p<0.001$) and 3-month ($p<0.001$) follow-up, with no statistically significant change between the two follow-up time points, confirming sustained functional recovery. The complete pain and disability outcome data are presented in Table 2.

Patient satisfaction rates were high, with 38 of 43 patients (88%) reporting satisfaction with the treatment outcome at the 3-month follow-up. The 5 patients (12%) who reported dissatisfaction had poor improvements in both pain and functional outcomes.

Pairwise comparisons between time points demonstrated that the majority of improvement occurred between baseline and the 1-month assessments, with smaller additional gains observed between the 1-month and 3-month follow-up that did not reach statistical significance. This pattern suggests that maximal therapeutic benefit is achieved relatively early in the treatment course and is subsequently maintained. Detailed statistical comparisons with confidence intervals are provided in Table 3.

The treatment was well tolerated, with an excellent safety profile. No major complications, infections, or serious adverse events were reported during the study period. Minor adverse events were documented in 25 patients (58%), all of which were mild and self-limiting. The most common adverse event was mild injection site pain, occurring in 12 patients (28%) and resolving within 24–48 hours. Temporary

Table 2. Primary outcome measures over time

Outcome measure	Baseline (mean±SD / median [IQR])	1-month (mean±SD / median [IQR])	3-month (mean±SD / median [IQR])	p
VAS pain score (0–10)	7.6±1.1	2.5±1.0	2.3±0.9	<0.001
ODI score	48 [44–54]	22 [18–26]	20 [16–24]	<0.001

SD: Standard deviation; IQR: Interquartile range; VAS: Visual analog scale; ODI: Oswestry disability index

Table 3. Pairwise comparison (post-hoc analysis of changes between time points)

Comparison	VAS pain score (mean difference %95 CI)	ODI score (mean difference %95 CI)
Baseline vs 1-month	-5.1 (-5.6 to -4.6)***	-26 (-30 to -22)***
Baseline vs 3-month	-5.3 (-5.8 to -4.8)***	-28 (-32 to -24)***
1-month vs 3-month	-0.2 (-0.5 to 0.1) ^{NS}	-2 (-4 to 0) ^{NS}

Statistical significance: ***: $p < 0.001$. VAS: Visual analog scale; ODI: Oswestry disability index; CI: Confidence interval; NS: Not significant ($p > 0.05$)

Table 4. Reported adverse events during treatment period

Adverse event	n	%	Severity	Resolution time
Mild injection site pain	12	28	Mild	24–48 hours
Temporary stiffness	8	19	Mild	2–3 days
Minor bruising	5	12	Mild	5–7 days
No adverse events	18	42	N/A	N/A
Major complications	0	0	None	N/A

N/A: Not applicable

stiffness was reported by 8 patients (19%) and resolved within 2–3 days. Minor bruising at injection sites occurred in 5 patients (12%) and resolved within 5–7 days. Importantly, no patients discontinued treatment due to adverse events. Complete safety data are presented in Table 4.

DISCUSSION

Results of this study indicate that ultrasound-guided dextrose prolotherapy in refractory piriformis syndrome considerably improves function and reduces pain. The sustained improvements in VAS and ODI scores at 3 months suggest prolotherapy as a potential, minimally invasive treatment option.

These findings align with past studies that reported significant pain reduction with ultrasound-guided local anesthetic injections for piriformis syndrome, though our study uses dextrose to promote regenerative repair rather than temporary analgesia.^[3,14,15] The sustained ODI improvements mirror benefits seen in other enthesopathies, such as lateral epicondylitis.^[16] Prolotherapy likely stimulates fibroblast proliferation and collagen deposition, strengthening the piriformis musculo-tendinous junction and alleviating sciatic nerve irritation.^[6,16] The precise injection protocol (5% dextrose, 1 mL per site, 3 sessions) and ultrasound guidance enhance reproducibility, similar to structured regimens in low back pain studies.^[17]

The significant pain reduction observed (VAS improvement of 5.3 points) can be attributed to dextrose prolotherapy's well-established cellular mechanisms. Dextrose solutions

act by dehydrating cells at the injection site, leading to local tissue trauma, which in turn attracts granulocytes and macrophages and promotes healing.^[18] This cellular response is particularly relevant for piriformis syndrome, where chronic inflammation and tissue degeneration at the musculotendinous junction contribute to sciatic nerve compression.^[19] The observed sustained improvement at 3 months in our cohort supports the hypothesis that dextrose-induced tissue regeneration provides long-lasting structural benefits rather than merely symptomatic relief.

The cost-effectiveness profile of dextrose prolotherapy also merits consideration in the current healthcare landscape. Unlike botulinum toxin injections, which require specialized storage and handling,^[20,21] platelet-rich plasma injections, which are challenging to standardize and prepare,^[22] or repeated corticosteroid injections that carry cumulative risks,^[21] dextrose prolotherapy offers a simple, affordable intervention with minimal infrastructure requirements. The comprehensive safety profile, with no major complications among 43 patients, adds to the growing body of evidence supporting prolotherapy's safety in clinical practice.

While the diagnostic criteria for piriformis syndrome continue to evolve in the literature, our study employed well-established clinical diagnostic criteria, including the highly sensitive FAIR test and multiple provocative maneuvers, which have been validated in previous piriformis syndrome research.^[1,2,4] The reliance on comprehensive clinical examina-

tion by experienced physiatrists, combined with our rigorous exclusion criteria that eliminated patients with lumbar disc herniation, lumbosacral radiculopathy, and other differential diagnoses, enhanced diagnostic specificity and strengthened the internal validity of our findings.^[3] The consistency of treatment response across our cohort (91% achieving significant improvement) further supports the accuracy of our diagnostic approach and suggests that the clinical criteria used were sufficiently robust to identify patients who would benefit from this intervention.

Several limitations must be acknowledged in interpreting our findings. The retrospective design naturally limits causal inference and introduces potential selection bias, despite the pseudo-randomization process. The single-center design also limits generalizability, as treatment protocols and patient populations may vary across different healthcare settings. The absence of a control group prevents definitive attribution of improvements to prolotherapy versus natural history or concurrent exercises, and the lack of blinding may have influenced patient-reported outcomes, particularly satisfaction ratings. In addition, while the 3-month follow-up period demonstrates sustained improvement, a longer period may be necessary to assess the long-term durability of treatment effects or identify delayed complications.

An additional limitation of this study is the reliance on clinical diagnostic criteria without routine imaging for all patients. While our diagnostic approach employed well-established clinical tests, including the FAIR test and multiple provocative maneuvers, and we excluded patients with lumbar disc herniation confirmed by MRI, we did not perform routine imaging (such as MRI or ultrasound) for all patients to visualize piriformis muscle abnormalities directly. Future studies incorporating standardized imaging protocols could enhance diagnostic precision and provide additional morphological data to complement clinical findings.

This study represents the first systematic evaluation of dextrose prolotherapy specifically for piriformis syndrome, addressing a significant gap in regenerative medicine applications for peripheral nerve entrapment syndromes. The standardized ultrasound-guided injection protocol provides a reproducible framework that can be adopted by other practitioners and may serve as a foundation for future controlled trials. This provides a foundation for future research directions, including prospective randomized controlled trials comparing dextrose prolotherapy to established treatments, dose-response studies to optimize injection protocols, and long-term follow-up studies to assess the durability of treatment effects.

CONCLUSION

Ultrasound-guided dextrose prolotherapy appears to be a safe and effective treatment for refractory piriformis syndrome, significantly reducing pain and improving function. These results support its role as a minimally invasive alternative, with a structured injection protocol enhancing clinical outcomes. Prospective, controlled trials are needed to compare prolotherapy with other interventions and to refine treatment protocols.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences, Istanbul Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (No: 2022.03.78, Date: 28/03/2022).

Informed Consent: Informed consent was waived due to the retrospective design, with all data de-identified to protect patient confidentiality.

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Comparison of Excessive Daytime Sleepiness Among Clinical Types of Obstructive Sleep Apnoea Syndrome

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ABSTRACT

Objective: Excessive daytime sleepiness (EDS) is a key symptom in obstructive sleep apnoea syndrome (OSAS). The relationship between EDS and polysomnographic parameters across different OSAS phenotypes has not been fully elucidated. This study evaluated demographic characteristics, polysomnographic findings, and EDS severity among OSAS clinical phenotypes (classical OSAS, REM [rapid eye movement]-related OSAS, positional OSAS [P-OSAS], and REM+positional OSAS) and subgroups defined according to Epworth Sleepiness Scale (ESS) scores.

Materials and Methods: A retrospective analysis was conducted on patients with OSAS diagnosed by polysomnography. Participants were categorised into clinical phenotypes and stratified into the EDS (ESS score >10) and non-EDS (ESS score ≤10) groups. Demographic data, apnoea–hypopnea index (AHI), oxygen desaturation index (ODI), minimum oxygen saturation, and heart rate (HR) parameters were compared between the EDS and non-EDS groups.

Results: EDS was associated with male sex, the presence of comorbidities (particularly hypertension), and higher AHI, BMI, and body weight values ($p<0.05$). The highest EDS prevalence was observed in the classical OSAS group, followed by the P-OSAS group ($p<0.05$). Patients with EDS showed lower mean and minimum oxygen saturation levels and higher ODI values ($p<0.05$). No significant difference was observed in HR values among the OSAS phenotypes or between the ESS-based subgroups.

Conclusion: EDS was associated with OSAS disease severity. Among the clinical phenotypes, the risk of EDS was observed to be highest in patients with classical OSAS and P-OSAS. The early identification of OSAS subtypes, particularly the REM- and position-dependent forms, is essential for personalised treatment and improved clinical outcomes.

Keywords: Excessive daytime sleepiness, obstructive sleep apnoea syndrome, phenotype, positional

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INTRODUCTION

Obstructive sleep apnoea syndrome (OSAS) is a prevalent medical condition that affects approximately 24% of men and 9% of women, characterised by recurrent episodes of upper airway obstruction, oxygen desaturation, and sleep fragmentation.^[1] Existing evidence indicates that upper airway obstruction severity in OSAS varies with body position; in the supine position, the effect of gravity on the mandible and tongue leads to more pronounced upper airway obstruction, increasing OSAS severity.^[1] Approxi-

mately 60% of patients with OSAS demonstrate a predominance of respiratory events while sleeping in the supine position;^[2,3] in ~20% of patients, these events occur exclusively during supine sleep.^[3,4]

Medullary sensitivity to hypoxia and hypercapnia is known to decrease during rapid eye movement (REM) sleep, predisposing individuals to a higher frequency of respiratory events in this sleep stage.^[5] However, some researchers have reported no significant apnoea–hypopnea index (AHI) differences between the REM and non-REM (NREM) sleep stages.^[6,7]



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OSAS is conventionally classified according to the total AHI, without considering the influence of body position or sleep stages.^[4,5] However, definitions of positional and REM-related OSAS (P-OSAS and REM-OSAS, respectively) vary across studies. The most widely accepted criteria define REM-OSAS as an AHI during REM sleep (AHI-REM) at least twice that observed during NREM sleep (AHI-NREM) in patients with a total AHI of >5 events/hour. Similarly, P-OSAS is identified as an AHI in the supine position (AHI-supine) that is at least twice that in nonsupine (lateral) positions (AHI-lateral).^[2,8]

Findings related to increased daytime sleepiness in OSAS patients remain inconsistent. Although the findings of one study demonstrated that patients with P-OSAS experienced increased sleepiness in comparison with those with non-positional OSAS, another study found the opposite.^[2,3] Excessive daytime sleepiness (EDS) is associated with impaired attention, mood disturbances, and other neurocognitive deficits.^[4,5] The relationship between the Epworth Sleepiness Scale (ESS) score and OSAS severity remains under investigation. EDS is potentially associated with more nuanced and complex disease parameters in addition to total AHI; for example, Punjabi et al. found no significant association between REM-OSAS and EDS, whereas two other studies demonstrated a positive association.^[8,9] Therefore, variations in AHI related to sleep stage and body position should be considered in addition to total AHI when interpreting OSAS severity and planning treatment strategies.

In this study, we aimed to compare polysomnographic findings and levels of daytime sleepiness among OSAS patients according to their clinical subtypes and to review the corresponding treatment approaches.

MATERIALS and METHODS

This study included 290 patients aged 18–66 years who were diagnosed with OSAS via clinical and polysomnography findings. The patients were followed at the Sleep Center between January 2020 and January 2025, Bakırköy Dr. Sadi Konuk Training and Research Hospital. The inclusion criteria were as follows: age ≥ 18 years, total AHI >5 events/hour, a minimum of 4 hours of total sleep time (TST), at least 15 minutes of REM sleep, and at least 30 minutes spent in both supine and nonsupine positions during the study.

Patients who had previously been diagnosed with OSAS or received treatment, had malignancies and/or psychiatric diseases, did not provide consent, did not complete the full diagnostic process and questionnaire, did not receive at least a primary education, or had uncontrolled chronic diseases

(e.g., uncontrolled hypertension [blood pressure >140/90 mm Hg under medical treatment], diabetes [HbA1c level >8% under medical agents]), or cerebrovascular disease with modified Rankin Scale [mRS] scores >2 were excluded.

Our study was conducted in accordance with the tenets of the Declaration of Helsinki and approved by the local ethics committee (decision date: June 25, 2025; number: 11/05). Written informed consent was collected from each participant. No artificial intelligence (AI) tools were used.

Demographic and physical data (age, weight, and body mass index [BMI]), smoking status, comorbidities, and OSAS-related symptoms were recorded. Polysomnographic signals included electroencephalography (EEG), electro-oculography (EOG), submental electromyography (EMG), nasal pressure airflow, electrocardiography (ECG), thoracoabdominal respiratory effort, and oxygen saturation via pulse oximetry. Respiratory events were scored per the standard criteria established by the American Academy of Sleep Medicine (AASM) Task Force.^[10] The AHI was determined as the number of apnoeas and hypopneas per hour of estimated TST. OSAS severity is defined on the basis of the AHI. There are three severity classifications: mild (AHI 5.0–14.9 events/hour), moderate (AHI 15.0–29.9 events/hour), and severe (AHI ≥ 30.0 events/hour).^[10]

Polysomnographic assessments included the AHI, AHI-REM in patients with REM-OSAS, supine AHI in those with P-OSAS, TST, sleep efficiency, mean oxygen saturation (mean-SaO₂), minimum oxygen saturation (min-SaO₂), the oxygen desaturation index (ODI), and the mean heart rate (HR).

REM-OSAS was identified as a total AHI of >5/hour and a REM-AHI at least twice as high as the NREM-AHI. P-OSAS was defined as a total AHI of >5/hour with a supine AHI at least twice that of the nonsupine AHI.^[10] We divided the patients into four groups: classical OSAS, REM-OSAS, P-OSAS, and REM+P-OSAS.

Subjective daytime sleepiness was assessed via the ESS score, obtained using a self-administered questionnaire. The validity and reliability of the ESS in Turkish populations have been previously confirmed.^[11] Patients were asked to rate their likelihood of falling asleep during eight routine activities over the past month, using a scale from 0 to 3. The total ESS score was calculated as the sum of the eight items, ranging from 0 to 24, with higher scores (ESS >10) indicating increased levels of daytime sleepiness.^[12] Accordingly, the study cohort was stratified into two subgroups (ESS ≤ 10 and ESS >10) to explore factors potentially associated with EDS.

Table 1. Comparison of study subgroups and demographic values according to Epworth sleepiness scale score

	ESS score≤10		ESS score>10		Total		Chi-square	p
	n	%	n	%	n	%		
Female	65	62.5	39	37.5	104	100	5.340	0.021*
Male	90	48.4	96	51.6	186	100		
Smoking (-)	89	50.3	88	49.7	177	100	1.830	0.176
Smoking (+)	66	58.4	47	41.6	113	100		
Comorbidity (-)	59	68.6	27	31.4	86	100	17.870	<0.001*
Comorbidity (+)	51	39.2	79	60.8	130	100		
HT (-)	114	58.5	81	41.5	195	100	5.620	0.018*
HT (+)	41	43.6	53	56.4	94	100		
DM (-)	125	55.8	99	44.2	224	100	2.202	0.138
DM (+)	29	45.3	35	54.7	64	100		
CVD (-)	149	54.2	126	45.8	275	100	0.687	0.407
CVD (+)	6	42.9	8	57.1	14	100		
Cardiac disease (-)	136	53.5	118	46.5	254	100	0.876	0.921
Cardiac disease (+)	17	51.5	16	48.5	33	100		
Mild-moderate OSAS	123	66.8	61	33.2	184	100	36.326	<0.001*
Severe OSAS	32	30.2	74	69.8	106	100		
OSAS	19	25.3	56	74.7	75	100	52.457	<0.001*
REM-OSAS	55	73.3	20	26.7	75	100		
P-OSAS	30	41.7	42	58.3	72	100		
REM+P-OSAS	51	75	17	25	68	100		

*, p<0.05. Mann-Whitney U test. ESS: Epworth sleepiness scale; HT: Hypertension; DM: Diabetes Mellitus; CVD: Serebrovascular disease; OSAS: Obstructive sleep apnoea syndrome; P-OSAS: Positional-OSAS; REM-OSAS: Rapid eye movement related OSAS

Statistical Analysis

The data were analysed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). Categorical variables are presented as frequencies and percentages. The normality of distribution for continuous variables was assessed using the Shapiro–Wilk test. The continuous variables did not meet the assumption of normal distribution; thus, they are summarised using median, minimum, and maximum values. The chi-square test was used for comparisons between two categorical variables. When a significant difference was detected, pairwise comparisons of column proportions were conducted. The Mann–Whitney U test was employed to compare continuous variables between two categorical groups. For comparisons involving continuous variables across more than two categorical groups, the Kruskal–Wallis H test was used. In cases where the Kruskal–Wallis H test indicated a significant difference, pairwise comparisons were performed using the Bonferroni-adjusted Mann–Whitney U test. In all analyses, p<0.05 was considered to indicate significance.

RESULTS

Our study included 290 OSAS patients (104 female / 186 male). Seventy-five (25.8%) patients were diagnosed with REM-OSAS, 72 (24.8%) with P-OSAS, 75 (25.8%) with classical OSAS, and 68 (23.4%) with P+REM-OSAS. Of the 290 patients, 130 had comorbid diseases (94 with HT, 33 with cardiac disease, 64 with DM, 14 with cerebrovascular diseases with mRS scores <2, 15 with hyperlipidaemia, and 3 with benign prostate hypertrophy).

The distribution of the patients' demographic and clinical characteristics according to their ESS scores is shown in Table 1. The proportion of females was higher in the ESS ≤10 group (62.5%), whereas males predominated in the ESS >10 group (51.6%). This sex distribution difference between the groups was significant ($\chi^2=5.340$, p=0.021). No significant difference was observed in smoking status between the ESS groups ($\chi^2=1.830$, p=0.176). Patients with comorbidities experienced significantly higher sleepiness levels ($\chi^2=17.870$, p<0.001).

Table 2. Comparison of demographic and polysomnography values according to Epworth sleepiness scale score

	ESS scores≤10 median (min-max)	ESS score>10 median (min-max)	Total median (min-max)	Z	p
Age	49 (18–66)	50 (27–66)	50 (18–66)	-1.123	0.261
Height	1.7 (1.49–1.92)	1.7 (1.5–1.93)	1.7 (1.49–1.93)	-1.885	0.059
Weight	85 (46–135)	91.5 (62–145)	89 (46–145)	-3.709	<0.001*
BMI	30.09 (18–45.01)	31.25 (22.86–60.35)	30.928 (18–60.35)	-2.539	0.011*
AHI	18.5 (5.1–89.7)	33.2 (6.3–104.3)	21.55 (5.1–104.3)	-5.846	<0.001*
Supine-AHI	32.7 (6.5–114.1)	54.45 (11.9–134)	40.2 (6.5–134)	-3.281	0.001*
REM-AHI	41.1 (14.7–111.8)	48.5 (15.5–91.4)	44.7 (14.7–111.8)	-1.629	0.103
TST	374 (244.5–486.3)	390.75 (250–565.2)	382 (244.5–565.2)	-1.723	0.085
Sleep efficiency	78.9 (46.5–97.3)	81.7 (24.9–97.5)	80.1 (24.9–97.5)	-1.612	0.107
Mean-SaO ₂	94 (86–97)	93.4 (78–97.2)	93.6 (78–97.2)	-2.561	0.010*
Min-SaO ₂	85 (54–93)	81 (50–92)	83 (50–93)	-4.821	<0.001*
HR	66.75 (43.3–95.7)	68.4 (48.6–93.5)	67 (43.3–95.7)	-1.229	0.219
ODI	15.4 (2.7–90.5)	27.85 (5.2–96.5)	20.3 (2.7–96.5)	-3.026	0.002*

*: p<0.05. Mann-Whitney U test. ESS: Epworth sleepiness scale; BMI: Body mass index; AHI: Apnea-hypopnea index; REM: Rapid eye movement; TST: Total sleep time; Mean-SaO₂: Mean oxygen saturation; Min-SaO₂: Minimum oxygen saturation; HR: Mean heart rate; ODI: Oxygen desaturation index.

A significantly higher prevalence of HT was observed in the ESS >10 group ($\chi^2=5.620$, $p=0.018$). No significant difference in DM, CVD, or cardiac disease presence was found between the ESS groups ($p>0.05$). Patients with mild-to-moderate AHI were more frequently observed in the ESS ≤10 group (66.8%), whereas those with severe AHI were significantly more common in the ESS >10 group (69.8%) ($\chi^2=36.326$, $p<0.001$). Thus, the severe OSAS group demonstrated higher sleepiness levels than the mild-to-moderate OSAS group (Table 1).

ESS scores differed significantly among the OSAS clinical subgroups ($\chi^2=52.457$, $p<0.001$). The classical OSAS and P-OSAS groups demonstrated greater sleepiness levels (ESS >10) than the REM-OSAS and REM+P-OSAS groups (ESS ≤10) (Table 1).

No significant differences in age, height, TST, sleep efficiency, or HR values were observed between the ESS groups ($p>0.05$; Table 2). Weight, BMI, AHI, and ODI values were higher in the group demonstrating greater sleepiness (ESS score >10); furthermore, the mean and minimum O₂ saturation values were lower than those in the group demonstrating lower sleepiness (ESS score ≤10) (Table 2).

A significant female predominance was observed in the REM-OSAS group, whereas male predominance was observed in the P-OSAS, classical OSAS, and REM+P-OSAS groups ($p=0.001$) (Table 3). Smoking history was present in 113 patients (38.9%), and no significant difference was found among the clinical types (Table 3). HT and DM were the most common comorbid conditions in all clinical types, and there was no significant

difference in the incidence of comorbid diseases across the clinical types ($p>0.05$). Only DM demonstrated a significantly higher prevalence in the classical OSAS subgroup compared to the other OSAS subgroups ($p=0.031$) (Table 3).

No significant difference was observed in the median patient age across the OSAS clinical types ($p=0.994$; Table 4). The median BMI was 32.08 in classical OSAS patients and 29.39 in those with P-OSAS ($p=0.005$; Table 4). Patients with classical OSAS were significantly more likely to be overweight than those with REM-OSAS ($p<0.001$; Table 4).

The median total AHI was significantly higher in the classical OSAS subgroup compared to the other subgroups; this value was also higher in the P-OSAS group than in the REM-OSAS subgroup ($p<0.001$; Table 4).

The TST was significantly higher in the classical OSAS and REM-OSAS groups than in the REM+P-OSAS group ($p<0.05$). Mean-SaO₂ and min-SaO₂ were significantly higher in the P-OSAS subgroup compared to the classical OSAS subgroup ($p<0.05$). DSI was higher in the classical OSAS and P-OSAS subgroups than in the REM-OSAS and REM+P-OSAS subgroups ($p<0.05$). No significant difference was observed in the HR values across the clinical OSAS types (Table 4).

DISCUSSION

EDS is a common symptom in patients with OSAS, adversely affecting daily activities, reducing occupational performance, and increasing the risk of injury. Among OSAS patients,

Table 3. Comparison of OSAS clinical types according to demographic values and disease severity

	OSAS			REM-OSAS			P-OSAS			REM+P-OSAS			Total		Chi-square	p
	n	%		n	%		n	%		n	%		n	%		
Female	21	20.2		39	37.5		16	15.4		28	26.9		104	100	17.166	0.001*
Male	54	29		36	19.4		56	30.1		40	21.5		186	100		
Smoking (-)	48	27.1		49	27.7		38	21.5		42	23.7		177	100	2.939	0.401
Smoking (+)	27	23.9		26	23		34	30.1		26	23		113	100		
Comorbidity (-)	30	23.3		35	26.7		29	22.1		36	27.9		130	100	4.009	0.260
Comorbidity (+)	50	31.5		41	25.4		41	25.4		28	17.7		160	100		
HT (-)	44	22.6		51	26.2		50	25.6		50	25.6		195	100	4.078	0.253
HT (+)	31	33		24	25.5		21	22.3		18	19.1		94	100		
DM (-)	50	22.3		64	28.6		58	25.9		52	23.2		224	100	8.464	0.037*
DM (+)	25	39.1		11	17.2		13	20.3		15	23.4		64	100		
Cardiac disease (-)	65	25.6		65	25.6		64	25.2		60	23.6		254	100	3.506	0.885
Cardiac disease (+)	10	30.3		9	27.3		7	21.2		7	21.2		33	100		
Mild-moderate OSAS	26	14.1		59	32.1		44	23.9		55	29.9		184	100	43.361	<0.001*
Severe OSAS	49	46.2		16	15.1		28	26.4		13	12.3		106	100		

*: p<0.05. Kruskal-Wallis H Test. OSAS: Obstructive sleep apnoea syndrome; REM-OSAS: Rapid eye movement related OSAS; P-OSAS: Positional-OSAS; HT: Hypertension; DM: Diabetes mellitus

Table 4. Comparison of OSAS clinical types according to demographic, polysomnography and ESS values

	OSAS (A)			REM-OSAS (B)			P-OSAS (C)			REM+P-OSAS (D)			Z	p	Difference
	median (min-max)	median (min-max)		median (min-max)	median (min-max)		median (min-max)	median (min-max)		median (min-max)	median (min-max)				
Age	50 (29-65)	50 (18-66)		50 (18-66)	50 (18-66)		49.5 (24-66)	51 (24-65)		50 (18-66)	50 (18-66)		0.08	0.994	-
Height	1.7 (1.5-1.87)	1.65 (1.49-1.85)		1.65 (1.49-1.85)	1.71 (1.5-1.87)		1.7 (1.5-1.93)	1.7 (1.5-1.93)		1.7 (1.49-1.93)	1.7 (1.49-1.93)		11.322	0.010*	C>B
Weight	94 (62-145)	83 (60-117)		83 (60-117)	86 (60-135)		89 (46-135)	89 (46-135)		89 (46-145)	89 (46-145)		13.992	0.003*	A>B
BMI	32.08 (23.36-60.35)	30.86 (22.23-42.46)		30.86 (22.23-42.46)	29.39 (22.78-45.01)		31.25 (18-43.25)	31.25 (18-43.25)		30.93 (18-60.35)	30.93 (18-60.35)		12.864	0.005*	A>C
AHI	43.5 (5.5-104.3)	16.9 (5.1-58.7)		16.9 (5.1-58.7)	24.4 (5.6-89.4)		19.25 (5.2-89.6)	19.25 (5.2-89.6)		21.55 (5.1-104.3)	21.55 (5.1-104.3)		55.423	<0.001*	A>B, C, D
Supine-AHI	(-)	(-)		(-)	52.15 (6.5-134.1)		31.8 (9.2-94.1)	31.8 (9.2-94.1)		40.2 (6.5-134.1)	40.2 (6.5-134.1)		10.43	0.005*	C>B
REM-AHI	(-)	43.8 (14.7-92.4)		43.8 (14.7-92.4)	(-)		45.6 (15.5-111.8)	45.6 (15.5-111.8)		44.7 (14.7-111.8)	44.7 (14.7-111.8)		0.082	0.960	-
TST	401.5 (245-521.1)	390.5 (245-497)		390.5 (245-497)	374.5 (240.5-565.2)		363 (244.5-473.4)	363 (244.5-473.4)		382 (244.5-565.2)	382 (244.5-565.2)		12.193	0.007*	A,B>D
Sleep efficiency	83.7 (44.9-96.8)	80.3 (51.1-97.5)		80.3 (51.1-97.5)	78.4 (41-97.3)		77.65 (46.5-96.6)	77.65 (46.5-96.6)		80.1 (44.9-97.5)	80.1 (44.9-97.5)		10.81	0.013*	A>D
Mean-SaO ₂	93.1 (78-97)	94 (84.8-97)		94 (84.8-97)	93.9 (88.1-96.8)		93.4 (86-97.2)	93.4 (86-97.2)		93.6 (78-97.2)	93.6 (78-97.2)		8.909	0.031*	C>A
Min-SaO ₂	81 (50-93)	83 (50-90)		83 (50-90)	84 (64-91)		84 (54-92)	84 (54-92)		83 (50-93)	83 (50-93)		10.659	0.014*	C>A
HR	68.5 (51.8-91.7)	67.15 (43.3-93.5)		67.15 (43.3-93.5)	65.9 (49.8-87.1)		67 (50.3-95.7)	67 (50.3-95.7)		67 (43.3-95.7)	67 (43.3-95.7)		1.515	0.679	-
ODI	39.95 (4-96.5)	13.1 (3.8-47.1)		13.1 (3.8-47.1)	25.7 (2.7-67.3)		16 (3.2-87.1)	16 (3.2-87.1)		20.3 (2.7-96.5)	20.3 (2.7-96.5)		21.987	<0.001*	A,C>B, A>D
ESS score	12 (1-24)	6 (1-22)		6 (1-22)	10 (1-20)		5 (1-21)	5 (1-21)		8 (1-24)	8 (1-24)		42.721	<0.001*	A,C>D, A,C>B

*: p<0.05. Z: Kruskal-Wallis H Test. BMI: Body mass index; AHI: Apnoea-hypopnea index; REM: Rapid eye movement; TST: Total sleep time; HR: Mean heart rate; ODI: Oxygen desaturation index

58.3% experience varying degrees of daytime sleepiness.^[13] Distinct OSAS phenotypes have been identified in recent years, and the presence of EDS has become a key determinant in OSAS classification.

In this study, demographic characteristics, polysomnographic data, and daytime sleepiness rates were compared among patients with different clinical types of OSAS—namely, REM-OSAS, P-OSAS, REM+P-OSAS, and classical OSAS. Our findings indicated that EDS was more prevalent in male patients diagnosed with OSAS, in those with comorbidities—particularly HT—and in patients with higher AHI, BMI, and body weight values. When comparing the prevalence of EDS across OSAS clinical types, the highest rate was observed in the classical OSAS group, followed by the P-OSAS group. Regarding polysomnographic findings, patients with increased daytime sleepiness had lower mean-SaO₂ and min-SaO₂ levels and higher ODI values. TST and sleep efficiency were lower in the REM+P-OSAS clinical type compared to the other types.

Notably, sex-related differences have been demonstrated in previous studies. It has been suggested that OSAS is more prevalent in males due to patterns of fat distribution.^[14] Oestrogen and progesterone are believed to exert a protective effect by increasing upper airway muscle tone; however, this effect diminishes during REM sleep and after menopause, thereby increasing the risk of REM-OSAS in women and in older individuals.^[15] In our study, REM-OSAS was observed more frequently in women, although the age range was similar to that of patients with the other clinical types. Some studies have demonstrated increased daytime sleepiness in women,^[16,17] which is inconsistent with our study. Additionally, consistent with the literature, no significant difference was observed in the mean patient age between the EDS and non-EDS groups.^[17]

Obesity is considered a chronic inflammatory condition and is one of the most important risk factors for OSAS.^[18] Visceral fat accumulation and fat deposits in the upper airway contribute to hypoventilation and/or oxygen desaturation, leading to increased nocturnal awakenings and sleep fragmentation, resulting in EDS.^[18] In our study, consistent with the literature, a significant association was found between higher body weight and BMI values and the presence of EDS.^[19]

Numerous comorbid conditions are OSAS risk factors, such as cardiovascular diseases, HT, DM, and chronic obstructive pulmonary disease (COPD); a positive correlation between disease severity and comorbidity level has been demonstrated.^[20,21] In our study, EDS was observed at a higher rate in OSAS patients with comorbidities, particularly those with hy-

pertension. In one study, EDS was associated with increased cardiovascular risks in coronary artery disease patients, especially in those with OSAS.^[22] However, in our study, we did not detect a statistically significant increase in sleepiness among patients with cardiac disease. Nevertheless, we consider that the relatively small number of OSAS patients with concomitant cardiac disease (n=33) may have contributed to this finding.

Some studies have demonstrated no strong correlation between total AHI and ESS scores.^[8,23] Jung et al.^[24] demonstrated that ESS scores increase with OSAS severity. In our study, higher AHI scores were found to be associated with increased sleepiness. These findings are consistent with previous studies demonstrating higher mean ESS scores and a greater prevalence of EDS.^[25,26] Although some studies have shown a significant association between REM-OSAS and daytime sleepiness, others have found no such relationship.^[8,9,27] Furthermore, Punjabi et al.^[9] demonstrated a greater EDS prevalence in NREM-related OSAS via objective measures, including the Multiple Sleep Latency Test (MSLT). Our study and many previous studies employed the ESS, a subjective measurement tool, which may account for discrepancies across studies.

Moreover, body position plays a decisive role in OSAS severity. In particular, in the supine position, the gravitational effect on upper airway structures increases airway narrowing, thereby exacerbating OSAS.^[2] However, whether P-OSAS is associated with increased EDS remains unclear, as conflicting findings have been reported.^[2–4] In our study, patients with P-OSAS were found to have significantly increased daytime sleepiness, similar to that observed in classical OSAS patients.

REM+P-OSAS emerged as a clinically distinct phenotype. This group typically comprises women, individuals with lower BMI, and those with milder disease severity. Despite measurable respiratory events, these patients may exhibit lower subjective levels of sleepiness.^[3] In our study, both AHI and ESS scores were lower in this group than in the classical OSAS and P-OSAS groups.

One study demonstrated a positive correlation between the ESS score and AHI and a negative correlation between the ESS score and min-SaO₂.^[28] Another study revealed a mild correlation between the AHI and total ESS score in patients with sleep-related breathing disorders, as well as a mild negative correlation between the total ESS score and min-SaO₂, and between the total ESS score and mean-SaO₂.^[12] In contrast, other studies have failed to demonstrate a significant correlation between the ESS score and AHI or min-

SaO₂.^[29,30] In our study population, O₂ saturation parameters—such as mean-SaO₂ and min-SaO₂—were lower in the classical OSAS and high ESS score groups.

Adults with OSAS who experience EDS appear to be at a significantly higher risk for cardiovascular diseases than those without EDS.^[31] Increased sympathetic activation and cardiovascular instability during apnoeas in REM sleep are associated with more severe hypoxemia and an elevated risk of arrhythmias.^[32] In our study, no significant difference was observed in HR values among the clinical OSAS phenotypes or between the ESS subgroups.

Smoking can cause abnormal changes in the upper respiratory tract histologically and physiologically, and several mechanisms have been hypothesised to explain how smoking increases the risk of developing OSAS. Although a previous study has reported an association between smoking and both OSAS severity and increased daytime sleepiness, we did not observe EDS among OSAS patients who were smokers—consistent with the findings of another study.^[33,34]

To our knowledge, no previous study has compared EDS across all clinical phenotypes of OSAS; thus, we believe that the findings of our study provide a valuable contribution to the existing body of knowledge.

However, our study has several limitations. First, its retrospective nature limits the study design. Furthermore, relying on data obtained from a single-night polysomnographic assessment limits the generalisability of the findings. Multiple-night PSG assessments may provide more robust evidence. Additionally, although the ESS is a widely used tool, it is a subjective measurement method dependent on the patient's responses to the test scale and may not capture all dimensions of sleepiness as sensitively as objective tests such as the MSLT.

CONCLUSION

In our study, EDS in patients with OSAS was found to increase with disease severity, and patients with P-OSAS demonstrated a similar risk of EDS to those with classical OSAS. This finding underscores the need for a more sensitive and individualised approach during the diagnostic and therapeutic process. Considering patient quality of life, it may be appropriate to initiate positive airway pressure therapy in P-OSAS patients earlier and at lower AHI thresholds. OSAS is a heterogeneous disorder; thus, identifying REM subtypes and, especially, positional subtypes is of critical importance for developing personalised treatment strategies and improving clinical outcomes.

Disclosures

Ethics Committee Approval: The study was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Non-interventional Scientific Research Ethics Committee (No: 11/05, Date: 25/06/2025).

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Ultrasonography-guided Peripheral Nerve Blocks in Orthopedic Upper Extremity Surgery: A Narrative Review

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ABSTRACT

Peripheral nerve blocks are frequently preferred in orthopedic upper extremity surgeries because they provide adequate postoperative analgesia, reduce the need for general anesthesia, and accelerate recovery. The integration of ultrasound (USG) guidance into these techniques has improved block success rates and significantly reduced complications. USG-guided nerve blocks allow real-time visualization of neural structures and surrounding anatomy. The brachial plexus supplies most of the innervation of the upper extremity. In clinical practice, the four most commonly performed brachial plexus blocks are the interscalene, supraclavicular, infraclavicular, and axillary approaches. In addition, terminal nerves can be selectively blocked along their course. For example, in clavicular surgeries, the interscalene block is often combined with a cervical plexus block; in rotator cuff repair and shoulder arthroscopy, the interscalene block is preferred; in humeral shaft fractures and elbow arthroplasty, supraclavicular or infraclavicular blocks are commonly used; and in distal radius fracture fixation, wrist arthrodesis, and metacarpal fracture surgeries, the axillary block is frequently chosen. Median nerve blocks are useful in carpal tunnel release and tenosynovitis; ulnar nerve blocks are employed in Dupuytren's contracture and flexor tendon repair of the fourth and fifth fingers; while radial nerve blocks are beneficial in de Quervain's tenosynovitis, scaphoid fracture surgery, and dorsal hand lesions. This review discusses the anatomical basis, techniques, indications, and complications of cervical and brachial plexus blocks, as well as distal nerve blocks, which are widely utilized in orthopedic upper extremity surgery.

Keywords: Orthopedic surgery, peripheral nerve blocks, postoperative analgesia, regional anesthesia, ultrasonography, upper extremity

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INTRODUCTION

Upper extremity surgeries encompass a wide spectrum of orthopedic, traumatological, and reconstructive procedures, extending from the shoulder to the hand. These operations can cause severe pain intraoperatively and postoperatively. Regional anesthesia techniques are therefore highly valuable, as they provide surgical anesthesia, reduce opioid use, support early mobilization, and increase patient satisfaction.

One of the most significant developments in regional anesthesia in recent decades has been the use of peripheral nerve blocks (PNBs) under ultrasonographic (USG) guidance.^[1,2] USG enables real-time visualization of nerves, vascular structures, and needle advancement, significantly improving block success. Compared to landmark-based or nerve stimulator techniques, USG allows effective blocks with lower anesthetic volumes and reduces complication risks. USG

and nerve stimulators may also be used in a complementary fashion. Moreover, ultrasound facilitates quicker and more accurate placement of peripheral nerve catheters.^[3]

Among cervical and brachial plexus blocks, the interscalene, supraclavicular, infraclavicular, and axillary approaches are the most commonly used in orthopedic upper extremity surgery. Distal nerve blocks, on the other hand, can provide analgesia while preserving motor function—particularly valuable in hand surgery.^[4,5] Selection of the appropriate block should be guided by anatomical level, surgical site, and patient characteristics. With the safety and precision of USG, motor-sparing approaches are increasingly preferred.

This narrative review aims to summarize the anatomical basis, technical considerations, indications, and reported outcomes of USG-guided peripheral nerve blocks in upper extremity surgery.



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MATERIALS and METHODS

A literature search was conducted in PubMed and Google Scholar for articles published between June 2020 and June 2025 using the keywords ultrasound-guided, peripheral nerve block, upper extremity, and orthopedic surgery. Randomized controlled trials, observational studies, cohort studies, systematic reviews, and meta-analyses were included. Titles and abstracts were screened first, followed by full-text review. Additional manual searching was performed by screening reference lists and citations of key articles.

This review followed the SANRA (Scale for the Assessment of Narrative Review Articles) checklist to improve reporting quality.

ANATOMICAL INNERVATION OF THE UPPER EXTREMITY

The brachial plexus, formed by the anterior rami of spinal nerves C5–T1, provides the majority of upper extremity innervation. It is organized sequentially into roots, trunks (upper, middle, lower), divisions (anterior, posterior), fascicles (lateral, posterior, medial), and terminal branches. Major peripheral nerves arising from the plexus include the musculocutaneous, median, ulnar, radial, and axillary nerves.

A thorough understanding of this anatomy is essential for successful regional anesthesia.^[6] At the interscalene level, roots of the plexus lie between the anterior and middle scalene muscles—ideal for shoulder and upper arm surgeries. At the supraclavicular level, trunks are clustered, enabling blockade of the entire upper extremity. At the infraclavicular level, blocks target the fascicles around the axillary artery, suitable for procedures below the elbow and for catheter placement. The axillary block targets terminal branches and is frequently employed in hand surgery.

Additionally, the cervical plexus (C1–C4) contributes to upper extremity innervation. The supraclavicular nerves and phrenic nerve are particularly relevant for the shoulder region. Inadvertent phrenic nerve involvement during interscalene blocks may cause hemidiaphragmatic paralysis, highlighting the importance of careful planning. For tourniquet-related pain, thoracic nerves such as the intercostobrachial may also need to be blocked.

CERVICAL PLEXUS BLOCKS

The cervical plexus (C1–C4) contributes sensory and motor innervation to the cervical region and upper thorax. Its superficial branches provide sensation to the auricle, clavicle, deltoid, and upper shoulder, while deep branches supply

motor innervation to muscles including the sternocleidomastoid, trapezius, and diaphragm (via the phrenic nerve).^[7]

Superficial Cervical Plexus Block (CPB)

The superficial cervical plexus arises from C2–C4. Sensory innervation includes the auricle, clavicle, acromioclavicular joint, and anterolateral neck. Four terminal branches (lesser occipital, greater auricular, transverse cervical, and supraclavicular nerves) emerge near the posterior border of the sternocleidomastoid.^[8]

Superficial CPB is used for supraclavicular and subclavicular skin interventions such as lymph node biopsy, central venous catheterization, and clavicle fixation. In USG-guided CPB, the patient is placed supine, and a linear probe is positioned at the midline of the sternocleidomastoid muscle. The sensory branches beneath the fascia at the posterior muscle margin are targeted. The needle is advanced in-plane, and 5–10 mL of 0.25–0.5% ropivacaine is injected (Fig. 1).

Complications are less common than in deep blocks but may include intravascular injection, hematoma, infection, and systemic toxicity. Adequate anatomical knowledge and awareness of local anesthetic toxicity are essential to minimize risks.^[9]

Deep Cervical Plexus Block (CPB)

The deep CPB targets C2–C4 nerve roots between the anterior and middle scalene muscles, just anterior to the transverse processes. It can be used alone or in combination with interscalene blocks for shoulder surgery.

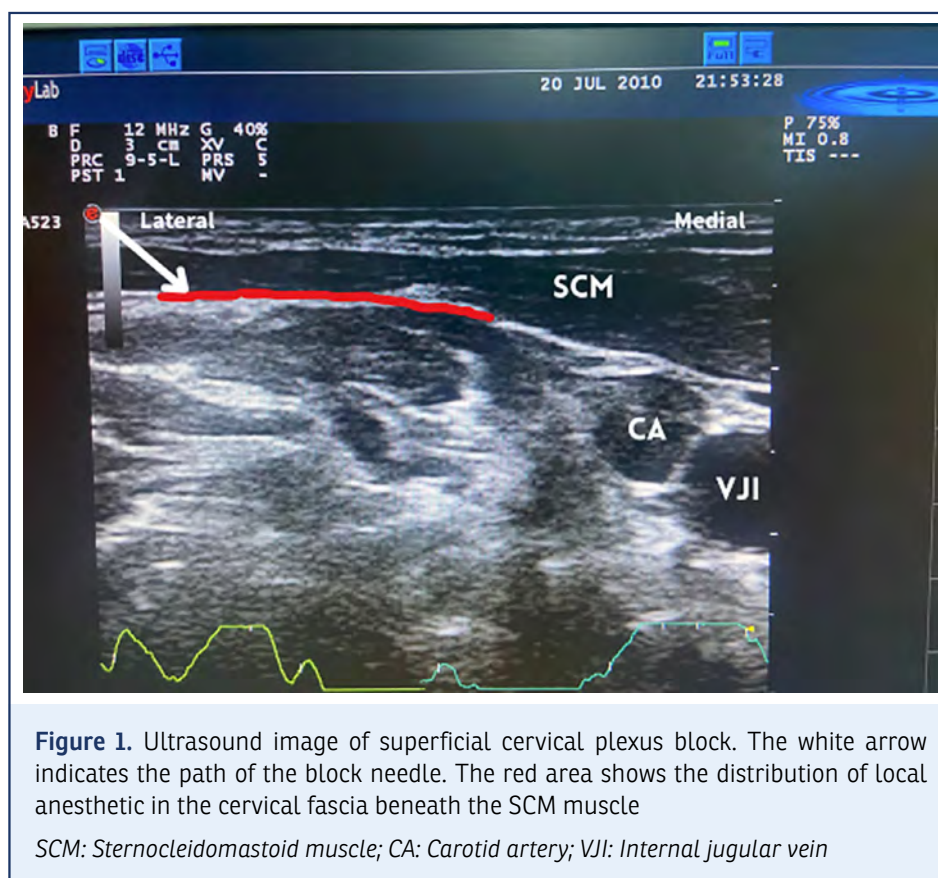
Because the injection is deeper, complications are more likely, including phrenic nerve palsy, vascular puncture, or epidural spread.^[10] Accidental injection into the vertebral artery carries a high risk, as even small anesthetic volumes can rapidly reach the CNS, producing neurotoxicity. Continuous patient communication during incremental injection is crucial to detect early warning signs (e.g., perioral numbness, confusion, tinnitus).

Unintended subdural injection is another risk, potentially causing abrupt loss of consciousness, hypotension, and requiring airway and hemodynamic support. For these reasons, deep CPB should be reserved for experienced practitioners and performed with extreme caution, especially in patients with limited pulmonary reserve.

BRACHIAL PLEXUS BLOCKS

Interscalene Block

The interscalene block is a regional anesthesia technique in which the brachial plexus is blocked at the C5–C7 root level, specifically targeting the upper (superior) and middle trunks.



It is particularly preferred for shoulder surgeries, proximal humerus interventions, clavicular procedures, and upper arm surgeries. However, because the lower trunk (C8–T1) is usually not affected, it is often insufficient when used alone for hand and forearm surgeries. The interscalene region is located behind the sternocleidomastoid muscle, between the anterior and middle scalene muscles.^[11] This anatomical relationship makes the block relatively easy to identify and apply safely.

For USG-guided interscalene block, the patient is positioned supine or in a slight lateral decubitus position, with the head turned contralaterally. A high-frequency (10–15 MHz) linear probe is placed laterally on the neck at the level of the cricoid cartilage (C6 level). On ultrasound, the scalene muscles appear beneath the sternocleidomastoid, and the hyperechoic, round-to-oval brachial plexus roots (typically C5, C6, and C7) are visualized between them. The needle is advanced from lateral to medial using an in-plane technique (Fig. 2). Typically, 10–15 mL of 0.5% ropivacaine, levobupivacaine, or bupivacaine is injected. Using higher volumes may increase lower trunk spread but also raises the risk of complications. The block is most effective in the C5–C6 dermatomes, providing anesthesia to the shoulder region and affecting muscles such as the deltoid, supraspinatus, biceps, and pectoralis major.

The most common and clinically important complication of the interscalene block is hemidiaphragmatic paralysis due to inadvertent phrenic nerve (C3–C5) blockade, which can occur in up to 100% of patients. This may cause severe respiratory distress in patients with COPD, obesity, or restrictive lung disease. Other complications include recurrent laryngeal nerve blockade (causing hoarseness), Horner syndrome due to sympathetic chain involvement, intravascular injection, neurotoxicity, and, rarely, epidural or subarachnoid spread.^[12] To reduce risks, low anesthetic volumes, frequent aspiration, and cessation of injection upon resistance are recommended. USG guidance is highly effective in minimizing these complications.

Supraclavicular Block

The supraclavicular block anesthetizes the brachial plexus at the trunk level (C5–T1) and is often referred to as the “spinal anesthesia of the arm.” Because the trunks are tightly clustered at this level, a single injection can provide dense anesthesia of the entire upper extremity. It is particularly suited for surgeries up to the proximal elbow, including arteriovenous (AV) fistula creation, humeral fracture fixation, and elbow arthroplasty. However, complete blockade of the ulnar nerve (C8–T1) is not always achieved.^[13]

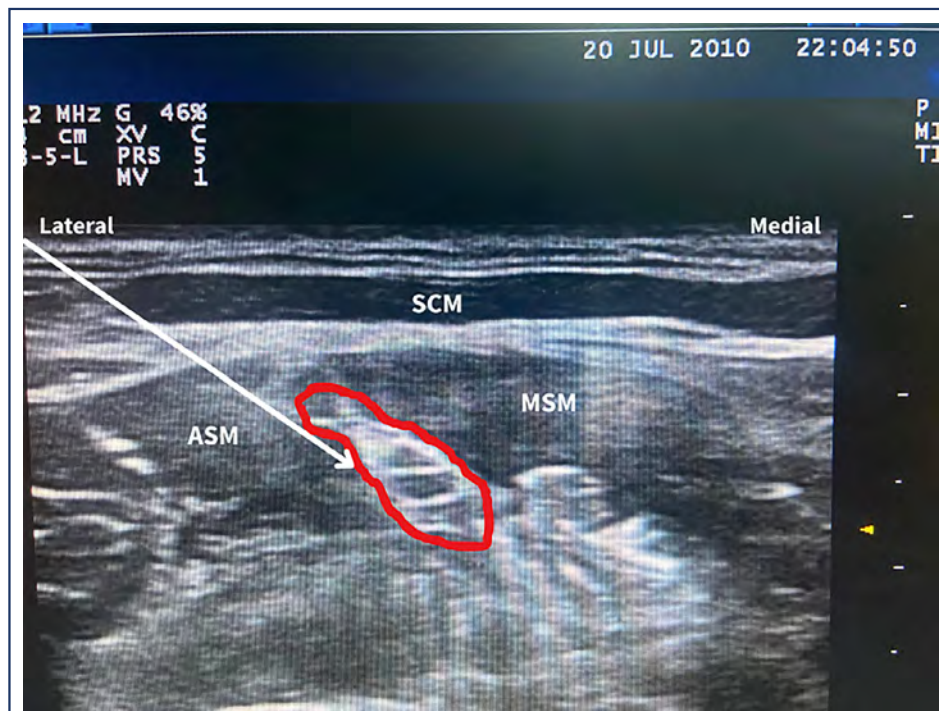


Figure 2. Ultrasound image of Interscalene block. The white arrow indicates the path of the block needle. The red line indicates the brachial plexus between the scalene muscles

SCM: Sternocleidomastoid muscle; ASM: Anterior scalene muscle; MSM: Middle scalene muscle

For USG-guided supraclavicular block, the patient is placed supine with the head turned contralaterally. A high-frequency linear probe is positioned just above the clavicle, beneath the scalene triangle (Fig. 3). On ultrasound, the brachial plexus appears as a hyperechoic “bunch of grapes” lateral to the subclavian artery. The needle is advanced from lateral to medial using an in-plane technique (Fig. 4), and 20–30 mL of 0.5% ropivacaine, levobupivacaine, or bupivacaine is administered. This block effectively covers most C5–T1 dermatomes, providing both sensory and motor blockade to the arm, forearm, and hand.

The most feared complication is pneumothorax, as the brachial plexus lies adjacent to the parietal pleura at this level. Over-advancement of the needle may puncture the pleura. The subclavian artery and vein are also nearby, creating risks of intravascular injection, hematoma, and neurotoxicity.^[14] These complications are significantly reduced with USG guidance. Other possible risks include bradycardia-hypotension, Horner syndrome, and occasional phrenic nerve involvement. Thus, careful anatomical identification, use of low anesthetic volumes, and frequent aspiration are essential.

Infraclavicular Block

The infraclavicular block targets the brachial plexus at the fascicular level (lateral, posterior, and medial). At this level, the fascicles are arranged clockwise around the axillary artery: the lateral fascicle lies superolateral, the posterior fascicle posterior, and the medial fascicle inferomedial. This block is suitable for elbow, forearm, and hand surgeries and is especially preferred when long-term analgesia is desired through catheter placement.^[15]

For USG-guided infraclavicular block, the patient lies supine with the arm abducted 90° and the head turned contralaterally. A linear or convex probe is placed just below the clavicle, inferomedial to the coracoid process (Fig. 5). On ultrasound, the axillary artery appears as a circular anechoic structure centrally, with the fascicles visible as hyperechoic structures surrounding it (Fig. 6). The needle is advanced from lateral to medial in-plane, and 20–30 mL of 0.25–0.5% ropivacaine, bupivacaine, or levobupivacaine is injected. Because the block covers all terminal branches from C5–T1, it provides a dense motor-sensory block of the hand, forearm, and elbow.



Figure 3. Probe position for supraclavicular block

Advantages include a lower risk of pleural injury compared to supraclavicular block, a flatter anatomy that facilitates catheter placement, less interference from shoulder movements, and reduced risk of diaphragmatic paralysis. Potential complications include vascular puncture, hematoma, and, rarely, pneumothorax. If USG imaging is suboptimal, nerve stimulator support is advised. The infraclavicular block is less affected by anatomical variations and is particularly advantageous in obese patients. When performed correctly, it offers an effective, safe, and long-lasting block, making it a preferred modern technique.

Axillary Block

The axillary block targets the brachial plexus at the level of the terminal branches: median, ulnar, radial, and musculocutaneous nerves. It is especially useful for surgeries of the forearm, wrist, and hand, including tendon repairs. The block carries minimal risk of phrenic nerve involvement, diaphragmatic paralysis, or pneumothorax, making it a safe alternative for patients with pulmonary compromise or coagulation disorders.^[16]

For USG-guided axillary block, the patient is placed supine with the arm abducted 90°. A linear probe is positioned in the axilla between the coracobrachialis and biceps brachii muscles. On ultrasound, the axillary artery appears as a round anechoic structure centrally, with nerves distributed around it: the median nerve anteromedial, the ulnar nerve inferior, the radial nerve posterior, and the musculocutaneous nerve lateral, often within the coracobrachialis (Fig. 7). Fractional injections are made for each nerve, totaling 20–30 mL of 0.25–0.5% ropivacaine, bupivacaine, or levobupivacaine. The musculocutaneous nerve must be separately targeted as it lies outside the main sheath.

The axillary block has a low complication rate and is well-suited for catheter placement. Its superficial location and relative distance from major vessels add to its safety. However, because the intercostobrachial nerve (T2) lies outside the brachial plexus at this level, tourniquet pain cannot be prevented with this block alone, requiring additional skin infiltration if necessary. Other potential complications include intravascular injection, hematoma, infection, and rare nerve injury. These risks can be minimized with careful needle advancement under USG guidance, frequent aspiration, and avoidance of high-pressure injection.

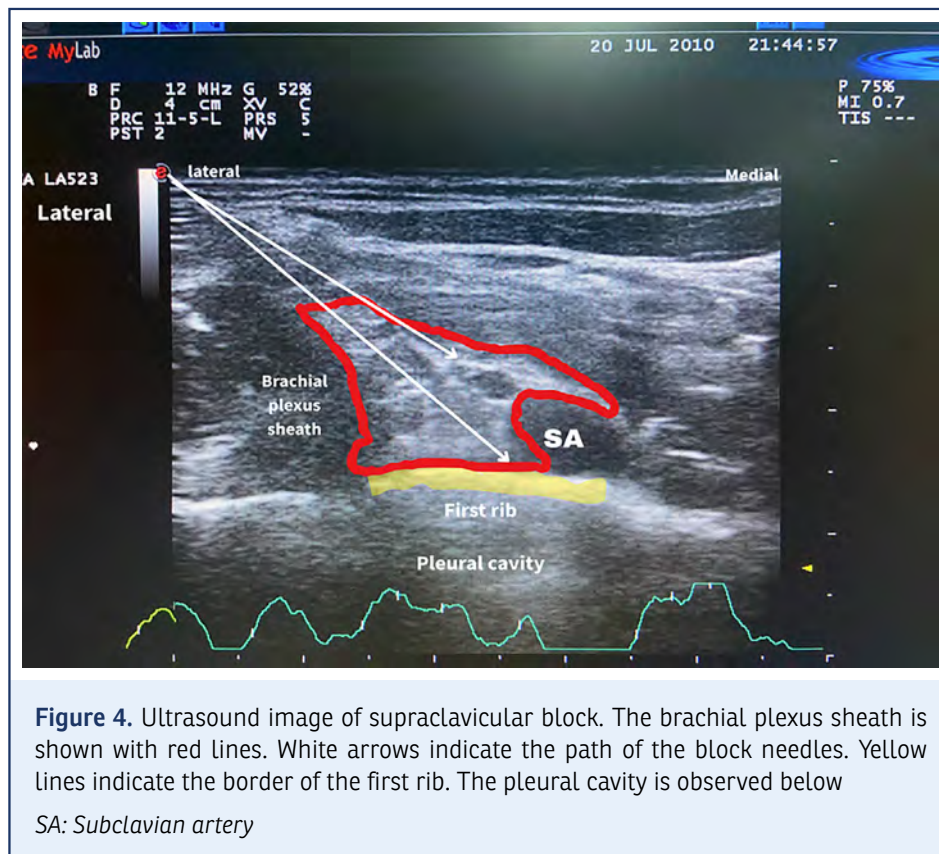
DISTAL NERVE BLOCKS

Distal nerve blocks are versatile techniques used in surgeries at the wrist and hand level, providing sensory blockade while preserving motor function. Their utility extends to minimally invasive tendon surgeries, carpal tunnel decompressions, postoperative pain control, and anesthesia for procedures involving the thenar region. At this level, the terminal branches of the brachial plexus—including the median, ulnar, radial, musculocutaneous, and medial antebrachial cutaneous nerves—are located superficially, making them accessible for blockade.

These blocks are especially advantageous in patients where motor preservation is desirable, such as cases requiring early postoperative hand physiotherapy.^[17]

Median Nerve Block

The median nerve arises from the lateral and medial cords of the brachial plexus, travels through the volar forearm, and enters the hand via the carpal tunnel. The block is typically performed at mid-forearm (distal to the pronator teres) or just proximal to the carpal tunnel. On ultrasound, the median nerve appears as a hypoechoic oval structure between the flexor digitorum superficialis and profundus muscles, medial to the radial artery. Clinically, this block is preferred for procedures involving the palmar thumb, index, and middle fingers.^[17]



Ulnar Nerve Block

The ulnar nerve originates from the medial cord of the brachial plexus, courses medially to the brachial artery, and passes through the groove between the olecranon and medial epicondyle at the elbow. It then travels along the medial forearm and enters the hand via Guyon's canal. USG-guided blockade is commonly performed in the distal third of the forearm, deep to the flexor carpi ulnaris muscle, where the nerve appears hypoechoic and oval, medial to the ulnar artery.

It is especially effective for procedures involving the palmar and dorsal aspects of the fourth and fifth fingers, as well as the ulnar wrist region. Motor involvement is minimal, affecting intrinsic hand muscles only mildly—an advantage for outpatient procedures.^[18]

Distal block applications under USG guidance are easy because the nerves are superficial and their relations with vascular structures can be visualized. The median nerve is located between the palmaris longus and flexor carpi radialis tendons at the wrist level, medial to the radial artery. The ulnar nerve is observed medial to the flexor carpi ulnaris tendon at the wrist, right next to the ulnar artery. The radial nerve mostly courses as a superficial branch on the dorsal surface, lateral to the radius, and is blocked by subcutaneous injection.

Distal nerve blocks offer a promising future with their ability to reduce opioid requirements. In general, injection of 5–8 mL of 0.25% bupivacaine or ropivacaine around the nerve is sufficient. In distal blocks, ensure circumferential spread without direct contact with the nerve. Additionally, a single injection surrounding the nerve is preferred over multiple injections. The most significant advantage of distal nerve blocks is that they provide analgesia while preserving motor function. In this way, they are preferred especially in cases where hand functions need to be monitored post-operatively. There is also no risk of serious complications specific to proximal blocks, such as diaphragmatic paralysis, pneumothorax, or vascular injury. Complications are usually pain at the injection site, hematoma, infection, and, very rarely, nerve irritation. Frequent aspiration should be performed before injection, and high-pressure injection should be avoided. Distal nerve blocks have been shown to reduce opioid requirements and increase patient satisfaction, especially in hand surgery.^[19]

Radial Nerve Block

The radial nerve originates from the posterior cord (C5–T1) and initially accompanies the axillary artery. It travels posterior to the humerus in the spiral groove, crosses toward the



Figure 5. Probe position for infraclavicular block

lateral epicondyle, and divides in the antecubital fossa into a superficial sensory branch and a deep motor branch.^[20]

Blockade can be performed at multiple levels—proximal, at the elbow, or distally. When performed proximal to the elbow, the needle is inserted ~4 cm above the lateral epicondyle, between the brachialis and brachioradialis muscles. Common anesthetic regimens include 5–10 mL of 0.25–0.5% bupivacaine, 5–15 mL of 0.2–0.5% ropivacaine, or 5–10 mL of 1% lidocaine. Ropivacaine is often favored in hand surgery due to its prolonged sensory effect with minimal motor block.

USG guidance allows precise deposition with smaller volumes, maximizing efficacy while minimizing systemic toxicity risk.^[21] Radial nerve blocks are useful in distal radius fractures, extensor tendon repairs, and wrist surgeries.

General Principles of Distal Blocks

- On USG, the median nerve lies between the palmaris longus and flexor carpi radialis tendons at the wrist, medial to the radial artery.

- The ulnar nerve is medial to the flexor carpi ulnaris tendon at the wrist, adjacent to the ulnar artery.
- The radial nerve is subcutaneous on the dorsum, lateral to the radius, and blocked with a superficial injection.

Typically, 5–8 mL of 0.25% bupivacaine or ropivacaine suffices. Circumferential spread around the nerve is essential, avoiding direct needle–nerve contact. A single perineural injection is generally preferred over multiple punctures.

Key advantages include preserved motor function, absence of major complications seen with proximal blocks (e.g., diaphragmatic paralysis, pneumothorax), and reduced opioid requirements, all of which enhance postoperative recovery and patient satisfaction.^[19]

COMPLICATIONS OF PERIPHERAL NERVE BLOCKS

Local Anesthetic Systemic Toxicity (LAST)

LAST is a rare but life-threatening complication caused by inadvertent intravascular injection or excessive systemic absorption. Symptoms can appear within seconds or be delayed up to 30 minutes. Neurological signs (dizziness, confusion, perioral tingling, tinnitus) typically precede cardiovascular collapse. If untreated, seizures, coma, and cardiovascular instability may occur.^[22]

Management requires immediate recognition and initiation of intravenous lipid emulsion (Intralipid) therapy, along with supportive care. Bolus and infusion regimens are weight-based, and escalation may be required in refractory cases.^[23,24] To reduce risk, the lowest effective dose should always be used, especially when multiple block sites are anesthetized.

Hematoma

Accidental vascular puncture during USG-guided blocks may lead to hematoma, particularly in patients with coagulopathies. Most resolve with compression; surgical intervention is rarely needed.

Nerve Injury

Although rare, nerve injuries may occur, most being transient (days to months). Permanent injury is reported in only 0.015–0.09% of cases.^[25,26] Intraneural or intrafascicular injection is the main cause. To prevent injury:

- Stop injection if paresthesia or high resistance is encountered.
- Confirm perineural spread with USG.

Risk is higher in patients with pre-existing neuropathies (e.g., diabetes). Symptoms include pain, paresthesia, or sensory–

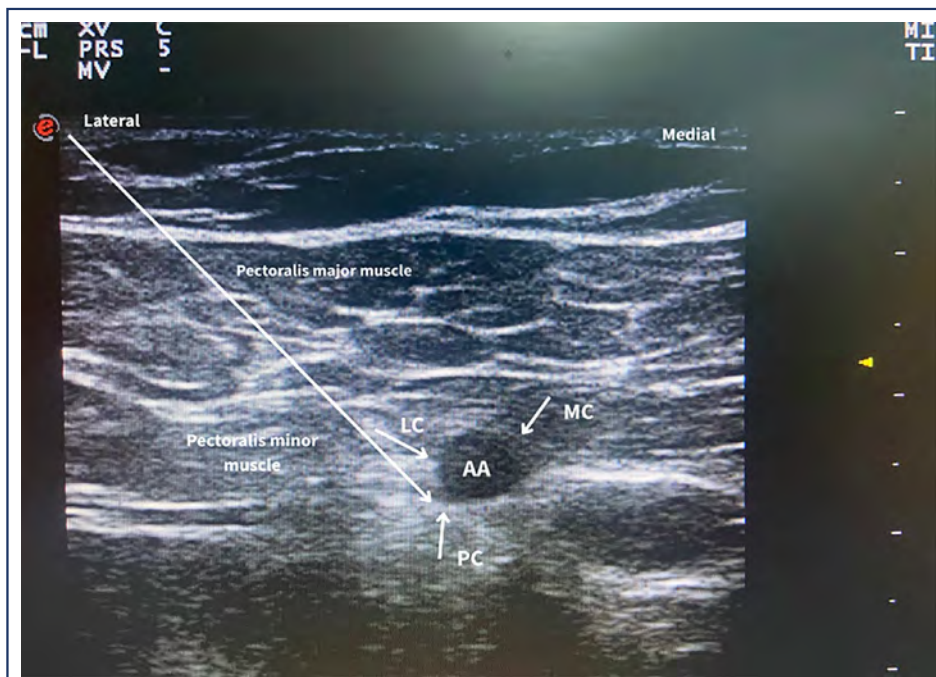


Figure 6. Ultrasound image of infraclavicular block. The white lines indicates needle trajectory. More than one injection may be required to block all three cords

PC: Posterior cord; MC: Middle cord; LC: Lateral cord; AA: Axillary artery

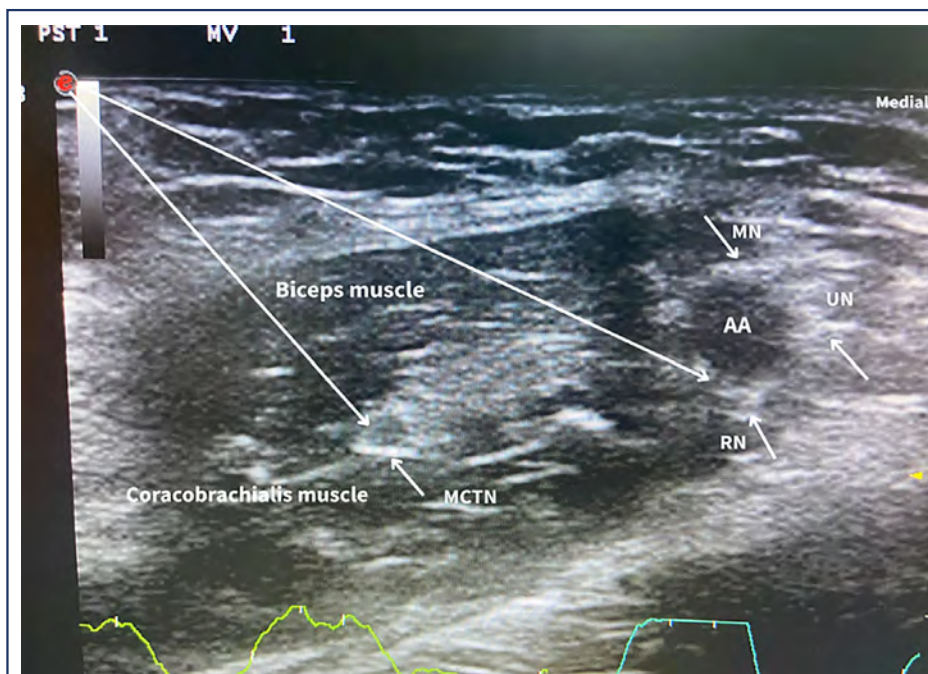


Figure 7. Ultrasound image of axillary block. The white lines indicates needle trajectory

AA: Axillary artery; MCTN: Musculocutaneous nerve; RN: Radial nerve; MN: Median nerve; UN: Ulnar nerve

motor deficits, which usually resolve within six months. Persistent cases require further evaluation.^[27]

Phrenic Nerve Paralysis

Nearly all interscalene blocks cause ipsilateral diaphragmatic paralysis, reducing vital capacity by ~25%. This is usually tolerated in healthy patients but may cause respiratory distress in those with COPD, obesity, or bilateral blockades.^[28]

Pneumothorax

Most often associated with supraclavicular blocks, pneumothorax results from needle puncture of the pleura. Clinical signs include sudden dyspnea, chest pain, and hypoxemia. USG guidance has significantly reduced its incidence.^[29]

Horner Syndrome

Horner syndrome (ptosis, miosis, enophthalmos, anhidrosis) occurs due to anesthetic spread to the cervical sympathetic chain, especially after interscalene blocks. Reported incidence exceeds 50% in some series. It is typically benign and transient but may alarm patients.^[30,31]

Total Spinal and Epidural Spread

Accidental subarachnoid injection may cause total spinal anesthesia, leading to apnea, hypotension, bradycardia, and loss of consciousness. Epidural spread produces milder but clinically significant bilateral block and hypotension.^[32]

Block Failure

Failure may occur even in experienced hands if anesthetic is deposited outside the neurovascular sheath. Obesity (BMI >25) increases failure rates due to obscured landmarks.^[26] Modern USG techniques, adjuvants, and improved training have improved success rates and reduced procedure time.^[33-35]

Patients should be counseled preoperatively regarding possible block failure and alternative analgesic options.

Infection

The risk of infection following a single-dose peripheral nerve block (PNB) is negligible. However, it is increased in certain patient populations, including hospitalized patients, trauma patients, immunocompromised individuals, males, and those not receiving antibiotic prophylaxis. Failure to follow infection-prevention guidelines may result in serious complications. Removing the catheter within 48–72 hours after placement for continuous blocks significantly reduces the risk of infection and prevents these potential consequences.

Allergic Reaction

Most adverse reactions to local anesthetics are non-allergic in nature. Nevertheless, mild allergic manifestations such as erythema or rash may occur, and in rare cases, severe reactions can progress to anaphylaxis. Medications and resuscitation equipment for symptomatic management should always be readily available in settings where PNBs are performed.

DISCUSSION

USG-guided PNBs are widely employed for intraoperative anesthesia and postoperative analgesia in orthopedic upper extremity surgeries. Each block carries distinct advantages, disadvantages, and potential complications (Table 1). Compared with traditional nerve stimulator techniques, USG-guided PNBs have been shown to increase success rates and reduce the need for supplemental analgesics or sedatives. For example, in rotator cuff surgeries, the rate of conversion to general anesthesia was significantly lower with USG-guided interscalene blocks than with nerve stimulator-guided procedures (0.5% vs. 6.7%, $p < 0.001$).^[36]

The supraclavicular block provides rapid onset and homogeneous anesthesia of the distal upper extremity. However, pneumothorax remains a risk, even with USG guidance. More than half of the pneumothorax cases reported in the literature are associated with this block, highlighting the need for caution in patients with underlying pulmonary disease.^[30] Additionally, the volume of local anesthetic appears to influence the incidence of phrenic nerve-related diaphragmatic paralysis; higher volumes are linked with greater paralysis, prompting recommendations for low-to-medium volumes for safety.^[33]

The infraclavicular block is advantageous for providing long-term analgesia in forearm and hand surgeries due to its homogeneous blockade of distal branches and ease of catheter placement. Compared with the supraclavicular block, it significantly prolongs motor block duration and shortens time to surgery.^[37] Moreover, the costoclavicular approach to the infraclavicular block has been shown to markedly reduce the incidence of hemidiaphragmatic paralysis and better preserve postoperative pulmonary function.^[38] Infraclavicular blocks are also associated with a lower risk of Horner syndrome compared with supraclavicular blocks.^[39]

By contrast, the axillary block minimizes the risk of pneumothorax and diaphragmatic paralysis due to its superficial anatomical location and distance from the pleura and phrenic nerve. It is therefore considered a particularly safe option for hand and wrist procedures.

Table 1. Ultrasonography-guided peripheral nerve blocks performed in upper extremity orthopedic surgeries

Block	Clinical application	Target nerves/structures	Advantages	Disadvantages	Complication
Cervical plexus block (superficial/deep)	Neck surgeries, clavicle fractures, adjunct in shoulder surgeries	Superficial: C2–C4 cutaneous branches; Deep: C2–C4 spinal nerve roots	Simple, safe	High risk in deep block, insufficient for shoulder	Phrenic nerve block, diaphragmatic paralysis, vertebral artery puncture, LAST
Interscalene block	Shoulder and upper arm surgeries	C5–C7 brachial plexus roots/trunks	Most effective for shoulder, rapid onset	Often spares C8–T1, short duration	Phrenic nerve paralysis, laryngeal nerve block, Horner syndrome
Suprclavicular block	Elbow, forearm, hand surgeries; sometimes shoulder	Brachial plexus trunks and divisions	Rapid and dense block, wide applicability	Risk of pneumothorax, less effective for shoulder	Pneumothorax, Phrenic nerve paralysis, Horner syndrome, LAST
Infracavicular block	Elbow, forearm, hand surgeries	Brachial plexus cords	Suitable for catheter placement	Technically more difficult, close to vascular structures	Hematoma, pneumothorax, LAST
Axillary block	Forearm and hand surgeries	Median, ulnar, radial, musculocutaneous nerves	Safe, no risk of pneumothorax	Additional injection may be needed for musculocutaneous nerve	Hematoma, infection, LAST
Median nerve block	Palmar surface of the hand, 2 nd –3 rd finger surgeries	Median nerve (forearm/hand)	Localized, targeted analgesia	Limited area, often requires combination	Nerve injury, LAST
Ulnar nerve block	Ulnar side of hand, 4 th –5 th finger surgeries	Ulnar nerve (elbow/wrist)	Sufficient for specific surgery	Limited scope, requires precise localization	Nerve injury, paresthesia, LAST
Radial nerve block	Dorsal hand, thumb surgeries	Radial nerve (elbow/wrist)	Sufficient for specific surgery, safe	Does not provide full hand analgesia, often requires combination	Nerve injury, hematoma, LAST

LAST: Local anesthetic systemic toxicity

This narrative review has several limitations. First, although studies from specific databases and within a defined time frame were screened, explicit inclusion and exclusion criteria were not applied. Second, unlike systematic reviews or meta-analyses, this review does not provide pooled quantitative outcomes. Finally, the narrative design may have led to the unintentional omission of relevant studies or disproportionate emphasis on certain findings.

CONCLUSION

With advances in ultrasonographic imaging and the increasing popularity of regional anesthesia, particularly brachial plexus nerve blocks, the use of these techniques in orthopedic upper extremity surgery has expanded considerably. USG-guided PNBs provide precise and targeted anesthesia and analgesia, reduce systemic opioid requirements, and help prevent opioid-related complications. Optimal outcomes are achieved when block selection is tailored to the patient and procedure and performed by experienced practitioners.

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Porcelain Gallbladder Undetected by Preoperative Imaging Findings: A Case Report and Literature Review

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ABSTRACT

Porcelain gallbladder is a rare condition, defined as calcification of the gallbladder wall. Its etiology is still not well established, but a relationship with gallstones of up to 95% is suggested, which causes an obstructive effect that triggers an inflammatory process with subsequent irritation and fibrosis of the gallbladder wall, either focal (affecting only the muscle layer) or transmural. It often has an asymptomatic course but may present as a case of chronic cholecystitis. It is a relevant pathology because a relationship with gallbladder cancer of up to 6% has been demonstrated, and in this regard, the role of prophylactic cholecystectomy is still debated. This article presents the case of a 51-year-old woman who consulted for abdominal pain in the right hypochondrium. An ultrasound was performed, diagnosing cholelithiasis with cholecystitis and a gallbladder with a thickened wall and mobile stones inside. A laparoscopic cholecystectomy was performed, with samples taken for pathology, and malignancy was ruled out.

Keywords: Abdominal pain, cholecystectomy, diagnosis, gallbladder, gallbladder neoplasms, treatment

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INTRODUCTION

Porcelain gallbladder is a rare condition characterized by calcification of the gallbladder wall, resulting in a bluish coloration due to calcium deposition, typically associated with chronic inflammation.^[1] This finding is usually incidental, with a prevalence ranging from 0.06% to 0.8% in cholecystectomy specimens. In 90–95% of cases, it is associated with gallstones, which constitute a significant risk factor.^[2]

It predominantly affects women, with a female-to-male ratio of approximately 5:1, and has a higher prevalence in the sixth decade of life.^[3] Around 18% of cases are asymptomatic; when symptoms occur, they resemble chronic cholecystitis, including abdominal pain, anorexia, nausea, vomiting, fever, and jaundice.^[4,5] Diagnosis is typically made through imaging studies such as abdominal radiography, ultrasound, or computed tomography, with gallbladder wall calcification being the most consistent finding.^[1,4]

Although rare, porcelain gallbladder is significantly associated with gallbladder cancer, particularly adenocarcinoma, occurring in 2–3% of cases.^[5] Selective mucosal calcification, in particular, has been linked to malignancy rates of up to 7%.

Preoperative diagnosis is important for surgical planning and to reduce complications such as bleeding, perforation, or conversion to open surgery. Imaging—such as ultrasound, CT, or MRI—can help assess the extent of calcification, detect chronic inflammation, identify adhesions, and rule out malignancy. This information is essential for anticipating technical challenges, selecting the surgical approach, and optimizing perioperative care.^[6]

The following case describes an incidental intraoperative finding of porcelain gallbladder, undetected by preoperative imaging. Given its unusual presentation and clinical relevance, we aim to highlight its features and the challenges it presents in surgical management.^[7,8]



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CASE REPORT

A 51-year-old woman with no relevant past medical history presented to the emergency department with an eight-month history of intermittent right upper quadrant pain, exacerbated by fatty meals. The pain was self-limiting and occasionally accompanied by nausea and bilious vomiting.

On admission, the patient was in good general condition: alert, oriented, afebrile, hydrated, with stable vital signs, and without respiratory distress. Physical examination revealed no scleral icterus or cardiopulmonary abnormalities. The abdomen was soft, tender in the right upper quadrant, without peritoneal signs, palpable masses, or organomegaly.

Laboratory tests showed mild leukocytosis; liver function tests were normal. Abdominal ultrasound revealed a normal-sized liver and a gallbladder with thickened walls (5 mm), mobile gallstones, and no biliary dilation. The common bile duct measured 2.9 mm. Pancreas, kidneys, and spleen were normal. The diagnosis was cholelithiasis with signs of cholecystitis.

The patient was admitted and underwent laparoscopic cholecystectomy. Intraoperatively, a porcelain gallbladder was identified. Resection of the gallbladder and cystic lymph node was performed. Histopathological examination revealed low-grade dysplasia of the gallbladder wall, without adenocarcinoma or high-grade dysplasia. The cystic lymph node was negative for malignancy (Figs. 1,2).

DISCUSSION

Porcelain gallbladder is a rare condition defined by the calcification of the gallbladder wall, giving it a bluish and hardened appearance resembling "porcelain".^[9]

This entity primarily affects individuals over 60 years old and is associated with gallstones in up to 95% of cases.^[2]

Its etiology remains unclear, but various theories have been proposed regarding its development. Chronic inflammation of the gallbladder has been identified as a potential cause, leading to hemorrhage and scarring of the gallbladder wall.

Additionally, the accumulation of gallstones, obstruction of the cystic duct, and subsequent bile stasis may irritate the gallbladder wall due to the precipitation of calcium carbonate in the mucosa.

Calcification patterns are classified based on their extent: complete intramural calcification, which affects the entire wall thickness, and selective mucosal calcification, which only affects the muscular layer of the gallbladder wall. Patients with a complete calcification pattern may have a lower risk of developing malignancy.^[2,7,10]

Many cases are diagnosed incidentally during abdominal imaging studies. On an abdominal X-ray, intramural calcification may appear as a rounded opacity in the right upper quadrant, though focal calcifications might not be visible.^[5]

It is essential to identify undiagnosed cases of porcelain gallbladder through diagnostic imaging in order to antici-

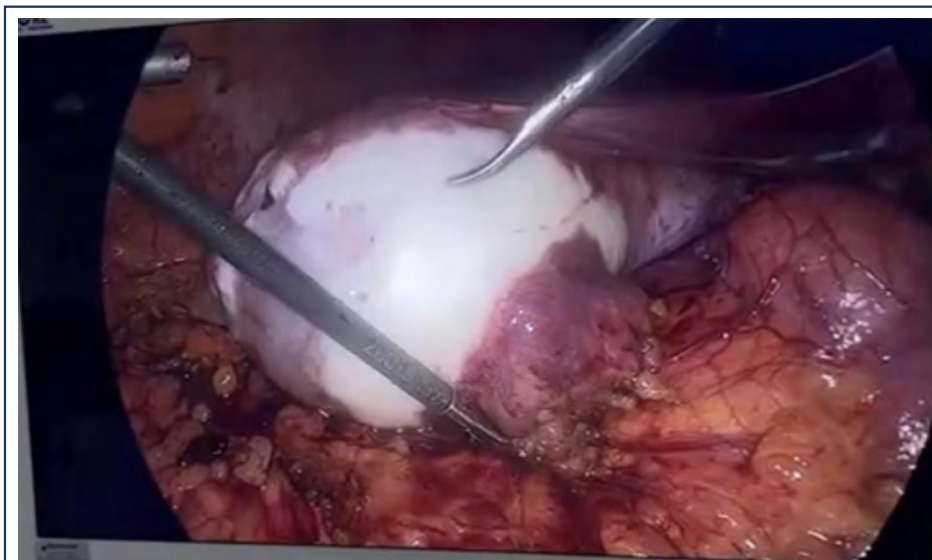


Figure 1. Intraoperative laparoscopic view of a porcelain gallbladder. The gallbladder wall appears whitish, calcified, and glossy, characteristic of this condition, during dissection of Calot's triangle



Figure 2. Laparoscopic view of a porcelain gallbladder from an inferior angle. Note the diffuse calcification and thickening of the wall, with a smooth, porcelain-like surface

pate surgical complexity.^[11–14] Calcification of the gallbladder wall can complicate dissection during cholecystectomy and increase the risk of bleeding or bile duct injury. Moreover, preoperative imaging is key to assessing oncologic risk, reducing complication rates, and avoiding unplanned intraoperative decisions.^[15,16]

Ultrasound findings may reveal different patterns: a hyper-echoic crescent structure with posterior acoustic shadowing; a biconvex curvilinear echogenic structure with acoustic shadowing; or irregular clusters of echoes with posterior acoustic shadowing. These findings are crucial in ruling out differential diagnoses such as a gallbladder filled with gallstones (which would present with the “wall-echo-shadow” sign) and emphysematous cholecystitis (characterized by “ring-down artifacts” due to trapped gas movement). However, ultrasound does not always allow for a definitive diagnosis of porcelain gallbladder due to its limited ability to distinguish between large gallstones, wall thickening, or mural calcification.^[11]

Taylor et al.^[15] described three ultrasound patterns that may hinder diagnosis:

1. **Semilunar pattern:** A posterior acoustic shadow that can mimic a single large gallstone.
2. **Curvilinear pattern:** A continuous echogenic band that may be confused with thickened wall, intraluminal gas, or vascular calcification.

3. **Irregular clumps:** Discontinuous echogenic foci that can be mistaken for chronic cholecystitis, adenomyomatosis, or calcified polyps.

Because of these challenges, it is recommended to supplement ultrasound with contrast-enhanced abdominal computed tomography in patients with high clinical suspicion—namely, those with chronic cholelithiasis, atypical biliary symptoms, or incidental findings on abdominal X ray or ultrasound.^[16,17]

The clinical relevance of this condition lies in its high risk of associated gallbladder malignancy. Previously, its incidence was believed to range from 12% to 62%. However, recent studies suggest a much lower incidence.^[3] A 2012 study by Schnelldorfer et al.^[9] found that patients with gallbladder calcification have a 6% risk of developing malignancy compared to 1% in those without this condition. Since many patients are asymptomatic, diagnoses are often delayed, contributing to a poor 5-year survival rate of only 19%.

Prophylactic cholecystectomy is not routinely recommended, but it remains a controversial topic.^[1,5] Most sources agree that patients should be assessed individually; prophylactic cholecystectomy is recommended in symptomatic patients, patients with radiographic findings suggestive of malignancy such as a gallbladder mass, focal wall thickening, or local invasion; patients with clinical signs highly suggestive of gallbladder cancer (jaundice, Courvoisier signs, or unexplained weight loss); or young patients with low surgical risk. It is not usually indicated in asymptomatic

ic patients without the findings described above, given the low probability of developing cancer.^[12,17,18]

Conservative management may be reasonable when cancer risk factors or suggestive signs are unclear, or in patients with a high surgical risk.^[10]

This approach is generally recommended for incidental findings when surgical risks outweigh cancer development risks. Serial ultrasound evaluations of the gallbladder may support this decision.^[1]

Additionally, in patients without clear biliary symptoms, no history of chronic cholelithiasis, or no findings on initial imaging, a conservative strategy is recommended. If nonspecific ultrasound findings are present in asymptomatic patients, a follow-up ultrasound can be performed in 3–6 months to assess for any changes.^[12,17]

Histopathological examination of the porcelain gallbladder is crucial. If malignancy is detected, extended or radical cholecystectomy (wedge resection of the liver and gallbladder bed, followed by lymphadenectomy) is the treatment of choice.^[6]

Surgical management poses challenges due to the gallbladder's calcified wall, adhesions in the pericholecystic region and hepatic bed, as well as tissue friability, increasing the risk of bleeding and conversion to open surgery (5–25%).^[1]

Despite these difficulties, laparoscopic cholecystectomy remains the preferred approach.^[8,14]

CONCLUSION

In conclusion, porcelain gallbladder is a pathology with a low prevalence, and its diagnosis is usually incidental. Its association with malignancy development remains a condition of clinical interest. Laparoscopic cholecystectomy is the treatment of choice in symptomatic patients or those with findings suggestive of malignancy. The use of various diagnostic tools is necessary to clarify the actual cancer risk in these patients.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of the clinical details and images.

Resources

We reviewed relevant literature on porcelain gallbladder, its diagnosis and management, using PubMed and Google Scholar. The diagnosis was mainly based on abdominal ultrasound findings. Laparoscopic cholecystectomy was done following the standard surgical protocols. The manuscript was prepared using Microsoft Word following the journal's formatting guidelines.

Disclosures

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from the patient for publication of the clinical details and images.

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