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CONTENTS

EDITORIAL

ORIGINAL ARTICLES

TURKISH JOURNAL OF SURGERY
OFFICIAL JOURNAL OF TURKISH SURGICAL ASSOCIATION

CASE SERIES

REVIEWS

LETTER TO THE EDITOR

TURKISH JOURNAL OF SURGERY
OFFICIAL JOURNAL OF TURKISH SURGICAL ASSOCIATION

FROM THE EDITOR-IN-CHIEF'S DESK

Celebrating Science, Collegiality, and Shared Purpose: Reflections Following the 24th National Congress of Surgery

Prof. Umberto Veronesi

Prof. Orlo Clark

We remember Prof. Veronesi and Prof. Clark with great respect and affection. Their legacy lives on in the hearts and minds of surgeons around the world …

(Adapted from the AI Panels at the 24th National Congress of Surgery)

Time seems to speed up when engaged in meaningful work. What felt like a distant goal just months ago now appears to have passed in the blink of an eye. The days leading up to the 24th National Congress of Surgery were marked by anticipation, preparation, and extensive collaboration. Reflecting on the congress, it's clear how quickly those moments have become memories. This feeling underscores that our most valuable professional experiences are often defined not by how long they last but by their significance. The scientific discussions, shared successes, and collegial interactions from those days will remain impactful long after the congress ends.

The 24th National Congress of Surgery attracted 595 distinguished national speakers and 17 renowned international experts, with more than 2800 attendees, offering an excellent platform for scientific exchange and professional networking. A collaborative session with the British Journal of Surgery, led by Prof. Anders Bergenfelz, further enhanced international academic ties and encouraged dialogue on current surgical issues. A standout innovation of the congress was the integration of artificial intelligence into the scientific program. AI participated as a panel member, highlighting the increasing role of new technologies in medical education and research. Additionally, virtual recreations of Prof. Orlo Clark and Prof. Umberto Veronesi—whose contributions to surgery remain highly influential—were brought to life using AI and participated in panel discussions. This pioneering effort effectively connected the legacy of iconic surgeons with future technological advancements, providing an unforgettable experience for attendees.

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Among the many accomplishments of this year's congress, I am particularly proud of another milestone. In the current issue, the abstracts presented at the National Congress of Surgery are published as a supplement to the Turkish Journal of Surgery. This supplement serves not only as a permanent scientific record of the congress but also as a testament to the vitality, productivity, and academic rigor of our surgical community. Disseminating congress abstracts through the Turkish Journal of Surgery, the official journal of the Turkish Surgical Society, extends the reach of the scientific contributions shared during the meeting, allowing them to be accessed, cited, and built upon by a wider audience. It also reflects the growing integration between our national scientific congress and our journal, both of which share a mission to advance surgical science and education.

I would like to express my sincere appreciation to all authors, reviewers, editors, and members of the surgical committee whose efforts made these achievements possible. Seeing the collective work of our colleagues preserved in the journal's pages is a source of great pride and a reminder of the remarkable scientific energy that continues to drive Turkish Journal of Surgery forward.

As always, I sincerely thank our readers for their continued trust and support.

Prof. M. Umit UGURLU
TurkJSurg Editor-in-Chief

EDITORIAL
Turk J Surg 2026;42(2):154-155

Advancing pilonidal sinus care through structured international collaboration: The PiloNERDs

Dietrich Doll

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INTRODUCTION

Pilonidal sinus disease (PSD) remains one of the most frequent benign surgical conditions affecting adolescents and young adults worldwide. While particularly common in Türkiye, PSD also represents a substantial clinical burden across Northern Europe and North America, with steadily increasing incidence reported throughout large parts of Asia. Despite its global prevalence, management strategies remain strikingly heterogeneous.

Türkiye occupies a unique position in this landscape (1). The disease is encountered with high frequency, and Turkish surgeons have demonstrated strong and sustained academic engagement, reflected in numerous publications (2), focused conference sessions, and lively national discourse. This commitment was most recently highlighted by the dedicated Pilonidal Sinus Disease Congress in İstanbul in 2025, organised under the leadership of Çiğdem Arslan—a clear signal of national momentum and professional investment in advancing pilonidal care.

Yet, despite this impressive national activity, international integration of data, methodology, and outcome assessment remains weak. Surgical techniques vary widely between centres; definitions of recurrence and healing lack harmonisation; and follow-up periods are frequently too short to allow meaningful comparison. For a disease of such prevalence and socio-economic impact, fragmented evidence is no longer acceptable. Our patients deserve standards derived from structured, transparent, and reproducible science.

The Turkish Journal of Surgery plays an important role in shaping academic dialogue and disseminating high-quality surgical research. Given the substantial burden of PSD within Türkiye's young population (3), the journal is uniquely positioned to foster broader scientific alignment and international visibility in this field.

However, publications and meetings alone are no longer sufficient.

The next step must be deliberate and organised cross-border collaboration: Shared registries, harmonised outcome definitions, consensus on meaningful long-term follow-up, multicentre data pooling, and open methodological exchange. Without such structure, variability will persist, and progress will remain incremental rather than transformative.

In response to this need, PiloNERDs International (Pilonidal Network for Expertise, Research, and Development) was established as a clinician-led, globally connected framework dedicated exclusively to pilonidal disease. Its purpose is practical and outcome-oriented. By aligning definitions, encouraging rigorous long-term assessment, facilitating collaborative research projects, and providing structured educational resources, the network seeks to elevate both scientific quality and everyday surgical care.

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Türkiye—with its high case volume and demonstrably strong professional interest—represents a pivotal partner in this endeavour. Greater international collaboration will not dilute national expertise; rather, it will amplify it. Shared datasets increase statistical power. Harmonised methodology enhances comparability. Transparent exchange accelerates innovation. Most importantly, structured cooperation directly benefits the predominantly young patients entrusted to our care.

The surgical community stands at a point where isolated excellence must evolve into coordinated progress. The urgency is clear. Scientific rigour, methodological discipline, and collaborative openness are no longer optional—they are prerequisites for responsible patient care.

Discover more at www.pilonerds.com.

Clinicians and researchers are therefore warmly invited to engage actively with PiloNERDs International: To contribute data, participate in collaborative projects, refine definitions, and help shape the standards that will define the next generation of pilonidal surgery.

Keywords: General surgery, international PiloNerds network, pilonidal sinus surgery, scientific surgery

Footnotes

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

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ORIGINAL ARTICLE
Turk J Surg 2026;42(2):156-166

Public awareness, health care-seeking behaviors, and barriers to care for acute abdominal pain in Jordan: A cross-sectional study

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ABSTRACT

Objective: Acute abdominal pain (AAP) is a leading cause of visits to the emergency department (ED) and is often a condition requiring immediate attention and timely management to prevent potentially serious complications like sepsis. Despite the importance of this topic, public knowledge about AAP and when to seek care remains underexplored, particularly among non-medical populations. This study aimed to assess public knowledge, attitudes, and practices regarding AAP, identify their sources of health information about the condition, and pinpoint barriers to seeking medical care in Jordan.

Material and Methods: A cross-sectional survey was conducted among Jordanian adults using a self-administered questionnaire that was developed after a thorough literature review, tested and validated in a pilot study. Convenience and snowball sampling methods were used to collect data, which were analyzed using descriptive and inferential statistics, including linear regression analysis to identify predictors of knowledge and attitudes.

Results: A total of 1.566 Jordanians participated in the study, with a median age of 26 years (interquartile range: 23-41). The most commonly perceived cause of AAP was the digestive system (86%), with changes in bowel habits (57%) and bloating (51%) being the most recognized associated symptoms. The mean knowledge score was 6.9±3.0, with most participants having fair (53.8%) or good (35.3%) knowledge scores. The vast majority (91.8%) had a positive attitude regarding the importance of raising and awarding about AAP, with a mean score of 7.89±1.66 out of 10. Age, female gender, marital status, parenthood, and prior abdominal surgery were positively associated with both better knowledge and attitude scores (p-values <0.05). However, when experiencing AAP, 35.5% reported that they would take painkillers and wait, and 30% would rest at home, while only 19.7% would seek medical help. Moreover, 4% stated that they would not seek care even in the presence of red flag symptoms. The main barriers to seeking care included long waiting times (47%) and lack of confidence in healthcare providers (31%). Regarding the sources of information about AAP, doctors and health professionals were the primary source of AAP knowledge (61%), followed by personal experiences and advice from friends and family (41%).

Conclusion: Most participants had fair to good knowledge and a positive attitude toward AAP, yet a significant proportion opted for self-management over seeking medical help. The main barriers to seeking care included long waiting times, and distrust in healthcare providers. Well-coordinated education campaigns and system-level interventions are advocated to overcome the existing barriers and improve outcome for AAP in Jordan.

Keywords: Acute abdominal pain, knowledge, attitudes, and practices, acute abdomen, public awareness, Jordan

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INTRODUCTION

Abdominal pain is a general term that includes both acute and chronic discomfort in the abdomen and is one of the most common reasons for emergency department visits; it accounts for up to 10% of all emergency department visits (1,2). Acute abdominal pain (AAP), on the other hand, refers to a sudden severe onset of pain typically lasting less than seven days, which often requires immediate medical attention to diagnose and manage potentially serious or life-threatening underlying pathology (3), including infections, inflammation, vascular occlusion, bowel obstruction or perforation, hepatobiliary diseases, or referred pain from the lungs due to pneumonia, inferior myocardial infarction, or multiple other extra-abdominal causes that could "mimic" acute abdomen (4-6). Moreover, AAP must be approached in a time-sensitive manner to prevent severe potential complications such as sepsis, tissue necrosis or gangrene, fistula formation, and even death (6). Despite

advancements in the diagnostic approach to AAP, especially owing to the utilization of advanced imaging modalities such as computed tomography scans, the rate of initial misdiagnosis remains as high as 6% (6-9).

Public knowledge and awareness regarding AAP, including when to seek medical care, remain insufficiently explored, particularly among non-medical populations. A recent study from Saudi Arabia explored general public knowledge about AAP and revealed that the vast majority of the population involved had inadequate levels of awareness about the condition (10). However, to our knowledge, no other studies have specifically addressed this topic within the Middle East Region.

This study highlights the importance of improving public awareness, attitudes, and practices related to the AAP while also identifying barriers that delay timely medical help and factors influencing healthcare-seeking behavior from the public's point of view. By conducting a cross-sectional study among the Jordanian population, we aim to address these gaps and improve outcomes through early recognition and intervention.

MATERIAL and METHODS

Study Design and Study Population

This is an observational cross-sectional study among the Jordanian population conducted throughout November and December 2024. The present study followed the strengthening the reporting of observational studies in epidemiology statement guidelines from the enhancing the quality and transparency of health research network (11), and the study's protocol received approval from the Research Ethics Committee of the School of Medicine at Balqa Applied University (IRB number: 2025/2024/6/67, date: 24/02/2025).

The study's inclusion criteria specified that participants must reside in Jordan, be over 18 years of age, and lack formal training or education in medical sciences. The exclusion criteria included individuals under 18 years of age, those currently working or studying in the medical field, and individuals who did not fully complete the questionnaire.

Study Sample and Data Collection

Assuming the Jordanian population to be 11,536,562, as reported by the Worldometer website, a reliable source for real-time statistics and demographic data across various domains (12), the minimum required sample size was calculated as 385 via an online sampling calculator (OpenEpi) (13), with the following parameters: A confidence level of 95%, a margin of error of 5%, and an assumed response distribution of 50%. However, we collected a significantly larger sample of 1566 participants.

To achieve a high response rate for the online questionnaire, the convenience sampling method was used. The survey was uploaded electronically to a Google form and distributed via social media platforms, both through personal outreach and public dissemination by data collectors. To prevent duplicate entries, participants were required to provide an email address linked to the form. Before data collection, all the participants were informed about the study's purpose and assured of the voluntary nature of their participation. Electronic consent was obtained through a consent question at the beginning of the survey. The participants completed the survey anonymously at their convenience and did not receive any form of compensation for their participation.

Surveying Tool

The questionnaire was designed based on a comprehensive literature review and initially developed in English by a team of three medical professionals, including a general surgeon. It was then translated into Arabic by a professional translator, followed by back-translation into English by a different translator to ensure fidelity to the original content. The initial version of the questionnaire was validated for content validity by a panel of experts (including a general surgeon, a practicing physician, and a public health expert), and a subsequent pilot study was conducted to check for face validity, internal consistency, and reliability. This pilot study included an open-ended question for participants to provide feedback on the clarity and comprehensibility of the survey items. A total of 78 participants from the target population participated in the pilot study, and their feedback was used to refine and amend the survey instrument as needed.

The study included two primary scales: A knowledge scale and an attitude scale. The knowledge scale achieved a Cronbach's alpha of 0.68, indicating acceptable reliability for exploratory research. The Spearman's rho correlation coefficient between the two attitude-related questions was 0.83, indicating strong internal consistency. Data collected during the pilot study were excluded from the final analysis. The finalized version of the survey was presented in Arabic, the official language of Jordan (Supplementary Table S1).

Our questionnaire consisted of seven sections and thirty-five questions. The demographic information included eleven items: Age, sex, marital status, geographical region, educational level, presence of children, medical background, history of abdominal surgery (including type), and experiences with misdiagnosis. General knowledge was evaluated through two questions addressing participants' understanding of AAP-associated symptoms and underlying causes. The knowledge score section included 15 questions derived from a thorough literature review, with correct responses scored as 1 and incorrect responses as 0, resulting in total scores ranging from 0 to 15. Higher scores indicate greater understanding of the condition, categorized as poor (0-3), fair (4-7), good (8-11), or excellent (12-15). Attitudes

toward the AAP were assessed via two questions addressing interest in the condition and perceived importance, with responses recorded on a 5-point Likert scale and summed to provide a total score of 10, where higher scores represented more positive attitudes. Practices explore initial actions taken after an AAP episode and the symptomatic threshold for seeking medical care. Barriers to seeking help were tested via multiple-choice questions, including concerns about transportation difficulties, long waiting times, lack of trust in healthcare providers, financial constraints, and others. Another question tested perceived barriers or reasons for avoiding direct surgical consultation, including fear of immediate surgery without confirmation, the time required to seek a surgeon's opinion, etc. Finally, sources of information about AAP/abdominal pain were tested in another one of the multiple-choice questions, including options for consultations with doctors or health professionals, personal or shared experiences from friends and family, reputable medical websites (e.g., Mayo Clinic, WebMD), etc.

Statistical Analysis

The data analysis was conducted via JAMOVI (version 2.5) (14). Descriptive statistical measures, including percentages, frequencies, means, and standard deviations, were used to summarize the participants' demographic characteristics. Normality was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests, which confirmed that the age, total knowledge and attitude scores did not follow a normal distribution. Consequently, non-parametric tests were used, and Spearman's correlation was applied to examine the relationships between total knowledge and attitude scores and age. The Mann-Whitney U test and Kruskal-Wallis H test was used to analyze the associations with the other demographic characteristics. P-values ≤0.05 were considered statistically significant.

RESULTS

Socio-demographic Characteristics

A total of 1566 Jordanians, with a median age of 26 years (interquartile range: 23-41), participated in the study. Most of them lived in the middle region of Jordan, including the capital Amman, Zarqa, Balqa, and Madaba (979, 62.5%), and 70% (n=1104) were females Table 1 lists the remaining socio-demographic characteristics of the participants in detail.

Previous Abdominal Surgery

A total of 174 participants (11.11%) declared that they had previous abdominal surgery. In more details, these surgeries included in descending frequencies the following: appendectomy (41.95%, n=73), cholecystectomy (32.18%, n=56), bowel obstruction surgery (2.87%, n=5), perforated ulcer surgery (0.57%, n=1), intestinal volvulus surgery (1.15%, n=2), partial bowel resection (2.30%, n=4), and abdominal aortic rupture surgery (1.15%, n=2). Additionally, 19% (n=33) of them were identified as non-surgical cases (misdiagnosed) before undergoing surgery.

Knowledge

General Knowledge about the Causes and Symptoms Associated with AAP

With respect to the perceived causes of AAP among the included Jordanian population, the digestive system (86%, n=1346) was the most frequently reported cause, followed by the appendages of the digestive system (44%, n=689), urinary system (35%, n=548), muscular system (32%, n=501), and reproductive system (28%, n=438). Less frequently cited causes included the circulatory system (14%, n=219), heart disease (6%, n=93), and the respiratory system (4%, n=62). With respect to the symptoms identified by participants as associated with AAP, changes in bowel habits, including diarrhea or constipation (57%, n=892), bloating (51%, n=798), and muscle cramps in the abdominal wall (51%, n=798), were the most common. Other frequently reported symptoms included vomiting (43%, n=673) and nausea (42%, n=657), whereas loss of appetite (22%, n=344), rapid heart rate (17%, n=266), fever (15%, n=234), and dry mouth (8%, n=125) were less common.

Table 1. Demographic characteristics of the study participants, n=1566

Demographic characteristics	n	%
Age (mean, SD)	31.5,11.8	
Gender		
Male	462	30.0
Area of residence		
North Region (Irbid, Ajloun, Jerash, Mafraq)	554	35.4
Central Region (Amman, Zarqa, Balqa, Madaba)	979	62.5
South Region (Karak, Ma'an, Tafila, Aqaba)	33	2.1
Marital status		
Single	866	55.3
Married (or previously married)	700	44.7
Have children		
Yes	610	39.0
Education level		
Below secondary education	39	2.5
Completed secondary education	202	12.9
Undergraduate degree (bachelor's)	1141	72.9
Postgraduate education	184	11.7
Medical insurance coverage		
Yes	1117	71.3
History of abdominal surgery		
Yes	174	11.11

SD: Standard deviation.

AAP Knowledge Scale Results

The mean knowledge score was 6.9±2.47, with 53.8% (n=842) of the participants showing fair knowledge, 35.3% (n=552) good knowledge, 7.21% (n=112) poor knowledge, and 3.64% (n=57) excellent knowledge. Nearly half believed that the condition should always be approached as an emergency and that it might require emergency surgery (639, 40.8%). However, only 9.2% (n=144) considered consulting a surgeon in the emergency department as an initial step to be appropriate. Table 2 presents the percentage of correct answers per question.

Knowledge Scores by Demographics

Age was weakly yet significantly associated with better knowledge scores (r=0.147, p<0.001), and females had significantly higher scores than males did (8.11±1.46 vs. 7.38±1.97, p<0.001). Moreover, married participants, parents and those who had undergone urgent abdominal surgery scored higher (p<0.001, p<0.001, p=0.008, respectively). Geographical region significantly influenced scores, after post-hoc analysis to identify specific differences, participants from northern Jordan scored higher those from middle Jordan did (p=0.017*), as demonstrated in Tables 3 and 4.

Attitudes

Attitudes Scale Results

When asked about interest in learning more about AAP, 49% (n=767) expressed some level of interest, and 18% (n=283) were very interested (Figure 1). Regarding the perceived importance of raising public awareness about AAP, 44% (n=688) agreed, while 41% (n=649) strongly agreed (Figure 2). The mean attitude scores out of 10 was 7.89±1.66, with the majority (1438, 91.8%) showing a positive attitude (scores of 6-10) and only 8.2% (n=128) displaying a negative to neutral attitude (scores of 1-5).

Attitude Scores by Demographics

Age was positively correlated with attitude (r=0.147, p<0.001). Gender differences were significant, with females scoring higher than males (p<0.001). Married individuals, parents, and those who had previously undergone abdominal surgery scored

Table 2. Knowledge scores: detailed responses and percentages for each question, n=1566

	Question	Correct answer	n	%
1.	Please choose the correct statement from the following regarding the appropriate description of the levels of acute abdominal pain reported in the questionnaire.	1) Acute abdominal pain means very severe and sudden pain	653	41.7
2.	How should acute abdominal pain be treated according to your point of view:	1) It should always be treated as an emergency to determine its causes and treat it	639	40.8
3.	Where is the appropriate place to provide initial diagnosis and treatment for acute abdominal pain?	4) Hospital emergency department (emergency physician consults general surgeon first)	144	9.2
4.	Do you think that severe abdominal pain may require emergency surgery?	1) Yes	742	47.4
5.	Which of the following is a risk factor for developing severe abdominal pain that requires immediate medical attention?	2) Previous abdominal surgery	428	27.3
6.	Which of the following is a serious complication of untreated acute abdomen?	2) Infection spread to blood (sepsis)	510	32.6
7.	Which of the following conditions is not usually associated with an acute abdomen?	1) Irritable bowel syndrome	442	28.2
8.	What symptom might indicate a perforated peptic ulcer in a patient with an acute abdomen?	2) Sudden, severe pain with abdominal wall stiffness	915	58.4
9.	What is the most common cause of severe abdominal pain requiring emergency surgery in Jordan?	1) Appendicitis	920	58.7
10.	What is the treatment for acute appendicitis?	2) Appendectomy	1267	80.9
11.	Which of the following symptoms is a sign of gastrointestinal bleeding?	1) Change in stool color to dark black	1180	75.4
12.	In cholecystitis, where is the pain most often located?	2) Upper right abdomen	640	40.9
13.	Can angina (heart attack) present as severe abdominal pain?	1) Yes	736	47
14.	Which of the following symptoms might indicate intestinal obstruction as the cause of acute abdominal pain?	4) All of the above	941	60
15.	Pancreatitis usually presents as pain in which area?	2) Pain in the upper abdomen extending to the back	668	42.7

significantly higher scores (p<0.001, p<0.001, and p=0.0008, respectively), as illustrated in Table 3.

Correlation Between Knowledge and Attitude Scores

A moderate positive correlation was observed between knowledge and attitude scores (r=0.239, p<0.001), suggesting that higher knowledge scores are associated with more positive attitudes toward raising awareness about AAP.

Predictors of Knowledge and Attitude Scores

Using linear regression analysis, when compared to males, females had significantly higher knowledge scores (Estimate =1.079, p<0.001) and attitude scores (Estimate =0.704, p<0.001). In addition, participants from northern Jordan had higher attitude scores compared to those from southern Jordan (Estimate =-0.336, p=0.247) and middle Jordan (Estimate =-0.219, p=0.013), Table 5.

Practices

Regarding the initial steps that would be taken if experiencing AAP, 35.5% (n=556) of the participants reported that they would take painkillers and wait, 30% (n=470) would rest at home, and only 19.7% (n=309) would seek medical help (Figure 3). The participants were also asked about the thresholds and symptoms that would prompt them to seek medical care; more than a half reported that they would seek urgent medical care if their symptoms were associated with bleeding, for example, vomiting blood (64%, n=1002), and only 4% (n=63) reported that they would not seek care for any of the red flag symptoms listed (Figure 4).

Barriers to Seeking Medical Attention

Concerns regarding consulting a surgeon as an initial step in the emergency department in cases of AAP were commonly reported by participants. The most common concern, cited by 45% (n=705), was the fear of having surgery performed immediately without confirmation (Table 6). The barriers to seeking medical care in general in the case of facing AAP attacks were variable among participants. The most commonly cited concern was waiting times, reported by 47% (n=736), followed by a lack of confidence in healthcare providers' ability to manage AAP (485, 31%) (Table 7).

Sources of Knowledge

When asked about their main source of information regarding AAP, the majority (955, 61%) relied on consultation with doctors or health professionals (Figure 5).

Table 3. Differences in attitudes and knowledge scores in relation to the basic demographic characteristics of the participants, n=1566

Variable		Attitude			Knowledge		
		Mean score (SD)	**Test result**	**p-value**	**Mean score (SD)**	**Test result**	**p-value**
Age[a]	-		r=0.147	<0.001*	-	r=0.113	<0.001*
Gender[b]	Males	7.38 (1.97)	U=202851	<0.001*	6.10 (2.22)	U=187712	<0.001*
	Females	8.11 (1.46)			7.25 (2.49)		
Region[c]	North	8.08 (1.52)	χ^2=8.38	0.015*	7.16 (2.55)	χ^2=7.67	0.022*
	Middle	7.80 (1.73)			6.78 (2.40)		
	South	7.70 (1.63)			6.82 (2.80)		
Educational level[c]	Below secondary educ.	8.33 (1.24)	χ^2=6.51	0.089	6.74 (2.37)	χ^2=5.75	0.124
	Secondary educ.	7.94 (1.95)			6.53 (2.36)		
	Undergraduate	7.86 (1.62)			6.98 (2.50)		
	Postgraduate	8.00 (1.65)			6.96 (2.42)		
Marital status[b]	Single	7.71 (1.74)	U=261156	<0.001*	6.75 (2.60)	U=272257	<0.001*
	Married	8.12 (1.53)			7.11 (2.28)		
Do you have children?[b]	Yes	8.15 (1.53)	U=247594	<0.001*	7.13 (2.24)	U=262997	<0.001*
	No	7.73 (1.72)			6.77 (2.60)		
Previous abdominal surgery[b]	Yes	8.14 (1.49)	U=158531	0.008*	7.01 (2.48)	U=232022	0.02*
	No	7.84 (1.69)			6.68 (2.44)		
Insurance[b]	Yes	7.87 (1.70)	U=247158	0.647	7.31 (2.42)	U=157718	0.007*
	No	7.96 (1.56)			6.83 (2.47)		
Misdiagnosis history[b]	Yes	7.91 (1.72)	U=4595	0.36	7.31 (2.42)	U=157718	0.257
	No	**8.19 (1.45)**			**6.83 (2.47)**		

*: Indicates statically significant value at p-value <0.05, [a]: Spearman's rho test, [b]: Mann-Whitney U test, [c]: Kruskal-Wallis test, SD: Standard deviation, χ^2: Chi-square test statistic, r: Spearman's correlation coefficient; U: Mann-Whitney U test.

Table 4. Post-hoc analysis of knowledge and attitude scores across geographical regions of Jordan: Dwass-Steel-Critchlow-Fligner pairwise comparison, n=1566				
Attitude			**Knowledge**	
Comparison	**W value**	**p-value**	**W value**	**p-value**
Geographical regions				
North Jordan vs. Middle Jordan	-3.942	0.015*	-3.878	0.017*
North Jordan vs. South Jordan	-1.855	0.389	-1.256	0.648
Middle Jordan vs. South Jordan	-0.636	0.895	-0.204	0.989
*: Indicates statically significant value at p-value <0.05.				

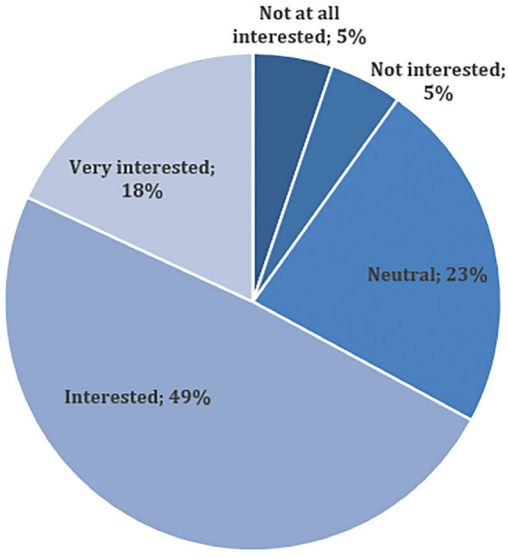

Figure 1. Interest level in learning more about AAP.
AAP: Acute abdominal pain

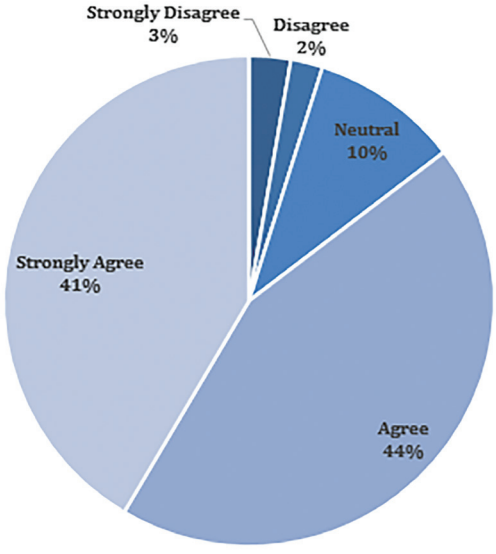

Figure 2. Perceived importance of raising public awareness about AAP.
AAP: Acute abdominal pain

DISCUSSION

This research included 1.566 Jordanians, with a median age of 26 years, the majority of whom were females (70%) and residents of the middle area of Jordan (62.5%). The mean knowledge score for AAP and its causes was 6.9±2.47 out of 15. The attitude levels were predominantly cautious, with a mean score of 7.89 out of 10. The participants prioritized rest or self-medication but would seek urgent care for severe symptoms such as vomiting blood or bloody stools. Most participants feared immediate surgery without confirmation of cause if surgical consultation was sought before an internal medicine doctor evaluated the presenting complaint. Barriers to seeking medical help are variable, with long waiting times being the most reported. A moderate positive correlation was found between knowledge and attitude scores, indicating that greater knowledge fosters better attitudes toward AAP awareness and care. To our knowledge, this is the first study to address these issues combined.

There is no conclusive evidence of the lifetime risk of intra-abdominal surgery; however, a study from North America in 2009 reported a prevalence between 8.2 and 29.1 for the population between 21 and 61 years old (15). In our study, 11.11% of participants had previously undergone abdominal surgery, falling within the same range, with appendectomy being the most commonly reported surgery, which is the most common type of abdominal surgical emergency, with a lifetime risk of 7-9% (16,17).

Among the enrolled Jordanian population, 35.5% had fair knowledge levels about AAP, which is significantly greater than the level of knowledge about AAP among the Saudi population, where 87.2% had poor knowledge scores (10); this could be attributed to differences in the knowledge scales used. The scale used in the Saudi study consisted of a concise 5-question scale, potentially limiting its ability to capture comprehensive knowledge about AAP, whereas our study used a broader and more detailed scale. Second, cultural and educational differences are likely to play a role. Demographic factors influenced knowledge scores, with age showing a weak positive correlation and female sex scoring higher. In Jordan, women's traditional role as household caregivers may enhances their awareness

Table 5. Predictors of knowledge and attitude scores using linear regression analysis, n=1566						
	Knowledge			**Attitude**		
Predictor	**Estimate**	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**
Gender						
Female-male	1.079	(0.813, 1.345)	<0.00*	0.704	(0.525, 0.883)	<0.001*
Area of living						
Middle Jordan–North Jordan	-0.183	(-0.442, 0.075)	0.164	-0.219	(-0.393, -0.046)	0.013*
South Jordan–North Jordan	-0.246	(-1.092, 0.600)	0.569	-0.336	(-0.904, 0.233)	0.247
Education						
Completed secondary education–Below secondary education	-0.255	(-1.083, 0.573)	0.545	-0.442	(-0.998, 0.114)	0.119
Undergraduate degree–Below secondary education	0.116	(-0.662, 0.894)	0.770	-0.517	(-1.040, 0.005)	0.052
Postgraduate education–Below secondary education	-0.104	(-0.942, 0.735)	0.809	-0.539	(-1.102, 0.025)	0.061
Marital status						
Single–Married	-0.162	(-0.670, 0.346)	0.532	-0.106	(-0.447, 0.235)	0.544
Children						
No–Yes	-0.144	(-0.667, 0.378)	0.588	-0.269	(-0.620, 0.082)	0.133
Medical insurance						
No–Yes	-0.226	(-0.495, 0.044)	0.101	0.173	(-0.009, 0.354)	0.062
Previous abdominal surgery						
No–Yes	-0.311	(-0.643, 0.021)	0.066	-0.103	(-0.325, 0.120)	0.366
*: Indicates statically significant value at p-value <0.05, CI: Confidence interval.						

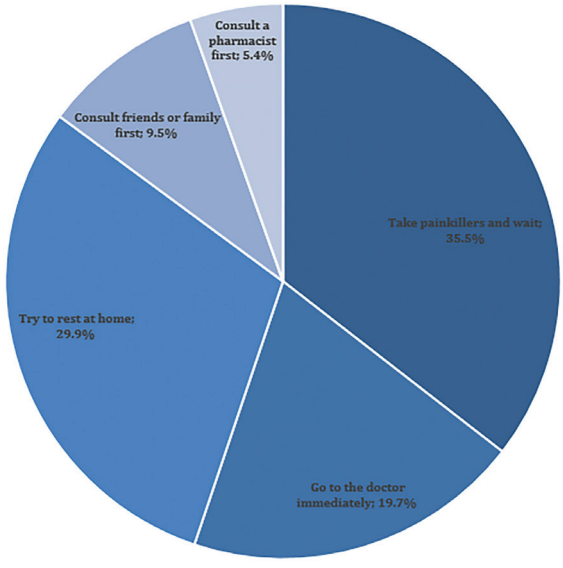

Figure 3. Initial actions taken during an episode of severe acute abdominal pain.

of conditions such as the AAP, whereas older participants may benefit from greater life experience with health issues. Conversely, in Saudi Arabia, males and younger participants had higher knowledge levels (10), possibly because of cultural norms and younger individuals' better access to online health resources (18). Compared with adults without children, parents also had better levels of knowledge, probably because becoming a parent often leads to increased interactions with healthcare systems, which can enhance health literacy and awareness of various medical conditions. Additionally, participants who had insurance had better knowledge scores, which was suggested in a recent study, indicating that health insurance literacy plays a crucial role in facilitating the effective use of healthcare services, including primary care and preventive care (19). Reasonably, a history of previous abdominal surgery led to significantly better knowledge scores, as undergoing abdominal surgery often involves preoperative and postoperative education, interactions with healthcare professionals, and firsthand experience with abdominal symptoms, all of which can contribute to a heightened awareness of abdominal health.

The vast majority of the population (91.8%) demonstrated a positive attitude toward the importance of raising awareness about the AAP, with a mean score of 7.89 out of 10, indicating widespread recognition of the topic's significance. Factors such as age, being female, parenthood, residing in northern Jordan, and a history of abdominal surgery positively influenced attitudes, likely for reasons similar to those enhancing knowledge scores. This finding is further supported by the moderate positive correlation observed between knowledge scores and attitude scores.

Notably, only 19.7% of participants reported that they would seek medical help immediately if facing an episode of severe AAP; on

Table 6. Perceived barriers to consulting a surgeon for acute abdominal pain, n=1566		
	n	%
1) Fear of having surgery done directly without confirmation.	698	45
2) Asking for a surgeon's opinion takes longer.	295	19
3) The decision to see a surgeon is up to the doctor who evaluated the case, and I have no right to discuss it.	296	19
4) All cases of acute abdominal pain do not need to be evaluated by a surgeon, but by an internist first.	412	26
5) A surgeon is not asked to perform surgery unless the internist or emergency physician decides to do so.	341	22
6) I don't know.	315	20

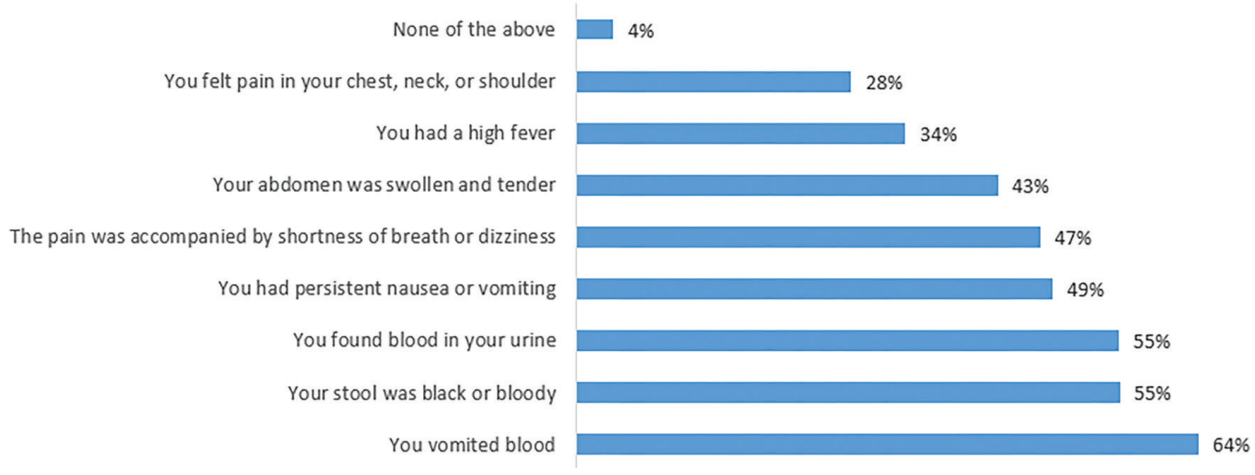

Figure 4. Symptoms prompting immediate medical consultation for acute abdominal pain.

the other hand, the majority of participants would rest at home or take painkillers and wait, but this may be appropriate if facing mild abdominal discomfort. In cases of AAP, serious underlying pathology is a considerable possibility, and timely evaluation and diagnosis are critical for appropriate management and avoiding life-threatening complications (20). This was previously reported in a study from the United States on factors associated with delayed health care seeking in cases of acute appendicitis; many individuals perceive their abdominal pain as mild or self-limiting, leading them to choose rest or over-the-counter pain relief instead of consulting a healthcare provider (21).

Our findings reveal critical gaps in participants' health-seeking behavior, particularly in recognizing and responding to serious or life-threatening symptoms. While the majority (61%) reported that they would seek medical attention for symptoms explicitly associated with trauma or visibly alarming conditions (e.g., vomiting blood or blood in stool/urine), less than half acknowledged the need for care and apparently underestimated the need for escalation when experiencing other red flag symptoms such as shortness of breath, dizziness, swollen and tender abdomen, persistent nausea/vomiting, or high fever.

Moreover, the fact that 4% of the participants avoid seeking care for any symptoms is alarming, indicating that the majority recognized the importance of medical intervention in at least some circumstances but that a percentage avoided seeking medical help despite highly alarming symptoms.

The fear of having surgery performed immediately without thorough confirmation, reported by 45% of participants, reflects significant anxiety about the surgical process, which is almost identical to the findings of a study on the global pooled prevalence of preoperative anxiety among 14,000 surgical patients, where preoperative anxiety was reported to be 48%. Addressing this issue requires better public education on the step-by-step evaluation process and collaborative decision-making between surgeons and patients (22). Moreover, a study among the Saudi population reported the same prominent concern about consulting a surgeon for their condition, reported by 32.1% of their sample. This is supported by our findings that 26% of the participants preferred initial consolation by an internist, rather than a surgeon, regardless of the underlying context of the abdominal pain.

People with AAP have reported facing multiple barriers that prevent them from seeking medical help. Longer waiting times to receive care are a rising global concern that could delay diagnosis and treatment, leading to increased all-cause mortality (23,24); it was reported as a concern by almost half of the participants in our study. Alarmingly, more than one-third of the population reported fear of possible complications of the

Table 7. Barriers to seeking immediate medical care for acute abdominal pain, n=1566		
Barrier	**n**	**%**
1) Transportation problems: Difficulty accessing transportation to get to the medical facility.	318	20
2) Waiting times: Concern about long waits at medical facilities.	738	47
3) Trust in healthcare providers: Lack of confidence in healthcare providers' ability to effectively manage acute abdominal pain.	485	31
4) Financial constraints: Concern about medical costs.	469	30
5) Previous negative experiences.	327	21
6) Lack of information: Not enough information about where to seek medical care.	332	21
7) Fear of side effects of treatment: Concern about possible side effects of proposed treatments.	528	34
n: Number of participants.		

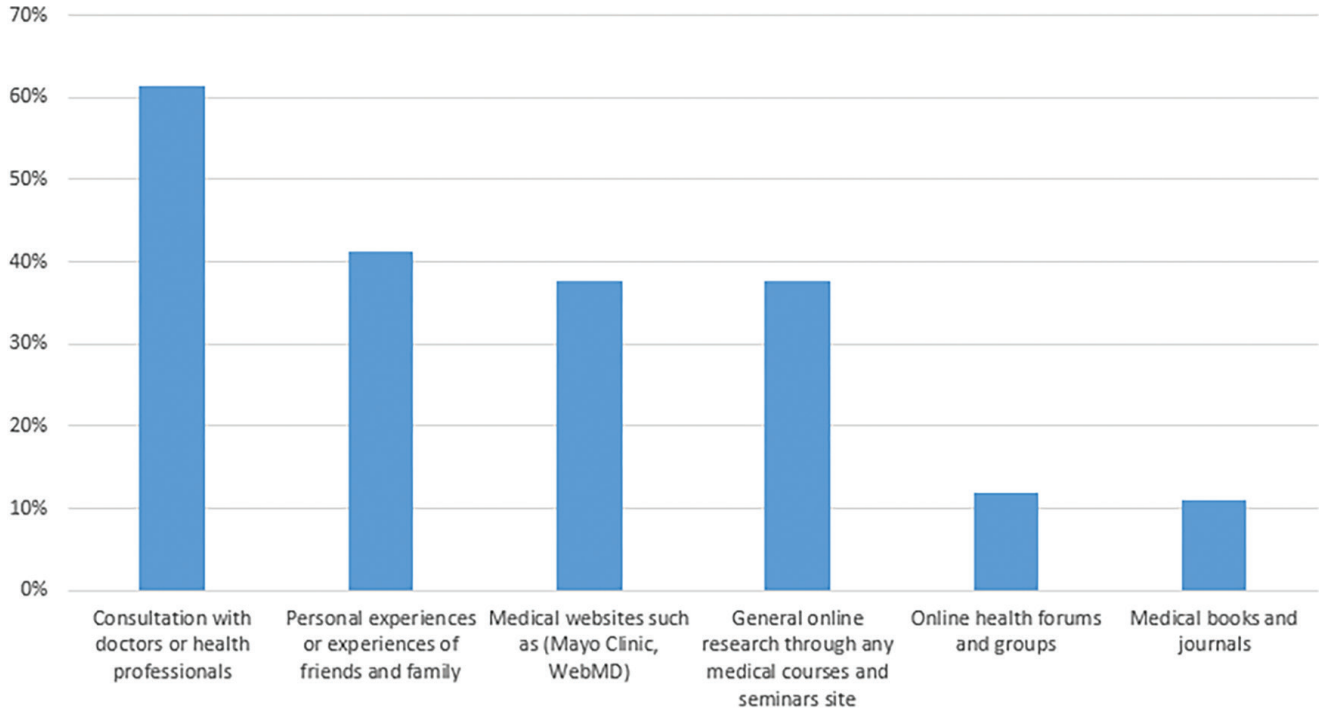

Figure 5. Sources of information about acute abdominal pain/abdominal pain in general.

proposed treatment and a lack of trust in healthcare providers. This would mean a need to reassure patients of their concerns through better communication and patient-centered care to regain trust and reduce apprehension. On the other hand, 61% of the participants reported relying on doctors and healthcare professionals as the main source of information. This represents the fact that despite the reported distrust, foundational reliance on expert guidance was still in place, and this reliance could be leveraged as an opportunity for educating patients and building better relationships between healthcare providers and the community.

The personal experiences of family members with abdominal pain were reported by 41% of the population as sources of information, which is very close to the findings of a study from Qatar, where 38% of the population sought health-related information through family or friends (25). Other sources of information included internet searches through social media, medical websites, or health forum groups, reported by more than one-third of the population. These results are similar to the findings of a study in Saudi Arabia concerning the sources of health-related information, where physicians were sought as the primary source of information, and internet sources were not the first or second sources (26). However, the utilization of internet searches for medical information is known to have established drawbacks in relation to the quality and accuracy of the information (27). Therefore, it is important that public health practitioners and health professionals are involved in the design and evaluation of web-based health and medical information.

Study Limitations

The key strength of our study lies in its originality, both nationally and internationally. To the best of our knowledge, this is the first study to comprehensively examine public awareness of AAP, behaviors in response to severe abdominal pain, perceived barriers to surgical consultations in emergency settings, and obstacles to seeking medical care, providing a holistic understanding of the challenges faced by the general population. We also draw attention to several gaps in these aspects, guiding targeted educational campaigns to improve the public's understanding of AAP symptoms and the importance of seeking timely medical attention. By further identifying the barriers, this can also drive healthcare providers and policymakers to implement changes that improve the accessibility and efficacy of emergency care, ultimately enhancing outcomes. Our study employed a validated questionnaire with pilot testing, ensuring the reliability and content validity of the findings. Moreover, our sample size significantly exceeded the minimum requirement, enhancing the representativeness of the sample for the Jordanian population.

On the other hand, our study has several limitations. First, the lack of a consistent definition of the AAP in the literature posed challenges during the development of the questionnaire. Although the questionnaire was validated, it was based on expert consensus and a literature review, which introduces subjectivity into its design and may not fully capture the nuances of the AAP or the complexity of public understanding. Additionally, the use of a convenience sampling method may have introduced selection bias, as participants recruited through social media and personal outreach might not represent the entire population, particularly those with limited internet access, lower socio-economic status or older ages. The reliance on self-reported data introduces the potential for recall bias and social desirability bias as well. Therefore, these limitations should be considered in future The verbal consent we received before starting data collection was later formally obtained from the ethics committee at BAU due to logistical issues.

CONCLUSION

This study provides valuable insights into public awareness, attitudes, behaviors, and barriers in seeking medical attention related to the AAP in Jordan. Over half of the participants demonstrated fair levels of understanding about the condition, and the majority had positive attitudes with respect to raising awareness about the topic. On the other hand, concerning behaviors were observed, as approximately one-third of the population opted for self-care instead of seeking medical attention, and approximately 4% of the population reported not wanting to seek medical help at all despite having potentially serious symptoms. Barriers such as long waiting times, fear of immediate surgery, and mistrust in healthcare were prominent. These findings highlight critical gaps in the literacy and behaviors regarding AAP among the adult population of Jordan, which may contribute to delayed medical care and potential adverse outcomes. We encourage tailored educational campaigns and healthcare system improvements to enhance timely recognition and intervention for the AAP. Future research of a more representative sample nationally and regionally with more comprehensive surveys is also recommended.

Ethics

Ethics Committee Approval: The present study followed the strengthening the reporting of observational studies in epidemiology statement guidelines from the enhancing the quality and transparency of health research network (11), and the study's protocol received approval from the Research Ethics Committee of the School of Medicine at Balqa Applied University (IRB number: 2025/2024/6/67, date: 24/02/2025).

Informed Consent: The informed consent for publication was obtained from the participants or their legal guardians or legally appointed representatives in cases where any identifiable data of participants are present in the manuscript file.

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Footnotes

During the preparation of this work the author(s) used ChatGPT in order to suggest a rephrase of the title for the. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication. Quillbot and ChatGPT tools were used solely for language refinement in the preparation of this manuscript. All scientific content, analyses, and interpretations were developed and approved by the authors.

Author Contributions

Surgical and Medical Practices - W.T.A.M., M.A., S.A., A.K.; Concept - W.T.A.M., M.A., S.A., A.K.; Design - S.A., A.K.; Data Collection or Processing - S.A., D.E.K., S.F.B., A.B., H.H., S.F.B., E.A.A.; Analysis or Interpretation - W.T.A.M., M.A., S.A.; Literature Search - W.T.A.M., M.A., S.A.; Writing - S.A., A.K., S.F.B., A.B., H.H., S.F.B., E.A.A.

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Supplementary Link: https://d2v96fxpocvxx.cloudfront.net/bda9171a-fae8-4995-8276-2138323f1e16/content-images/c66a8fdf-f33e-432c-bd2b-378430865b8f.pdf

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ORIGINAL ARTICLE
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Predictive value of the albumin-to-creatinine and bicarbonate-to-lactate ratios for 28-day mortality in acute mesenteric ischemia

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ABSTRACT

Objective: Acute mesenteric ischemia (AMI) is a life-threatening condition characterized by rapid deterioration, yet it is often identified late owing to vague and non-specific clinical findings. Identifying laboratory markers that can assist in early mortality prediction remains essential for improving outcomes. This study aimed to determine whether the bicarbonate-to-lactate ratio (HCO_3/lactate) and the albumin-to-creatinine ratio could serve as reliable predictors of early mortality in patients with AMI.

Material and Methods: This retrospective case-control study included 87 patients who underwent surgical treatment for acute arterial mesenteric ischemia caused by superior mesenteric artery embolism between 2015 and 2025. Demographic characteristics, comorbidities, laboratory findings, and mortality outcomes were evaluated. The predictive performance of the bicarbonate-to-lactate and albumin-to-creatinine ratios was assessed using receiver operating characteristic (ROC) analysis; independent predictors of mortality were identified through multivariate logistic regression.

Results: The 28-day mortality rate was 62.1%. In univariate analysis, lower bicarbonate and albumin levels, reduced HCO_3/lactate and albumin/creatinine ratios, and higher lactate, creatinine, and C-reactive protein values were significantly associated with mortality ($p<0.05$). ROC analysis identified values of <6 for the HCO_3/lactate ratio and <2.6 for the albumin/creatinine ratio as the best cut-off values. In the multivariate model, a HCO_3/lactate ratio <6 increased the risk of death by more than 13-fold, while an albumin/creatinine ratio <2.6 increased mortality risk by approximately 4.5-fold.

Conclusion: Both the HCO_3/lactate and albumin/creatinine ratios are simple, inexpensive, and easily obtainable biochemical markers that may assist clinicians in predicting early mortality in AMI. Their incorporation into early evaluation algorithms could enhance risk stratification, although validation through prospective studies is warranted.

Keywords: Acute mesenteric ischemia, bicarbonate-to-lactate ratio, albumin-to-creatinine ratio, mortality prediction, prognostic biomarkers

INTRODUCTION

Acute mesenteric ischemia (AMI) represents an uncommon yet catastrophic vascular emergency, arising from a sudden reduction in intestinal perfusion and frequently progressing to transmural bowel necrosis. Despite advances in diagnostic imaging and perioperative care, reported in-hospital mortality rates remain exceedingly high, often surpassing 50% (1). The clinical presentation of AMI is notoriously heterogeneous and frequently disproportionate to physical findings, particularly in elderly patients and those with comorbidities, which contributes to diagnostic delay and adversely affects survival. Consequently, the early recognition of patients at heightened risk of mortality continues to be a critical unmet need in clinical practice.

Various laboratory parameters, including serum lactate, blood urea nitrogen, and creatinine, have been investigated as prognostic indicators in AMI; however, their predictive performance remains suboptimal. Lactate reflects global hypoperfusion and anaerobic metabolism but lacks etiological specificity, whereas elevations in creatinine more commonly indicate systemic hypovolemia, renal hypoperfusion, or sepsis-related organ dysfunction rather than isolated mesenteric ischemia (2). Similarly, although serum albumin and bicarbonate have not been validated as independent prognostic biomarkers in AMI, hypoalbuminemia has consistently been linked to unfavorable outcomes, largely due to its behavior as a negative acute-

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phase reactant in the setting of inflammation, surgical stress, and critical illness (3).

In recent years, attention has shifted toward composite indices derived from routinely available biochemical measurements to enhance prognostic discrimination. The bicarbonate-to-lactate ratio (HCO_3/lactate) provides an integrated reflection of metabolic acidosis and tissue hypoxia, whereas the albumin-to-creatinine ratio may serve as a surrogate marker of both physiological reserve and renal function. Notably, a retrospective analysis in patients with occlusive arterial AMI demonstrated that a bicarbonate-to-lactate ratio below 10 was strongly associated with 30-day mortality, particularly in cases with abrupt symptom onset, where its predictive accuracy was reported to be exceptionally high (4). In contrast, while the serum albumin-to-creatinine ratio has been shown to predict in-hospital mortality in severe acute pancreatitis and exhibits a strong inverse relationship with short-term mortality in ST-elevation myocardial infarction, its role in the context of AMI has not yet been systematically examined (5,6).

It is essential to emphasize that these ratios do not represent disease-specific biomarkers; rather, they function as global indicators of critical illness, systemic inflammation, and metabolic derangement. Accordingly, their relevance in AMI lies in assessing whether such general critical illness markers preserve their prognostic utility within this uniquely lethal clinical entity. Against this background, the present study sought to investigate the prognostic value of the HCO_3/lactate and albumin/creatinine ratios in predicting early mortality in patients with AMI, with the hypothesis that these readily accessible indices may facilitate early risk stratification and support urgent clinical decision-making.

MATERIAL and METHODS

Study Design and Patient Population

This retrospective case-control study was conducted by reviewing the institutional electronic medical records of patients who underwent operative management for acute arterial mesenteric ischemia between January 2015 and December 2025. A total of 87 adult patients meeting the eligibility criteria were identified and included in the analysis.

Baseline demographic data [including age (years) and sex] and relevant clinical characteristics (such as documented comorbid conditions) were extracted. Laboratory parameters obtained at the time of initial hospital presentation and prior to surgical intervention were recorded. These included serum bicarbonate (mmol/L), lactate (mmol/L), creatinine (mg/dL), albumin (g/dL), and C-reactive protein [(CRP) mg/L]. In addition, composite indices—the bicarbonate-to-lactate ratio and the albumin-to-creatinine ratio—were calculated for each patient.

The primary endpoint of the study was 28-day mortality, defined as death from any cause occurring within 28-days following the index surgical procedure.

Eligibility Criteria

Patients were eligible for inclusion if they were 18 years of age or older and had a confirmed diagnosis of AMI secondary to embolic occlusion of the superior mesenteric artery requiring surgical intervention.

Patients were excluded if they had chronic mesenteric ischemia, received non-operative management, had incomplete clinical, laboratory, or radiological records, or had baseline renal dysfunction attributable to end-stage renal disease, which could confound serum creatinine measurements.

After enrollment, patients were stratified as survivors or non-survivors based on 28-day mortality, and all variables were analyzed accordingly.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Review Board of Amasya University (approval number: 2025/101; date: 12 June 2025). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Sample size estimation was performed using G*Power version 3.1, assuming a statistical power of 80% and a two-sided alpha level of 0.05. Based on these assumptions, a minimum of 31 patients per group was required, yielding a minimum total sample size of 62 participants.

The distribution of continuous variables was evaluated using the Shapiro-Wilk normality test. As most variables deviated from normality, non-parametric statistical methods were employed. Continuous data are presented as medians with interquartile ranges and are compared between groups using the Mann-Whitney U test.

Categorical variables are expressed as absolute numbers and percentages and compared using the chi-square test. Variables demonstrating statistical significance in univariate analyses were subsequently entered into a forward stepwise multivariable logistic regression model to identify independent predictors of 28-day mortality. Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 87 patients who underwent surgical treatment for AMI were included in the analysis. Of these, 63 patients (72.4%) were female. The median age of the study population was 76 years, with an interquartile range of 67 to 81 years. The most prevalent

comorbidities were coronary artery disease (57.5%), diabetes mellitus (57.5%), atrial fibrillation (55.2%), hypertension (44.8%), and chronic obstructive pulmonary disease (20.7%). The overall perioperative mortality rate observed in the cohort was 62.1% (Table 1).

Comparative univariate analyses demonstrated that several biochemical parameters differed significantly between survivors and non-survivors. These included lower serum bicarbonate levels (p<0.001), higher lactate concentrations (p<0.001), reduced bicarbonate-to-lactate ratios (p<0.001), elevated creatinine levels (p=0.019), decreased albumin levels (p=0.001), lower albumin-to-creatinine ratios (p=0.004), and increased CRP values (p<0.001) (Table 2).

Receiver operating characteristic (ROC) curve analysis was subsequently performed to assess the discriminative performance of the composite ratios. The analysis identified an optimal cut-off value of <6 for the bicarbonate-to-lactate ratio and <2.6 for the albumin-to-creatinine ratio in predicting mortality (Table 3). The corresponding ROC curves are illustrated in Figure 1. The cut-off values were determined as HCO_3/lactate <6 and albumin/creatinine <2.6. Multivariate analysis showed that an HCO_3/lactate ratio of <6 and an albumin/creatinine ratio of <2.6 were associated with 13-fold and approximately 4.5-fold increases in mortality, respectively (Table 4).

Table 1. Descriptive analysis results of demographic data

Variables		Count (%)	Median (IQR)
Gender	Male	24 (27.6%)	
	Female	63 (72.4%)	
Age, years			76 (67-81)
DM		50 (57.5%)	
AF		48 (55.2%)	
CAD		50 (57.5%)	
HT		39 (44.8%)	
COPD		18 (20.7%)	
Mortality	Alive	33 (37.9%)	
	Death	54 (62.1%)	

IQR: Interquartile range, DM: Diabetes mellitus, AF: Atrial fibrillation, CAD: Coronary artery disease, HT: Hypertension, COPD: Chronic obstructive pulmonary disease.

DISCUSSION

AMI is a severe vascular emergency that typically manifests as an acute abdomen and is associated with high mortality rates. Beyond clinical assessment, biochemical parameters play an important role in identifying patients at increased risk of adverse outcomes. Previous studies have reported the prognostic relevance of several biomarkers, including CRP, D-dimer, lactate, globulin, creatinine, and intestinal fatty acid-binding protein (I-FABP) (7-9). In the present study, univariate analysis revealed significant associations between mortality and lower

Table 2. Univariate analysis results of the variables

		Alive		Death		
Variables		**Count (%)**	**Median (IQR)**	**Count (%)**	**Median (IQR)**	**p-value**
Gender	Male	12 (36.4%)		12 (22.2%)		0.152
	Female	21 (63.6%)		42 (77.8%)		
Age			76 (66-79)		77 (69-82)	0.449
HCO_3			22 (20.3-24.6)		16.2 (12-17.4)	**<0.001**
Lactate			2.36 (1.78-3.2)		5.15 (3-8)	**<0.001**
HCO_3/lactate			9.32 (6.97-14.94)		2.93 (1.73-5.64)	**<0.001**
Creatinine			0.93 (0.68-1.23)		1.02 (0.9-2.1)	**0.019**
Albumin			2.94 (2.63-3.2)		2.47 (2.15-3.04)	**0.001**
Albumin/creatinine			3.37 (2.09-4.26)		2.17 (1.34-4.24)	**0.004**
CRP			74.85 (34.6-135)		203.1 (99-265.9)	**<0.001**

IQR: Interquartile range, CRP: C-reactive protein, Categorical data were analyzed using the Pearson chi-square test, continuous numerical variables were analyzed with the Mann-Whitney U test, and a p-value of <0.05 was considered statistically significant.

Table 3. ROC analysis results

Variable	AUC	95% CI	p-value
HCO_3/lactate	0.855	0.777-0.934	**<0.001**
Albumin/creatinine	0.686	0.575-0.797	**0.004**

AUC: Area under the curve, ROC: Receiver operating characteristic, CI: Confidence interval, a p-value of <0.05 was considered statistically significant.

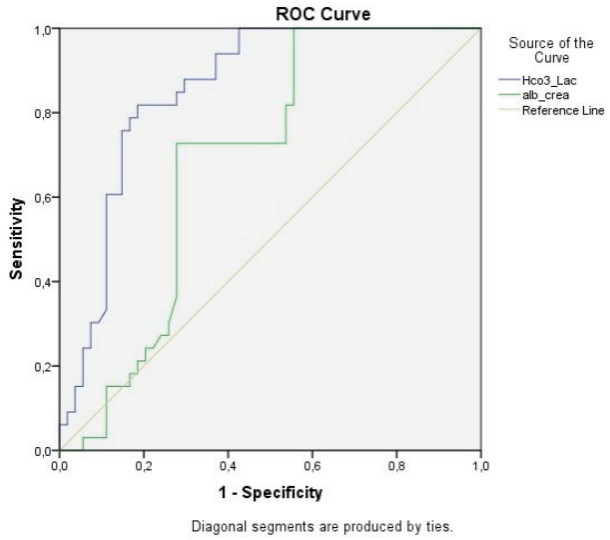

Figure 1. ROC analysis of predictive markers for mesenteric ischemia. ROC: Receiver operating characteristic.

Table 4. Multivariate analysis results of the variables

Variable	OR	95% CI	p-value
HCO_3/lactate <6	13.35	4.21-42.31	**<0.001**
Albumin/creatinine <2.6	4.46	1.43-13.94	**0.01**

OR: Odds ratio, CI: Confidence interval, a p-value of <0.05 was considered statistically significant.

bicarbonate and albumin levels, lower bicarbonate-to-lactate and albumin-to-creatinine ratios, and elevated CRP, creatinine, and lactate levels. However, multivariate analysis demonstrated that a bicarbonate-to-lactate ratio below 6 was linked to an approximately 13-fold increase in mortality risk, while an albumin-to-creatinine ratio below 2.6 was associated with nearly a 4.5-fold higher risk of mortality.

In the literature, the HCO_3/lactate ratio has been evaluated as a prognostic marker in AMI, and in some studies, a threshold value of <10 for this ratio has been identified with significant accuracy in predicting mortality (4). However, in the present study, this threshold was determined to be <6. Given that both studies had a retrospective design, this discrepancy is more likely attributable to differences in the clinical characteristics of the patient populations, the stage of mesenteric ischemia, and the timing of laboratory measurements rather than to methodological variations. In our study cohort, delayed presentation and more pronounced metabolic derangements may have contributed to the establishment of a lower HCO_3/lactate ratio as the prognostic threshold.

Previous studies have reported that preoperative bicarbonate and lactate levels are independent predictors of mortality in mesenteric ischemia. In a retrospective analysis by Uchino et al. (10), which examined factors affecting 90-day postoperative mortality in patients with non-occlusive mesenteric ischemia, low serum bicarbonate levels as well as elevated lactate levels were found to be significantly associated with mortality. In the present study, consistent with these findings, patients with fatal outcomes had significantly lower bicarbonate levels and higher lactate levels. This similarity supports considering biochemical parameters that reflect acid–base balance and tissue perfusion in the early stages of high-mortality conditions, such as mesenteric ischemia, during clinical decision-making.

Although the prognostic value of the serum albumin/creatinine ratio has not been directly investigated in patient populations specific to mesenteric ischemia, this ratio has been addressed in various other critical illness settings. For instance, in a study of patients with pancreatitis managed in intensive care units, the albumin/creatinine ratio was found to be significantly associated with both short- and long-term mortality (11). Similarly, in a retrospective analysis conducted by Hu et al. (12) in patients with chronic sepsis, lower albumin/creatinine ratios were associated with 30- and 60-day mortality, and the ratio was reported to be an independent prognostic marker. Differing pathophysiological processes and levels of systemic inflammatory burden in the patient groups assessed in these studies may have amplified the prognostic power of the albumin/creatinine ratio.

In the present study, the albumin/creatinine ratio was also identified as a statistically significant prognostic marker. Notably, a ratio of <2.6 was associated with an approximately 4.5-fold increase in mortality risk and an AUC of 0.686. Although the predictive power of this ratio was lower than the HCO_3/lactate ratio, it is considered potentially valuable as a secondary risk stratification tool in clinical practice.

Previous investigations have examined the prognostic significance of serum albumin and creatinine levels in patients with mesenteric ischemia. Toda et al. (13) demonstrated that, among patients with non-occlusive mesenteric ischemia treated conservatively, serum albumin concentrations were significantly higher in survivors compared with those who died. Likewise, Don and Kaysen (14) reported markedly lower albumin levels in patients who experienced fatal outcomes.

However, certain limiting factors should be considered when interpreting the clinical significance of albumin. Albumin is a negative acute-phase reactant and therefore decreases in the presence of a systemic inflammatory response. In addition, numerous conditions—such as malnutrition, chronic diseases, hemodilution, and liver dysfunction—can also affect albumin levels (14). Consequently, a decrease in albumin levels may reflect the patient's systemic physiological reserve and inflammatory burden rather than being a specific consequence of mesenteric ischemia.

Similarly, in the literature, low albumin levels have also been reported to be associated with poor clinical outcomes in ischemic stroke, myocardial infarction, and other organ ischemias (15,16). This suggests that albumin may serve not only as a prognostic marker in mesenteric ischemia but also as a general biomarker of ischemia-related pathophysiological stress.

In the systematic review and meta-analysis conducted by Wu et al. (17), it was reported that patients with elevated preoperative creatinine levels had a significantly increased risk of short-term postoperative mortality. The study also noted that advanced age, heart failure, and renal disorders further increased mortality risk.

In the present study, elevated preoperative creatinine levels were also found to be significantly associated with mortality. This finding may be explained by the detrimental effects of hypoperfusion and the systemic inflammatory response in AMI on renal function, leading to increased creatinine levels. Furthermore, creatinine is known to reflect not only renal function but also the patient's metabolic reserve and muscle mass (18). Therefore, the combination of impaired renal perfusion and accelerated catabolic processes in the acute phase may reinforce the prognostic significance of elevated creatinine levels in predicting mortality.

Our findings, consistent with previous literature, indicate that AMI is observed more frequently and is associated with higher mortality in elderly patients and those with comorbidities. Our mortality rate of 62.1% is parallel to the range of 60-80% reported in the literature (19). Furthermore, significant differences in classical biomarkers (CRP, creatinine, and albumin) observed in the univariate analysis support the crucial role of systemic inflammation and organ dysfunction in AMI.

Study Limitations

Several limitations of this study should be acknowledged. First, the retrospective design and relatively limited sample size may have contributed to instability in the multivariate regression model. This is reflected in the wide confidence intervals observed for certain predictors, particularly the HCO_3/lactate ratio, suggesting a potential overestimation of the effect size. In addition, collinearity among metabolic and inflammatory biomarkers cannot be fully excluded. Although the identified ratios demonstrated significant associations with mortality, these findings should be interpreted with caution and considered hypothesis-generating rather than definitive. Larger prospective studies are required to validate the prognostic thresholds identified in this analysis.

CONCLUSION

The findings of this study suggest that the HCO_3/lactate and albumin/creatinine ratios are easily accessible, cost-effective parameters that may be utilized to predict early mortality in patients with AMI. The integration of these ratios into clinical practice could make valuable contributions to individualized patient management and risk stratification. However, these results should be confirmed in larger-scale prospective studies.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Institutional Review Board of Amasya University (approval number: 2025/101; date: 12 June 2025). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Informed consent was not required due to the retrospective nature of the study.

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Footnotes

Author Contributions

Concept - İ.D., C.C.; Design - İ.D., C.C.; Data Collection or Processing - İ.D., F.C.; Analysis or Interpretation - S.O., C.C.; Literature Search - İ.D., S.O., F.C., C.C.; Writing - İ.D., C.C.

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ORIGINAL ARTICLE
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Early risk stratification of acute diverticulitis using procalcitonin, CRP, and CT imaging: A retrospective analysis

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ABSTRACT

Objective: Distinguishing mild (Hinchey 1a/1b/2) from severe (Hinchey 3/4) diverticulitis is critical for appropriate management. This study evaluated the predictive value of inflammatory biomarkers and imaging features for early risk stratification.

Material and Methods: We conducted a retrospective analysis of patients with acute diverticulitis between 2017 and 2024 at the hospital's general surgery department. Receiver operating characteristic analysis was used to determine optimal cut-off values for C-reactive protein (CRP) and procalcitonin, while computed tomography (CT) findings were assessed for their discriminative capacity.

Results: A total of 72 patients were included in the study. There were 59 patients in the mild diverticulitis group and 13 patients in the severe diverticulitis group. Patient demographics were similar between the groups. Procalcitonin demonstrated superior predictive performance [area under the curve (AUC) 0.795] compared to CRP (AUC 0.755). The cut-off values for procalcitonin and CRP were 0.095 and 104.5, respectively. Specific CT patterns showed high specificity for severe disease. The combination of biomarkers and imaging criteria significantly improved diagnostic accuracy, with pelvic abscess localization emerging as a key indicator of severity.

Conclusion: A biomarker-guided approach incorporating procalcitonin and targeted CT evaluation enables reliable early identification of severe diverticulitis. This strategy may enhance clinical decision-making regarding antibiotic selection and surgical consultation while reducing unnecessary interventions in mild cases.

Keywords: Acute diverticulitis, C-reactive protein, procalcitonin, disease severity

INTRODUCTION

Acute diverticulitis is a common colonic disease characterized by inflammation and infection of the colonic diverticula, and its presentation may vary from a simple, self-limiting clinical condition to life-threatening complications such as perforation, peritonitis, or bleeding (1). The Hinchey classification system was described in 1978 by Hinchey et al. (2). It contains four different levels of colonic diverticulitis. While mild cases (Hinchey 1a, 1b, and 2) can often be managed by antibiotics and outpatient care, more severe cases (Hinchey 3 and 4) require surgical treatment due to the high risk of their mortality and morbidity (3). Despite its clinical utility, distinguishing between mild and severe diverticulitis at initial diagnosis remains challenging, often leading to delayed interventions or unnecessary hospitalizations (4).

Computed tomography (CT) is the gold standard diagnostic tool for acute diverticulitis (5). Clinical and treatment decisions mainly depend on the CT results. However, clinical symptoms such as abdominal pain, fever, and leukocytosis lack specificity, while CT findings may not always correlate with disease severity in the early stages. Inflammatory biomarkers, particularly C-reactive protein (CRP), have emerged as potential predictors in risk stratification. Recent studies emphasized the importance of CRP in the severity of diverticulitis (6). However, CRP, a non-specific acute-phase reactant, rises proportionally to tissue inflammation, whereas procalcitonin, a more specific marker for bacterial infections, may better indicate

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systemic involvement (7). Nevertheless, standardized cut-off values for these markers in diverticulitis remain unclear, limiting their reliability in decision-making.

This study aims to investigate factors related to complicated diverticulitis in a single center. Moreover, it aims to determine optimal cut-off values for CRP and procalcitonin. The ability to predict severe diverticulitis at diagnosis could optimize patient triage, reduce healthcare costs, and improve outcomes by facilitating timely surgical consultation or intensive monitoring.

MATERIAL and METHODS

Study Design and Patient Selection

Data regarding patients who were treated with the diagnosis of acute diverticulitis at the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital's General Surgery Department between January 2017 and December 2024 were analyzed retrospectively. Patients were identified through hospital records using ICD-10 codes for diverticulitis (K57.0-K57.6). Inclusion criteria for the patients were aged over ≥18 years with radiologically confirmed acute diverticulitis, and availability of complete clinical, laboratory, and imaging data. Because of the retrospective design and non-standardized test ordering in routine practice, CRP and/or procalcitonin were not measured in all patients. Procalcitonin was typically requested selectively based on clinical severity, suspected systemic infection, or diagnostic uncertainty, and may also have been unavailable due to operational factors. Patients without the required biomarker measurements were excluded from analyses to ensure reliable estimation of biomarker cut-off values, acknowledging the potential for selection bias and limited generalizability. Also, patients with missing Hinchey classification and patients with diverticulitis secondary to malignancy or other inflammatory conditions were excluded from the study.

Data Collection

Demographical data, comorbid diseases, clinical features, laboratory parameters, imaging findings, hospitalizations, mortality, and morbidities were extracted from hospital electronic medical records. Patient stratification was performed exclusively based on contrast-enhanced CT findings at the time of admission. According to the Hinchey classification system, patients with localized pericolic inflammation or confined abscesses (Hinchey 1a, 1b, and 2) were categorized as having mild diverticulitis, whereas those with CT evidence of generalized purulent or fecal peritonitis, including free intraperitoneal fluid, extraluminal air, or diffuse contamination (Hinchey 3 and 4), were classified as having severe diverticulitis. CRP and procalcitonin were extracted as the first values obtained during the initial evaluation at emergency department admission. If multiple measurements were available, the earliest value was used. Symptom onset time was not consistently documented; therefore, all proposed cut-offs refer to admission values.

All abdominal CT examinations were performed using a multidetector CT scanner (SOMATOM go. Up, Siemens Healthineers, Erlangen, Germany) at our institution. Given the retrospective design, the use of intravenous iodinated contrast was determined at the discretion of the treating physician based on the patient's renal function at the time of imaging; therefore, the dataset includes both contrast-enhanced and non-contrast CT studies. When intravenous contrast was administered, imaging was obtained using a multiphasic abdominal CT protocol, including arterial, portal venous, and delayed phases, as per institutional routine and the clinical indication. Images were reconstructed with a slice thickness of 2 mm (including multiplanar reformations when available). Radiologic findings were extracted from the official radiology reports generated at the time of presentation. All CT examinations were interpreted and formally reported by on-duty attending radiologists. In keeping with the study's real-world design, images were not re-evaluated or independently re-read for research purposes; therefore, inter-observer agreement analyses were not performed.

Abscess on CT was defined as a well-demarcated, pericolic or pelvic fluid collection with well-bordered, heterogeneous content and possibly extraluminal air foci. Measurements were taken in axial and coronal planes, and the largest diameter was calculated in centimeters. An abscess size was identified among patients with severe diverticulitis; interventional thresholds were performed according to the existing literature.

Free fluid was defined as non-contrast-enhancing extraluminal fluid collection, typically in the pelvic recesses or pericolic spaces, without evidence of perforation. It was recorded as either present or absent.

Ethical Considerations

This study was approved by the Ethics Committee of the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital (approval number: 2025/01-06, date: 05/02/2025), and it was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards, and informed consent was waived due to the retrospective nature of the study.

Statistical Analysis

SPSS version 28.0 (SPSS Inc., IBM, Chicago, US) was used for statistical analysis. The data were presented as mean ± standard deviation, median, and interquartile range (IQR). The proportion or frequency was compared between the two groups using Fisher's

exact test or the χ^2 test, and differences in continuous variables were evaluated using the Student's t-test and the Mann-Whitney U test for non-parametric values. Receiver operator characteristics (ROC) curves were obtained for CRP (mg/L) and procalcitonin (ng/mL). The Youden index (Sensitivity + 1 – Specificity) was used to determine the cut-off values for both laboratory values.

RESULTS

Between January 2017 and December 2024, 121 patients with acute left colon diverticulitis were admitted to the hospital. Of them, 49 patients had no CRP and procalcitonin values and were excluded from the study. Finally, 72 patients were included in the study with acute diverticulitis, stratified into mild (Hinchey 1a/1b/2, n=59) and severe (Hinchey 3/4, n=13) diverticulitis groups (Table 1). Demographic analysis revealed no significant differences in age (mean 56.6±15.5 vs. 51.3±19.4 years, p=0.175) or sex distribution (48.6% male vs. 69.2%, p=0.100) between groups. Comorbidities, including diabetes (15.3% vs. 15.4%, p=1.000) and hypertension (37.5% vs. 23.1%, p=0.346), were similarly distributed. Abdominal pain was present in 94.4% of cases overall, without group differences (94.9% mild vs. 92.3% severe, p=0.558). However, although vomiting was more common in severe cases, this rate was not statistically significant (23.1% vs. 6.8%, p=0.106). Management strategies differed significantly. While hospitalization is required for all severe cases, 67.8% of mild cases are in need of hospitalization (p=0.015).

Laboratory results, CT imaging findings, and treatment status of the patients are summarized in Table 2. Between groups, only in inflammatory markers CRP and procalcitonin showed marked differences (p=0.004, p=0.001, respectively). Radiological

Table 1. Patient characteristics between the groups

	All patients	**Mild diverticulitis**	**Severe diverticulitis**	
	n=72	**n=59**	**n=13**	**p**
Gender, n (%)				0.100
Male	35 (49%)	26 (44%)	9 (69%)	
Female	37 (51%)	33 (55%)	4 (31%)	
Age, mean ± SD	56.6±15.5	57.8±14.5	51.3±19.4	0.175
Comorbidity, n (%)				
Diabetes mellitus	11 (15%)	9 (15%)	2 (15%)	1.000*
Hypertension	27 (37%)	24 (41%)	3 (23%)	0.346*
Cardiovascular disease	7 (10%)	7 (12%)	0	0.337*
Pulmonary disease	3 (4%)	3 (5%)	0	1.000*
Symptoms, n (%)				
Abdominal pain	68 (94%)	56 (95%)	12 (92%)	0.558*
Vomiting	7 (10%)	4 (7%)	3 (23%)	0.106*
Fever	5 (7%)	4 (7%)	1 (8%)	1.000*
Hinchey classification, n (%)				**<0.001**
1a	52 (72%)	52 (88%)	0	
1b	3 (4%)	3 (5%)	0	
2	4 (6%)	4 (6%)	0	
3	11 (15%)	0	11 (85%)	
4	2 (3%)	0	2 (15%)	
Treatment, n (%)				**0.015***
Outpatient	19 (26%)	19 (32%)	0	
Hospitalization	53 (74%)	40 (68%)	13 (100%)	
Number of attacks, n (%)				0.278
1	62 (86%)	49 (83%)	13 (100%)	
2	9 (12%)	9 (15%)	0	
3	1 (2%)	1 (2%)	0	

SD: Standard deviation, *: Fisher's exact test.

assessment through CT imaging yielded particularly discriminative findings. The presence of abscesses was significantly more common in severe cases (38.5%) compared to mild cases (11.9%, p=0.034), with pelvic abscesses showing the strongest association with severe disease (30.8% vs. 1.7%, p=0.003). Free fluid detection on CT scans emerged as a strongly associated finding for severe diverticulitis, present in all severe cases (100%) compared to only 11.9% of mild cases (p<0.001). Similarly, extraluminal air was observed in 92.3% of severe cases versus 10.2% of mild cases (p<0.001), further emphasizing the value of CT imaging in severity assessment.

The analysis of treatment strategies revealed significant differences in management between severity groups. All patients with severe diverticulitis required hospitalization (100% vs. 67.8% in mild cases, p=0.015), with a substantially higher rate of surgical intervention in this group (100% vs. 5.1%, p<0.001). Medical management showed distinct patterns between groups. While 94.9% of mild cases were managed with standard antibiotic regimens alone, severe cases frequently required antibiotic escalation (61.5% vs. 13.6%, p=0.001), with broader-spectrum coverage including piperacillin-tazobactam or carbapenems.

We performed a multivariate logistic regression analysis to determine the independent factors for the severity of acute diverticulitis. Among the clinical findings and laboratory values, CRP and procalcitonin were found to be significant in

Table 2. Comparison of laboratory, imaging findings, and treatment strategies between the groups

Laboratory findings, median (IQR)	**All patients**	**Mild diverticulitis**	**Severe diverticulitis**	
	n=72	**n=59**	**n=13**	**p**
Glucose	107 (IQR: 94-130)	105 (IQR: 93-125)	125 (IQR: 95-136)	0.183
Ure	33 (IQR: 26-44)	35 (IQR: 27-43)	32 (IQR: 26-55)	0.843
Creatinin	1 (IQR: 0.8-1.1)	1 (IQR: 0.8-1.1)	1 (IQR: 0.9-1.2)	0.621
CRP	71 (IQR: 30-131)	62 (IQR: 27-108)	136 (IQR: 74-198)	**0.004**
WBC	12.2 (IQR: 9.8-15.7)	11.8 (IQR: 9.9-14.4)	15 (IQR: 9.6-19.2)	0.319
Neutrophil	9.1 (IQR: 6.5-12.2)	8.7 (IQR: 6.5-10.6)	10.8 (IQR: 7.6-16.2)	0.091
Lymphocyte	1.9 (IQR: 1.3-2.8)	1.9 (IQR: 1.4-2.7)	1.5 (IQR: 1-3)	0.629
Hemoglobin	12.9 (IQR: 11.9-14.6)	12.9 (IQR: 11.9-14.5)	13.1 (IQR: 11.7-14.8)	0.524
Platelet	268 (IQR: 220-321)	264 (IQR: 220-307)	315 (IQR: 246-367)	0.072
Procalcitonin	0.04 (IQR: 0.01-0.19)	0.03 (IQR: 0.01-0.07)	0.36 (IQR: 0.09-0.77)	**0.001**
CT findings, n (%)				
Abscess	12 (17%)	7 (12%)	5 (38%)	**0.034***
Abscess localisation n (%)				**0.003**
Pelvic	5 (7%)	1 (2%)	4 (31%)	
Pericolonic	6 (8%)	5 (9%)	1 (8%)	
Retroperitoneal	1 (2%)	1 (2%)	0	
Abscess size, median (IQR)	4 (IQR: 2.3-6.8)	4 (IQR: 2-6)	6 (IQR: 2.5-7)	0.530
Free liquid n (%)	20 (28%)	7 (12%)	13 (100%)	**<0.001***
Extra-luminal air n (%)	18 (25%)	6 (10)	12 (92%)	**<0.001***
Treatment, n (%)				**<0.001**
Medical	56 (78%)	56 (95%)	0	
Surgery	16 (5%)	3 (5%)	13 (100%)	
Antibiotics, n (%)				**0.001***
Standard	56 (78%)	51 (86%)	5 (38%)	
Wide spectrum	16 (22%)	8 (14%)	8 (62%)	
Morbidity, n (%)	3 (4%)	2 (3%)	1 (8%)	0.455
Mortality, n (%)	2 (3%)	1 (2%)	1 (8%)	0.331*

*: Fisher's exact test, IQR: Interquartile range, CT: Computed tomography, CRP: C-reactive protein, WBC: White blood cell.

the univariate analysis. In the mulivariable logistic regression, procalcitonin was found to be the only predictive marker for the severity of acute diverticulitis (Table 3).

ROC curve analysis established optimal discriminatory thresholds for CRP and procalcitonin (Figures 1 and 2). CRP showed an area under the curve (AUC) of 0.755 [95% confidence interval (CI): 0.601-0.909, p=0.004], with an optimal cut-off value of 104.5 mg/L providing 69.2% sensitivity and 71.2% specificity. Procalcitonin exhibited even stronger predictive capability with an AUC of 0.795 (95% CI: 0.652-0.937, p=0.001). The optimal cut-off was determined to be 0.095 ng/mL, yielding 76.9% sensitivity and 78.0% specificity.

DISCUSSION

This comprehensive study provides robust evidence supporting the use of inflammatory biomarkers for early and accurate differentiation between mild and severe diverticulitis. In this study, we aimed to obtain optimal cut-off values for CRP and

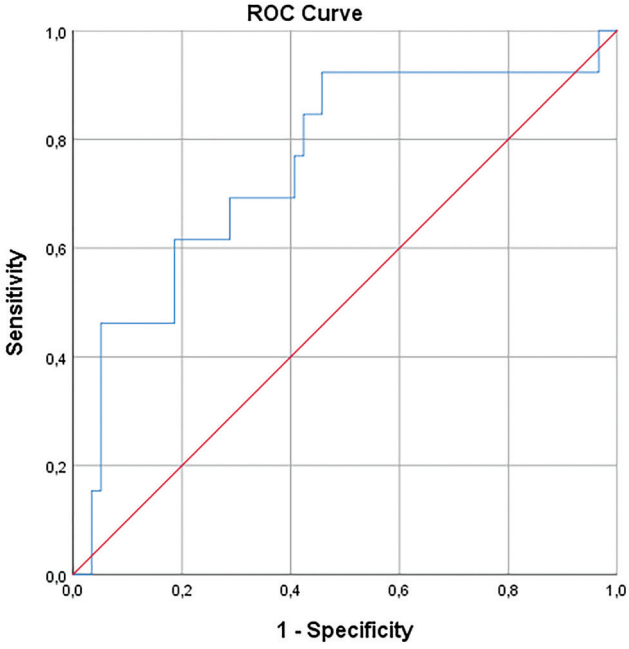

Figure 1. ROC curve for C-reactive protein. Cut-off value: 104.5 [sensitivity: 69.2%; specificity: 71.2%, AUC (95% CI): 0.755 (0.601-0.909), p=0.004].

ROC: Receiver operator characteristics, AUC: Area under the curve, CI: Confidence interval

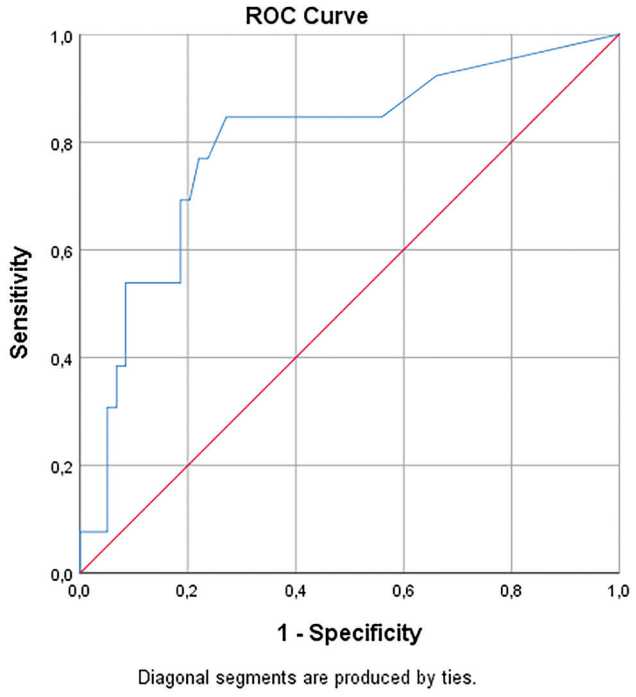

Figure 2. ROC curve for procalcitonin. Cut-off value 0.095 [sensitivity: 76.9%; specificity: 78%, AUC (95% CI): 0.795 (0.652-0.937), p=0.001].

ROC: Receiver operator characteristics, AUC: Area under the curve, CI: Confidence interval

Table 3. Univariable and multivariable logistic regression analysis regarding severity of diverticulitis

n=72	OR	95% CI	p	OR	95% CI	p
Gender	2.856	0.790-10.323	0.109			
Age	0.972	0.934-1.013	0.176			
Abdominal pain	0.643	0.061-6.724	0.712			
Fever	1.146	0.117-11.186	0.907			
Diabetes mellitus	1.010	0.191-5.341	0.991			
Vomitting	4.125	0.789-21.299	0.091			
Creatinine >1 mg/dL	1.220	0.700-2.124	0.557			
White blood cell >11000 µL	1.077	0.972-1.195	0.158			
Hemoglobin	1.069	0.768-1.486	0.693			
C-reactive protein >104.5	5.559	1.506-20.512	**0.010**	1.979	0.413-9.479	0.393
Procalcitonin >0.095	11.795	2.824-49.265	**<0.001**	8.283	1.637-41.907	**0.010**

OR: Odds ratio, CI: Confidence interval.

procalcitonin in predicting severe diverticulitis, with cut-off values of 104.5 mg/L and 0.095 ng/mL, respectively. These biomarkers performed remarkably well in our ROC analysis and may provide valuable findings to clinical examinations. While CRP and procalcitonin have been associated with severe disease in recent studies, their combined application in a newly described risk assessment model might be essential.

For clinical use, this study suggests that elevated levels beyond these thresholds should prompt clinicians to consider early imaging, closer monitoring, or surgical consultation, particularly when clinical signs are evident. Although the primary aim of this study was not to develop a formal diagnostic algorithm, our results suggest that these biomarkers can play a role in a tailored decision-making process. Incorporating them into an evidence-based clinical pathway may facilitate earlier identification of patients at risk for complicated disease.

The exceptional performance of procalcitonin (AUC 0.795) compared to CRP (AUC 0.755) in our study likely reflects fundamental differences in their pathophysiological origins. While CRP is a general acute-phase reactant produced in response to interleukin-6 stimulation (8), procalcitonin is more specifically upregulated during severe bacterial infections and systemic inflammatory responses (7,9). This biological distinction explains why procalcitonin showed greater specificity (78% vs. 71.2%) for detecting complicated diverticulitis cases, which typically involve transmural inflammation and micro-perforation (10). Our optimal procalcitonin cut-off of 0.095 ng/mL aligns with recent multicenter studies (11,12), though slightly lower than thresholds reported in septic populations (13), reflecting the localized nature of diverticular inflammation.

The CRP cut-off value of 104.5 mg/L defined in our study deserves special attention. This value is lower than that found by Mäkelä et al. (6), who recommended 150 mg/L to diagnose inflammation in clinical practice, suggesting that the assessment of diverticulitis severity requires adjusted thresholds. There are various cut-off results regarding CRP and procalcitonin in recent studies. Nizri et al. (14) found that above 90 mg/L CRP levels are associated with a higher risk of complicated diverticulitis. Kechagias et al. (15) showed that CRP levels above 173 mg/L result in surgical or invasive drainage treatments. Both studies also showed that higher CRP levels are associated with higher Hinchey scores. The strong correlation between CRP levels and the Hinchey classification supports its role as a continuous marker of disease progression rather than a simple present/absent indicator.

Procalcitonin has been gaining popularity in recent years. It has been used as an inflammatory marker in various kinds of diseases (16). However, there is no clear consensus on the optimal cut-off value for the severity of acute diverticulitis. Schena et al. (7) examined 503 acute left colon diverticulitis. They found that procalcitonin levels greater than 0.05 ng/mL have emerged as an independent risk factor for acute diverticulitis (7). In another study, Jeger et al. (17) found that procalcitonin levels above 0.1 ng/mL were related to complicated diverticular diseases. In this study, a procalcitonin level of 0.095 ng/mL was found to be related to severe diseases. Moreover, according to the multivariate logistic regression analysis, CRP and procalcitonin were found to be independent risk factors for severe diverticulitis. Our findings are also consistent with the existing studies. Yet, these findings should be supported by the large, prospective cohorts.

Our CT findings provide compelling evidence that imaging should serve as more than just a diagnostic tool for diverticulitis. The near-pathognomonic association of free fluid (100% vs. 11.9%, $p<0.001$) and extraluminal air (92.3% vs. 10.2%, $p<0.001$) with severe cases suggests these features should trigger immediate surgical consultation (5). Notably, the anatomical distribution of abscesses emerged as a critical prognostic factor - pelvic abscesses (30.8% in severe cases) were associated with poor outcomes, likely due to the challenging surgical access and higher risk of fistula formation (3). The 4.2 cm median abscess size in severe cases (IQR 2.5-7 cm) provides an essential benchmark for intervention thresholds, supporting recent guidelines recommending drainage for collections >3-4 cm (4).

The development of a weighted scoring system incorporating both biomarkers and imaging features represents the most clinically significant output of this research. Patients meeting all three high-risk criteria (CRP ≥104.5 mg/L, procalcitonin ≥0.095 ng/mL, and free fluid on CT) had a 97% probability of severe disease in our cohort. This finding may inform the establishment of a rapid assessment protocol in the emergency department. Thus, a faster emergency surgical consultation can be provided for patients with severe imaging findings, accelerating the treatment process. The combination of biomarker thresholds (CRP ≥104.5 mg/L and procalcitonin ≥0.095 ng/mL) together with key CT features such as free fluid or extraluminal air may represent a pragmatic high-risk profile for early surgical consultation and closer monitoring. However, we did not formally derive or externally validate a weighted score, and prospective validation is needed before implementation as a clinical decision rule.

Our study revealed significant differences in broad-spectrum antibiotic utilization between severity groups, with 61.5% of severe cases requiring escalated coverage compared to only 13.6% of mild cases ($p=0.001$). This disparity highlights the critical need for precise risk stratification to guide appropriate antibiotic selection while avoiding unnecessary broad-spectrum use in mild diverticulitis (18,19).

Procalcitonin was the only biomarker that remained independently associated with severe diverticulitis in multivariate analysis, underscoring its superior prognostic value compared with conventional inflammatory markers. Unlike CRP, which reflects a nonspecific acute-phase response, procalcitonin is selectively upregulated in the setting of systemic bacterial infection and correlates more closely with bacterial burden and disease severity (8,9). This biological specificity likely explains its persistent association with complicated diverticulitis, which is frequently characterized by transmural inflammation and microperforation. Our findings are consistent with previous studies demonstrating procalcitonin as an independent predictor of disease severity and need for surgical intervention in acute diverticulitis (7,18). Notably, the optimal cut-off identified in our cohort (0.095 ng/mL) closely aligns with thresholds reported in prior prospective and multicenter studies, supporting the external validity of our results. Collectively, these data suggest that procalcitonin may serve as a key biomarker for early risk stratification, particularly when integrated with CT findings, and may help guide timely escalation of care in patients with severe disease.

These findings suggest a stratified antibiotic approach: narrow-spectrum regimens (e.g., amoxicillin-clavulanate) may suffice for mild cases without high-risk biomarkers, while severe cases with elevated procalcitonin or CRP ≥104.5 mg/L warrant broader coverage (e.g., piperacillin-tazobactam). This aligns with recent guidelines emphasizing biomarker-guided therapy, though prospective validation of our specific thresholds is needed (10-12,16). The absence of statistically significant differences in mortality (7.7% vs. 1.7%, p=0.331) and morbidity (7.7% vs. 3.4%, p=0.455) between severity groups should be interpreted with caution, as our study was likely underpowered to detect these clinically important outcomes due to the limited number of severe cases.

Study Limitations

While providing clinically relevant findings, our study has several limitations that merit discussion. First, this study has a relatively small number of patients diagnosed with severe diverticulitis (n=13). This restricted sample size might reduce the reliability of the statistical analysis, particularly those involving ROC curves and the determination of optimal diagnostic thresholds. While the findings offer valuable insights into potential predictive markers of CRP and procalcitonin, the sturdiness and generalizability of these results are limited. In addition, symptom onset timing could not be reliably captured in this retrospective dataset; thus, our biomarker thresholds are anchored to admission (baseline) measurements and may differ if tests are obtained later in the disease course. A post-hoc power analysis was not performed; however, we acknowledge that the small cohort size for this subgroup may introduce variability and limit the ability to draw definitive conclusions. Future studies with larger sample sizes are warranted to validate these findings. Second, the single-center nature limits generalizability, though our patient demographics match population-level diverticulitis epidemiology. Therefore, future research should focus on:

- Multicenter validation of our cut-off values,
- Prospective evaluation of the proposed decision pathway,
- Cost-effectiveness analysis of biomarker-guided imaging strategies,
- Investigation of serial biomarker measurements for monitoring treatment response.

CONCLUSION

This study confirms that integrating CRP, procalcitonin, and CT findings enables early, accurate differentiation of severe diverticulitis. The proposed biomarker thresholds and imaging criteria provide a practical framework for risk stratification, guiding timely surgical intervention for high-risk cases while optimizing antibiotic use in mild diseases. Implementing this approach may improve outcomes through targeted management, though prospective validation is warranted to confirm clinical utility. These findings support moving toward precision medicine strategies in diverticulitis care.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital (approval number: 2025/01-06, date: 05/02/2025), and it was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Informed Consent: Informed consent was waived due to retrospective nature of the study.

Footnotes

An abstract of this study was presented as an oral presentation at the 3rd International Turkish Colon and Rectum Surgery Congress in Belek, Antalya, Türkiye, between 16 and 20 May 2025.

Author Contributions

Concept - S.Ö., S.Y., K.T.; Design - S.Ö., S.Y., K.T.; Data Collection or Processing - O.B.N., A.C.E.; Analysis or Interpretation - H.Y.; Literature Search - O.B.N., A.C.E., H.Y.; Writing - O.B.N., A.C.E., G.A.

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

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ORIGINAL ARTICLE
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The colorectal cancer screening gap in Türkiye: A tripartite survey of barriers among patients and surgeons

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ABSTRACT

Objective: Colorectal cancer (CRC) screening uptake in Türkiye remains suboptimal, despite the presence of a national screening program. Understanding whether barriers arise primarily from patient-related factors or system-level constraints is essential for effective policy planning. This study aimed to evaluate barriers to CRC screening across the screening pathway using patient, procedural, and provider perspectives.

Material and Methods: A descriptive cross-sectional study was conducted between January and June 2025 at a tertiary training and research hospital. Three distinct groups were surveyed: 100 screening-naïve outpatients aged 50-70 years, 100 patients undergoing diagnostic or screening colonoscopy, and 50 general surgeons performing or referring for colonoscopy. Study-specific questionnaires, pilot-tested for clarity but not formally validated, were used to assess screening awareness, attitudes, perceived barriers, and strategies for improvement. The data were analyzed descriptively.

Results: Among screening-naïve outpatients, 54% had no prior awareness of CRC screening, and only 28% had received a physician recommendation for screening. Fear of a serious diagnosis (45%) and pain or discomfort (40%) were commonly reported concerns; however, most respondents indicated that these would not deter screening. Among patients undergoing colonoscopy, 77% underwent the procedure for symptoms rather than preventive screening, while post-procedure satisfaction was high. Surgeons predominantly identified system-level barriers, particularly long waiting times (90%) and an insufficient number of trained endoscopists (92%), as major limitations in effective screening delivery.

Conclusion: The primary perceived barrier to CRC screening in Türkiye appears to be limited system capacity rather than patient reluctance. Improving screening uptake will likely require coordinated public awareness efforts, structured national reminder systems, and expansion of the number of adequately trained endoscopists, alongside endoscopy infrastructure.

Keywords: Colonoscopy, colorectal cancer, public health, screening

INTRODUCTION

Colorectal cancer (CRC) represents a significant and growing public health challenge in Türkiye. With approximately 21,700 new cases diagnosed annually, CRC is the third most common cancer in the country and accounts for nearly 9% of all new cancer diagnoses. It is also the second leading cause of cancer-related mortality, resulting in an estimated 11,700 deaths annually (1). In parallel with global trends, the incidence and mortality rates of CRC in Türkiye have gradually increased in recent years, highlighting the need for effective preventive strategies (2).

Screening plays a critical role in reducing the CRC burden, as methods such as colonoscopy allow for the early detection of malignancy and removal of precancerous polyps (3). Although Türkiye has an established national CRC screening program targeting adults aged 50-70 years, participation remains suboptimal (4,5). Barriers to screening arise at both the patient and healthcare system levels.

While these barriers have been individually acknowledged, there is a lack of comprehensive studies that simultaneously examine both patient and healthcare provider perspectives within the Turkish context (6,7). Within the Turkish healthcare system, general surgeons play a central role in the CRC screening cascade, frequently acting as the primary point of referral for colonoscopy and often performing the procedure themselves. Therefore, this study aimed to investigate the barriers to CRC screening across multiple points in the screening pathway, with particular attention to the role of general surgeons. By evaluating awareness, attitudes, practice patterns, perceived obstacles, and suggestions for

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improvement among patients and surgeons, we sought to identify key determinants of low screening participation and to inform strategies to enhance early detection efforts.

MATERIAL and METHODS

Study Design and Patient Population

This descriptive, cross-sectional study was conducted between January and June 2025 in the general surgery outpatient clinics and endoscopy unit of a single tertiary research and training hospital. This study aimed to explore the knowledge, attitudes, and perceived barriers related to CRC screening from both patient and surgeon perspectives using a pragmatic survey-based approach. Three distinct participant groups were included. Participants were recruited using consecutive sampling during routine outpatient visits and endoscopy scheduling throughout the study period.

The outpatient group included 100 screening-naïve patients aged 50-70 years who presented to the general surgery outpatient clinic for non-emergency reasons and had no prior history of colonoscopy. Patients with a previously known diagnosis of colorectal cancer, inflammatory bowel disease, or cognitive impairment that could affect their comprehension of the questionnaire were excluded.

The colonoscopy group comprised 100 patients aged 50-70 years who were scheduled for diagnostic or screening colonoscopy. All participants in this group were undergoing their first colonoscopy. Each participant completed two surveys: one before and one immediately after the procedure. Patients who underwent urgent or therapeutic colonoscopy or those with known malignancies were excluded.

The surgeon group comprised general surgery specialists practicing in Türkiye who had formal training in colonoscopy and were actively performing or referring patients for the procedure. Surgeons were invited via professional networks and email. A total of 200 surgeons were invited on two separate occasions, and 50 surgeons responded, yielding a 25% response rate.

Data Collection Tools

Three structured questionnaires were developed by the study investigators based on the current CRC screening guidelines and relevant literature. The questionnaires included multiple-choice and Likert-type items addressing awareness, attitudes, perceived barriers, clinical practices, and suggested improvement strategies related to CRC screening and colonoscopy.

The outpatient questionnaire assessed demographic characteristics, awareness of CRC screening, perceived personal risk, sources of information, and willingness to undergo screening. The colonoscopy questionnaire evaluated the indications for the procedure, pre-procedural concerns, bowel preparation experience, perceived educational impact, and post-procedural satisfaction. The surgeon questionnaire focused on professional background, colonoscopy practice patterns, patient education practices, perceived patient- and system-level barriers, and recommendations for improving screening uptake.

The questionnaires were pilot-tested to assess clarity and face validity and were reviewed by practicing surgeons for clinical relevance. No formal psychometric validation was performed, and the instruments were used for exploratory and descriptive purposes. The complete survey instruments used for the outpatient, colonoscopy patient, and surgeon groups are provided in Supplementary Appendix.

Data Collection Procedure

Outpatient and colonoscopy patient surveys were administered in person by trained research staff in a private setting to ensure the confidentiality of the participants. Pre- and post-procedure surveys for the colonoscopy group were completed on the same day as the procedure. All colonoscopies were performed under sedation using propofol administered by an anesthesiologist according to institutional practice. Post-procedure questionnaires were administered only after patients had fully recovered from sedation and were ready for discharge to ensure that responses were not influenced by residual sedative effects. The surgeon survey was distributed electronically via a secure online platform, and the responses were collected anonymously.

Statistical Analysis

Data were analyzed using R (version 4.1.1). Given the exploratory objectives of the study, the analysis was limited to descriptive statistics, and no inferential comparisons were performed. The sample size was determined pragmatically based on feasibility and patient volume during the study period rather than by formal power calculation. Continuous variables are expressed as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables are presented as frequencies and percentages.

Ethical Considerations

The study was approved by the Local Institutional Ethics Committee of Ankara Bilkent City Hospital (approval number: 451, date: 07.08.2024). Written informed consent was obtained from all participants prior to their participation. All procedures were performed in accordance with the principles of the Declaration of Helsinki.

Artificial Intelligence (AI) Use Statement

During the preparation of this manuscript, ChatGPT (OpenAI) was used for language editing and clarity. All authors critically reviewed and verified the content and take full responsibility for the accuracy, integrity, and originality of the manuscript.

RESULTS

Outpatient Survey

A total of 100 screening-naïve outpatients were enrolled in the study (median age: 55 years; range: 50-65; 51% female). Educational attainment included primary school in 31%, high school in 32%, and university or higher education in 37%. Thirty-three percent were current smokers, and 17% had a family history of cancer. The baseline characteristics, screening awareness, perceived barriers, and motivators are presented in Table 1.

Overall, awareness of CRC screening was limited. Fifty-four percent of the participants reported no prior awareness of CRC screening, and 65% were unable to identify the recommended starting age. Only 19% of the respondents correctly identified 50 years as the appropriate age to begin screening. Perceived personal risk was low, with only 24% believing they were at increased risk for CRC and 36% uncertain. Notably, among participants with a family history of cancer, 29% did not perceive themselves to be at increased risk.

Knowledge of CRC risk factors varied. Smoking (67%), red meat consumption (60%), and older age (52%) were commonly identified as risk factors, although 20% of participants incorrectly considered a high-fiber diet a risk factor. Overall, 40% of the respondents correctly identified three or more established CRC risk factors.

The most common sources of information on CRC were non-medical, including friends or acquaintances (29%) and media (22%). Only 14% reported receiving information from a healthcare professional. Consistent with this finding, only 28% of the participants stated that a physician had ever recommended CRC screening.

Concerns related to colonoscopy were common but did not appear to be absolute barriers. Fear of a serious diagnosis (45%) and pain or discomfort (40%) were the most frequently reported concerns, followed by fear of complications (33%) and privacy concerns (27%). Only 7% reported bowel preparation as a major concern. Despite these fears, 86% of participants stated that such concerns would not prevent them from undergoing screening. Among the 14% who expressed unwillingness, the most common reasons were fear of the procedure (n=8) and the belief that screening was unnecessary (n=6).

Symptom development was the strongest motivator for undergoing colonoscopy (94%), followed by a family member's cancer diagnosis (60%). When asked how physicians could better encourage screening, participants most frequently suggested providing more information (73%), emphasizing the importance of screening (67%), and addressing fears related to the procedure (54%).

Table 1. Demographic characteristics and screening awareness among outpatients

Variable	(n=100) (%)
Age (years), median (range)	55 (50-65)
Female sex	51 (51)
Education level	
Primary school	31 (31)
High school	32 (32)
University or higher	37 (37)
Current smoker	33 (33)
Family history of cancer	17 (17)
Prior awareness of CRC screening	46 (46)
Correctly identified starting age (50 years)	19 (19)
Perceived increased risk for CRC	24 (24)
Knowledge of ≥3 risk factors	40 (40)
Incorrectly identified high-fiber diet as risk factor	20 (20)
Sources of information about CRC	
Friends/acquaintances	29 (29)
Media	22 (22)
Healthcare professional	14 (14)
Received physician recommendation for CRC screening	28 (28)
Main fears about colonoscopy	
Fear of serious diagnosis	45 (45)
Pain/discomfort	40 (40)
Privacy concerns	27 (27)
Fear of complications	33 (33)
Bowel preparation	7 (7)
Would these fears prevent screening? (yes)	14 (14)
Motivators for undergoing colonoscopy	
Development of symptoms	94 (94)
Family member's cancer	60 (60)
Desire for more information	31 (31)
Suggestions for physicians to encourage screening	
Provide more information	73 (73)
Address fears	54 (54)
Emphasize importance	67 (67)

CRC: Colorectal cancer.

Pre- and Post-colonoscopy Patient Survey

A total of 100 patients undergoing colonoscopy were included (median age: 52 years; range: 51-65; 54% male). All patients in this group were undergoing their first lifetime colonoscopy. The pre- and post-procedure knowledge, attitudes, and colonoscopy-related experiences of patients undergoing their first colonoscopy are presented in Table 2.

Table 2. Demographics, knowledge, and experience of patients undergoing colonoscopy	
Variable	**(n=100) (%)**
Age (years), median (range)	52 (51-65)
Male sex	54 (54)
Education level	
Primary school	42 (42)
High school	30 (30)
University or higher	28 (28)
Current smoker	35 (35)
Family history of cancer	19 (19)
Previously completed FOBT	25 (25)
Reason for colonoscopy	
Diagnostic (symptomatic)	77 (77)
Routine screening	23 (23)
Knowledge of ≥3 CRC risk factors	55 (55)
Incorrectly identified high-fiber diet as risk factor	11 (11)
Adequately informed by physician before procedure	
Yes	12 (12)
Some information	73 (73)
None	15 (15)
Source of information about CRC	
Friends/acquaintances	9 (9)
Media	13 (13)
Healthcare professional	78 (78)
Felt more informed about CRC during bowel preparation	68 (68)
Pre-procedure anxiety	24 (24)
Believed colonoscopy reduces future cancer risk	62 (62)
Additional information desired	
Potential complications/risks	63 (63)
Procedure details	52 (52)
Potential benefits	38 (38)
Post-procedure satisfaction	
Very good	81 (81)
Good	15 (15)
Negative	4 (4)
Would undergo colonoscopy again if needed	100 (100)
Would recommend colonoscopy to relatives	
Definitely	88 (88)
Somewhat	12 (12)
CRC: Colorectal cancer, FOBT: Fecal occult blood test.	

Most colonoscopies were performed for diagnostic rather than screening purposes, with 77% of patients undergoing colonoscopy due to symptoms and only 23% for routine screening. Rectal bleeding was the most common presenting symptom. Prior participation in fecal occult blood testing was limited (25%).

Knowledge of CRC risk factors was limited, with only 17% of patients recognizing family history as a risk factor. Although physicians were the main source of CRC information (78%), only 12% of patients reported feeling adequately informed about the procedure beforehand, and 73% reported receiving only partial information. Pre-procedure anxiety was reported by 24% of patients, and bowel preparation was rated difficult by 49%. During the preparation process, 68% reported increased awareness of CRC screening, and 62% believed that colonoscopy would reduce their future cancer risk.

The post-procedure experience was highly positive. Overall satisfaction was rated as very good by 81% of patients, and 100% stated that they would undergo colonoscopy again if needed and would recommend the procedure to their relatives. No procedure-related complications were observed during the study period.

Surgeon Survey

A total of 50 general surgeons participated in the survey. Most respondents were male (78%) and worked in training and research hospitals (68%), followed by university hospitals (18%) and district state hospitals (14%). The majority were within their first five years of independent practice (72%). The demographic characteristics and CRC screening practices of the participating surgeons are shown in Table 3, while surgeon-reported patient- and system-level barriers and proposed improvement strategies are detailed in Table 4.

Nearly all surgeons reported access to a colonoscopy unit at their institution (98%), and 58% performed colonoscopy regularly. The average procedural volume was 10±3 colonoscopies per day and 70±15 per month, with 62% allocating at least 15 minutes per procedure. Patient education practices varied, with 40% of respondents providing detailed face-to-face counseling, while bowel preparation instructions were frequently delegated to non-physician staff.

Despite general support for CRC screening, only 68% of surgeons routinely recommended colonoscopy for eligible patients. When asked whether they actively attempted to persuade reluctant patients to undergo colonoscopy, 46% of surgeons reported doing so routinely, while 40% stated that they did so occasionally. The most commonly cited barriers preventing surgeons from routinely recommending or actively encouraging CRC screening were lack of time (84%) and low motivation or burnout (30%) (Table 4).

Surgeons also commonly perceived patient-related reasons for refusal. The most frequently cited concerns were fear of pain or complications (78%) and concerns related to privacy or

Table 3. Demographic and practice characteristics of participating surgeons	
Variable	**(n=50) (%)**
Male sex	39 (78)
Institution type	
Training and research hospital	34 (68)
University hospital	9 (18)
District state hospital	7 (14)
Hold academic title	7 (14)
Years in independent surgical practice	
0-5 years	36 (72)
6-10 years	5 (10)
>10 years	9 (18)
Have colonoscopy unit at institution	49 (98)
Perform colonoscopy personally	
Regularly	29 (58)
Sometimes	16 (32)
Never	5 (10)
Average procedures	
Daily	10±3
Monthly	70±15
Allocate ≥15 min per procedure	31 (62)
Method of providing patient information	
Detailed face-to-face	20 (40)
Written materials	11 (22)
Delegated to other staff	19 (38)
Who provides bowel prep instructions	
Nurse	16 (32)
Endoscopy personnel	13 (26)
Other surgeon staff	11 (22)
Surgeon personally	10 (20)
Adequate bowel prep among patients	
76-100%	11 (22)
51-75%	26 (52)
25-50%	8 (16)
25%	5 (10)
Colonoscopy in adults >70 years	
Depends on condition	22 (44)
Yes, should continue	17 (34)
No	11 (22)

embarrassment (68%). Moreover, 80% of surgeons believed that public knowledge of CRC screening was inadequate.

System-level constraints were identified as major barriers to effective CRC screening implementation. Long waiting times for colonoscopy appointments were reported by 90% of surgeons, and limited consultation time by 54%. In addition,

Table 4. Perceived barriers and improvement strategies reported by surgeons	
Variable	**(n=50) (%)**
Common patient concerns	
Pain/complications	39 (78)
Privacy concerns	34 (68)
Preparation burden	33 (66)
Belief procedure unnecessary	7 (14)
Perception of patient knowledge (inadequate)	40 (80)
National screening program effectiveness	
Effective	6 (12)
Partly effective	38 (76)
Not effective	6 (12)
Routinely recommend colonoscopy for eligible patients	34 (68)
Attempt to persuade reluctant patients	
Yes	23 (46)
Sometimes	20 (40)
No	7 (14)
Reasons for not recommending/encouraging	
Lack of time	42 (84)
Low motivation/burnout	15 (30)
Limited access to colonoscopy	10 (20)
Doubt about patient receptivity	7 (14)
System-level barriers	
Long waiting times	45 (90)
Limited consultation time	27 (54)
Lack of robust national program	21 (42)
Complex referral process	18 (36)
Perceived adequacy of colonoscopy access	
Adequate only in major cities	25 (50)
Limited nationwide	21 (42)
Adequate overall	4 (8)
Number of trained endoscopists sufficient	4 (8)
Suggested strategies to improve screening	
Organized national reminder systems	46 (92)
Increase media awareness	39 (78)
Proactive family physician referrals	32 (64)
Strategies to enhance provider motivation	
Increase consultation time	46 (92)
Provide concise guidelines and seminars	43 (86)
Redistribute workload to more hospitals	27 (58)

42% of surgeons cited the absence of a robust national screening program, describing it as largely opportunistic and not systematically integrated into the primary care. Furthermore, 92% stated that the number of physicians trained to perform

colonoscopy was insufficient. Half of the respondents (50%) believed that access to colonoscopy was adequate only in major cities, while 42% reported limited access nationwide (Table 4).

To improve CRC screening uptake, surgeons most frequently emphasized the need for organized national screening and reminder systems (92%), increased media-based public awareness (78%), and stronger involvement of family physicians in proactive referral (64%). To enhance provider motivation and capacity, the suggested strategies included increasing consultation time (92%), providing concise guideline documents and regular educational seminars (86%), and redistributing the screening workload across additional hospitals (58%).

DISCUSSION

This study demonstrates a clear gap between patients' willingness to undergo CRC screening and the capacity of the healthcare system to effectively deliver and promote preventive screening in Türkiye. Although patient awareness of CRC screening and individual risk factors was limited, most respondents reported a willingness to undergo colonoscopy when recommended by a physician. Simultaneously, surgeons identified organizational and capacity-related constraints, rather than patient refusal, as the primary barriers to effective screening implementation. Consistent with these findings, CRC screening in practice appears to be largely symptom-driven rather than preventive.

Despite the presence of a national CRC screening program in Türkiye, participation is limited. A recent meta-analysis reported that only 19.3 percent of eligible individuals were aware of stool-based screening tests, and only 13.2 percent had ever completed one, while awareness of colonoscopy was higher at 31.7 percent, with an uptake of only 10 percent (8). Our findings closely reflect this trend. More than half of the screening-naïve outpatients reported no prior awareness of CRC screening, most were unable to identify the recommended starting age, and nearly one-third of individuals with a family history did not perceive themselves to be at increased risk. Sources of information were predominantly non-medical, whereas physician-mediated education was infrequent. Taken together, these findings indicate that the national screening program is not consistently integrated into routine clinical encounters, limiting its effectiveness in reaching the target population.

In addition to limited awareness, psychological and perceptual factors influence screening behavior. Fear of pain or discomfort, embarrassment, and anxiety related to a potential cancer diagnosis have been consistently reported as common barriers, and qualitative research suggests that asymptomatic individuals often assign low priority to preventive screening (9-11). Similarly, in our cohort, concerns related to receiving a serious diagnosis, procedural discomfort, and embarrassment were frequently reported by patients. Importantly, most participants indicated that these concerns would not ultimately prevent them from undergoing colonoscopy if recommended by a physician. Notably, once patients underwent the procedure, their experience was largely positive and educational, and many reported an increased understanding of CRC and screening. In contrast to this strong desire for information, only a small proportion of patients felt adequately informed prior to colonoscopy, suggesting that patient-level concerns are modifiable when clear communication and guidance are provided in the healthcare system.

However, system-level barriers emerged as prominent obstacles to effective CRC screening in Türkiye. Evidence from primary care settings indicates that fewer than one-third of family physicians routinely recommend stool-based screening tests, and only a small proportion advise screening colonoscopy at appropriate intervals (12). Reflecting this limited provider engagement, a systematic review reported that only 14-28 percent of patients had ever received a physician recommendation for CRC screening, which is notable given that physician recommendation is a key determinant of screening adherence (8,13). Reflecting this broader trend, surgeons in our study cited limited consultation time and professional burnout as key constraints to routinely recommending or actively encouraging screening. This limited proactive recommendation at the provider level aligns with the low rate of clinician-provided screening information reported by screening-naïve outpatients. Furthermore, most colonoscopies in our cohort were performed for the diagnostic evaluation of symptoms rather than for primary preventive screening, underscoring the predominance of reactive, symptom-driven care over organized screening.

To address system-level barriers, surgeons emphasized the need for more organized national screening and reminder systems, increased public awareness, and stronger involvement of family physicians in proactive referrals. International experience supports this approach, as organized screening programs in Europe and East Asia employ mailed invitations, centralized registries, and coordinated public campaigns, with primary care serving a central role (9,14,15). However, improving awareness alone is unlikely to translate into higher screening uptake in the absence of adequate endoscopic capacity (16). In our study, the shortage of trained endoscopists and limited procedural availability emerged as major constraints. Although Ministry of Health data indicate that large numbers of stool-based screening tests are distributed annually, these figures do not provide information on population coverage or downstream colonoscopy completion (17). In this context, a limited endoscopic workforce represents a critical bottleneck. Evidence from international screening programs indicates that both general surgeons and gastroenterologists deliver high-quality colonoscopy and that current screening-related demand

can only be met through their complementary and shared contributions (18,19). Without the corresponding expansion of endoscopic capacity and infrastructure, efforts to scale up organized screening programs are likely to encounter substantial implementation barriers.

A key strength of this study is its tripartite design, which incorporates perspectives from screening-naïve outpatients, patients undergoing colonoscopy, and practicing surgeons, allowing for the assessment of barriers across multiple stages of the CRC screening pathway. The inclusion of patient experiences before and after colonoscopy also provided insights into modifiable patient-level barriers.

Study Limitations

This study has several limitations. First, it was conducted at a single tertiary training and research hospital, where patient presentations and referral patterns are more likely to be symptom-driven than in primary or secondary care, which may limit its generalizability. Second, most participating surgeons were affiliated with tertiary institutions, and their reported practices may not reflect the screening workflows or resource constraints in smaller or rural settings. The surgeon survey may also be subject to non-response bias, as respondents might differ systematically from non-respondents in their screening practices or perceptions. Third, although the tripartite design captured perspectives from screening-naïve outpatients, colonoscopy patients, and surgeons, the absence of family physicians and gastroenterologists limited the comprehensive assessment of the CRC screening pathway. Fourth, the descriptive design precludes causal inference and identification of independent predictors of screening behavior. Finally, the questionnaires were pilot-tested but not formally validated, which may have introduced a measurement bias. Accordingly, the findings should be interpreted as an exploratory assessment of perceived barriers rather than definitive evidence to guide nationwide screening policy.

CONCLUSION

The principal challenge in CRC screening in Türkiye appears to be the gap between patient willingness and healthcare system capacity rather than patient reluctance. While patient-level barriers are potentially modifiable, limited endoscopic capacity, including the availability of trained endoscopists, remains a critical constraint for implementing preventive screening.

Ethics

Ethics Committee Approval: The study was approved by the Local Institutional Ethics Committee of Ankara Bilkent City Hospital (approval number: 451, date: 07.08.2024).

Informed Consent: Written informed consent was obtained from all participants prior to their participation.

Footnotes

Authorship Contributions

Concept: M.O., E.Ç.; Design: M.O., E.Ç.; Data Collection or Processing: M.B.; Analysis or Interpretation: M.O. M.B.; Literature Search: M.O., E.Ç.; Writing: M.O., İ.K., E.Ç.

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ORIGINAL ARTICLE
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Anxiety and screening attitudes in breast cancer patients and their first-degree relatives: A comparative pilot study

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ABSTRACT

Objective: Breast cancer is the most common type of cancer in women. Identifying women at risk of breast cancer and ensuring their participation in cancer screening programs have been shown to reduce mortality rates. Therefore, it is important to identify the determinants of attitudes toward breast cancer screening, among which anxiety may play a significant role. This study aimed to explore the screening attitudes and anxiety levels of women with breast cancer and those of their female first-degree relatives within a patient-relative dyadic framework.

Material and Methods: Breast cancer patients and their female first-degree relatives between the ages of 18-65 were included in this cross-sectional study as a patient-relative dyad. The patients were administered a socio-demographic questionnaire, the breast cancer worry scale, and the attitude towards cancer screening scale.

Results: A total of 37 dyads participated in the study. The median age of the entire cohort was 47. Screening participation was reported in 37.1% (13/35) of patients pre-diagnosis and in 29.1% (7/24) of eligible relatives. A negative correlation was found between patients' anxiety and their relatives' screening attitudes (r=-0.395, p=0.016 Spearman's correlation), whereas a positive correlation was found between patients' attitudes and their relatives' attitudes (r=0.501, p=0.002 Spearman's correlation).

Conclusion: Higher levels of anxiety in breast cancer patients were associated with less favorable screening attitudes among their relatives, whereas screening attitudes were positively correlated within patient-relative dyads. These findings suggest that anxiety and screening attitudes may cluster within patient-relative dyads. Further research is required to determine the clinical implications.

Keywords: Breast cancer, screening tests, anxiety

INTRODUCTION

Breast cancer is the most common cancer in women and one of the leading causes of cancer-related deaths (1,2). Early detection through screening remains the primary strategy for mortality reduction (3). The World Health Organization recommends mammography for screening purposes, while clinical and self-breast examinations are emphasized primarily for breast awareness (4). Türkiye's current screening policy includes biannual mammography and clinical breast examinations for individuals aged 40 to 69 (5).

Identifying the population's risk factors is an essential step in the decision-making process for screening policies. Key risk factors for breast cancer include aging, reproductive factors such as early menarche, late menopause, and late pregnancy and hormone replacement therapy (6). Family history, an unmodifiable risk factor that necessitates earlier screening, is present in 5-10% of breast cancer cases (7). A woman who has a relative with breast cancer has a higher risk of developing the disease than the general population (8). Screening for these high-risk groups is important not only for reducing mortality and morbidity but also for ensuring cost-effectiveness (9).

The attitudes of high-risk women toward screening programs are important for early detection of breast cancer. Given the importance of screening for breast cancer, it is essential to examine the factors that may negatively influence attitudes

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toward screenings. Several factors that adversely affect screening attitudes include low socio-economic status, lack of private health insurance, medical mistrust, insufficient health information, and anxiety, which is a significant contributing factor. Anxiety in breast cancer patients also leads to depressive symptoms and decreased quality of life and is linked to a higher risk of mortality (10,11). Considering that anxiety can significantly influence screening attitudes, particularly in family systems where illness experiences are shared, this study aimed to explore associations between anxiety and screening attitudes in patient-relative dyads.

MATERIAL and METHODS

Study Design

After obtaining ethical approval, this cross-sectional study was conducted among female patients with breast cancer aged 18 to 65 who visited a medical oncology clinic in a tertiary facility serving over eighty thousand cancer patients annually and who were accompanied by a female relative. Those who agreed to participate were included in the sample as patient-relative pairs. Informed consent was obtained from all participants and the entire study was conducted in accordance with the Declaration of Helsinki. All participant data were anonymized prior to analysis to ensure confidentiality. The primary outcome was to identify differences between patients and at-risk relatives in worry about breast cancer and attitudes toward breast cancer screening.

Ethical approval was obtained from the Marmara University Faculty of Medicine Clinical Research Ethics Committee (approval number: 09.2023.111, date: 20.01.2023). This study was conducted per the Declaration of Helsinki and the Research and Publication Ethics, and patient data were anonymized before analysis.

Participants

Patients presenting to the medical oncology outpatient clinic aged 18 to 65 and diagnosed with breast cancer, together with their first-degree female relatives, were included in the study as dyads. First-degree relatives are defined as parents, children, and siblings. Individuals facing medical or social barriers to completing the surveys, male breast cancer patients, and female relatives with a history of breast cancer were excluded from the study. Data were collected through face-to-face surveys conducted with patients and their relatives on various weekdays at the clinic. This descriptive study did not use systematic sampling; instead, a convenience sample was employed, which we acknowledge as a limitation with regard to generalizability. The sample size was calculated to be 70 using the publicly available statistical software OpenEpi, version 3. The analysis was performed with a 95% confidence interval, 80% power, a mean difference of 2.7, and a standard deviation of 4 for each group.

Data Collection

After providing informed consent, each participant was asked to complete questionnaires to collect socio-demographic data. The socio-demographic questions were developed based on a literature review and assessed participants' ages, economic status, educational background, and family structure. Additionally, factors that may affect cancer risk, such as age at menopause, age at first menstruation, use of hormone replacement therapy, and smoking history, were included. Furthermore, the breast cancer risk among relatives aged 35 to 65 was calculated using the NCI breast cancer risk calculator in an exploratory, hypothesis-generating subanalysis (12). The NCI Breast Cancer Risk Assessment Tool estimates both the 5-year and lifetime absolute risks of developing invasive breast cancer based on age, reproductive history, family history in first-degree relatives, and selected clinical factors. In this study, lifetime risk projections were used to better characterize participants' long-term susceptibility. Risk calculations were performed for first-degree relatives aged 35-65 years in accordance with the eligibility criteria of the NCI tool. Relatives younger than 35 years of age or those with missing required variables were excluded from this analysis. As a result, NCI-based risk estimation was feasible in 16 relatives, and this subgroup was analyzed separately.

The breast cancer worry Breast Cancer Worry Scale (BCWS), developed by Lerman et al. (13) was used to assess concerns regarding breast cancer. The validity and reliability of the BCWS have been confirmed both in its original version and in Turkish (14). The instrument comprises six questions on a 5-point Likert scale, with responses ranging from 0 to 4. Total scores range from 0 to 24, with lower scores reflecting lower cancer-related worry and higher scores reflecting higher cancer-related worry.

The Attitude Towards Cancer Screening Scale (ATCS), developed by Yıldırım Öztürk et al. (15), was used to evaluate knowledge and attitudes related to breast cancer screening tests and the validity and reliability have been previously demonstrated, with a Cronbach's α coefficient of 0.95 in prior studies. The ATCS comprises 15 items rated on a five-point Likert scale, yielding total scores between 15 and 75. Although no formal cutoff values have been defined, scores closer to 15 reflect a negative attitude toward cancer screening, whereas scores approaching 75 indicate a positive attitude (15).

In this study, screening participation was defined differently for breast cancer patients and their first-degree relatives. For relatives, participation was assessed according to risk-adapted screening recommendations. Several international guidelines propose earlier initiation of breast cancer screening for women at increased risk due to family history, with variations in the recommended starting age and screening modality depending on risk stratification models and healthcare settings (16-18).

In the present study, we adopted the National Comprehensive Cancer Network recommendations, which advise initiating screening earlier than for the average-risk population—approximately at 30 years of age—for women with a first-degree relative diagnosed with breast cancer. Accordingly, first-degree relatives aged ≥30 years who had undergone mammography and/or breast magnetic resonance imaging in line with high-risk screening recommendations were classified as screening participants. For patients, screening-related attitudes were evaluated based on screening experiences of prior to diagnosis and general perspectives toward screening, as they were no longer eligible for routine population-based screening following a breast cancer diagnosis.

Following completion of the anxiety survey, relatives of patients were provided with brief educational information regarding breast cancer risk and screening practices. Screening appointments were arranged after survey completion for eligible participants who explicitly requested them.

Statistical Analysis

Data were analyzed using IBM SPSS 26.0 (IBM SPSS Statistics for Windows, version 26.0. Armonk, NY: IBM Corp). Categorical variables were compared using the chi-square test, and Fisher's exact test was applied when expected cell counts were small. To control for Type I error due to multiple comparisons, the Bonferroni correction was applied. Continuous variables were analyzed using the Mann-Whitney U and Kruskal-Wallis H tests. Non-parametric Spearman correlation was used, and a p-value of <0.05 was deemed statistically significant.

RESULTS

The study involved 37 dyads. The median age of the entire cohort was 47 years [interquartile range (IQR) 32-58], with 34 (45.9%) having attained higher education. Among them, 43 (58.1%) were married, and 27 (36.4%) were employed. Most participants (75.7%) reported income that matched their expenditures. Table 1 presents socio-demographic data in pairs. Their relatives were, on average, 22 years younger than the patients (p=0.001, Mann-Whitney U test). Patients and their relatives were comparable in terms of education, employment, and income level.

Breast cancer risk factors and screening characteristics are presented in Table 2. The frequency of postmenopausal women was higher in the patient group than in the relatives group (p=0.001, chi-square test). Menopausal age, age at menarche, smoking habits, and alcohol consumption were similar between the two groups. Regarding screening participation, 35 patients were eligible for screening prior to diagnosis, of whom 13 (37.1%) had participated, compared to 7 of the 24 eligible relatives (29.1%). Screening participation rates were similar between patients and relatives (p=0.585, chi-square test).

The median total scores for ATCS and BCWS among all participants were 71 (IQR 61-75) and 15 (IQR 10.75-21), respectively. There were no statistically significant differences in attitude and anxiety scores between patients and their relatives (Table 3). The NCI breast cancer risk was calculated for 16 eligible relatives, revealing a median risk percentage of 17.6% for life-time risk developing breast cancer among them. In the analysis of anxiety and attitude scores relative to socio-demographic factors,

Table 1. Socio-demographic characteristics of the study population

	Patients (n=37)	Relatives (n=37)	p
Age (years)	54 (48-62)	32 (21-45)	0.001
Education level			
High school or lower	24 (64.9)	16 (43.2)	
University or higher	13 (35.1)	21 (56.8)	0.064
Marital status			
Married	26 (70.3)	17 (45.9)	
Single/divorced/widowed	11 (29.7)	20 (54.1)	0.035
Employment			
Currently employed	14 (37.8)	13 (35.1)	
Unemployed	23 (62.2)	24 (64.9)	0.810
Income level			
Less than expenditure	5 (13.5)	3 (8.1)	
Equal to expenditure	28 (75.7)	30 (81.1)	
Higher than expenditure	4 (10.8)	4 (10.8)	0.619

Data were presented as median (interquartile range) or as frequencies and percentages. Categorical variables were compared using the chi-square and Fisher's exact tests, and continuous variables were analyzed using the Mann-Whitney U test.

Table 2. Breast cancer risk factors and screening characteristics of the study population			
	Patients (n=37)	**Relatives (n=37)**	**p**
Menopause status			
Premenopausal	6 (16.2)	28 (75.7)	
Postmenopausal	31 (83.8)	9 (24.3)	0.001
Menopause age (yr)			
<45	9 (29.0)	4 (44.5)	
45-48	11 (35.5)	1 (11.1)	
49-52	7 (22.6)	3 (33.3)	
53+	4 (12.9)	1 (11.1)	0.52
HRT	5 (13.5)	1 (2.7)	
Age of menarche (yr)			
7-11	9 (24.3)	4 (10.8)	
12-13	19 (51.4)	26 (70.3)	
14+	9 (24.3)	7 (18.9)	0.195
Number of children			
0	7 (18.9)	19 (51.4)	
1-3	20 (54.1)	14 (37.8)	
4+	10 (27.0)	4 (10.8)	0.01
Smoking	4 (10.8)	5 (13.5)	0.724
Alcohol consumption	0 (0.0)	3 (8.1)	0.239
Screening participation (of eligible)	13 (of 35)	7 (of 24)	0.585
Data were presented as frequencies and percentages. Categorical variables were compared using the chi-square and Fisher's exact tests.			

Table 3. Anxiety, attitude, and risk scores of the study population			
	Patients (n=37)	**Relatives (n=37)**	**p**
Attitude	73 (57-75)	69 (62.5-75)	0.399
Anxiety	14 (10-18.5)	15 (11.5-20.5)	0.423
Risk (%)	-	17.6 (15.5-18)	-
Data were presented as median (interquartile range). Risk identifies the lifetime percentage risk of developing breast cancer for relatives, as calculated by NCI scores, only for 16 eligible relatives aged 35-65. Continuous variables were analyzed using the Mann-Whitney U test.			

cancer risk, and screening characteristics, married relatives showed higher anxiety scores (median 20 versus 12.5, p=0.03, Mann-Whitney U test). Additionally, patients experiencing earlier onset of menopause had higher attitude scores (medians: 75, 71, 62, 70.5; p=0.05, Kruskal-Wallis H test), while relatives with at least one child exhibited higher anxiety scores (18.5 compared to 13; p=0.01, Mann-Whitney U test). These are adjusted p-values after Bonferroni correction.

The correlation analysis revealed a moderate positive association between patients' attitudes and those of their relatives (r=0.501, p=0.002, Spearman's correlation). In addition, a moderate negative correlation was found between patients' anxiety and their relatives' attitude (r=-0.395, p=0.016, Spearman's correlation). As relatives' risk of breast cancer increased, their anxiety scores increased, indicating a moderate positive correlation (r=0.576, p=0.02, Spearman's correlation, Figure 1).

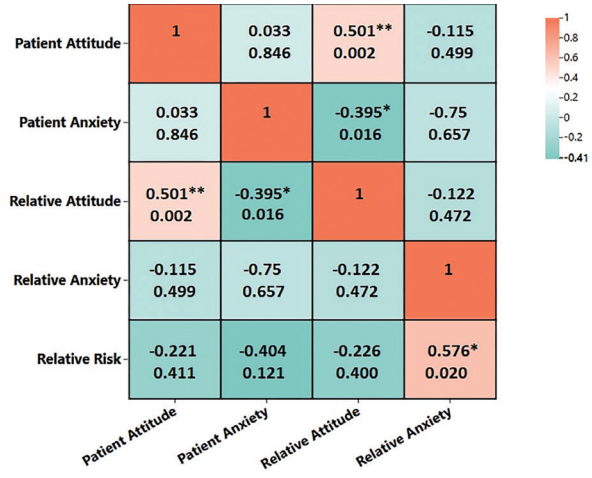

Figure 1. Correlation heatmap between anxiety and attitude scores of patients and their relatives. The data in each cell represents the correlation coefficient (top) and p-values (bottom).

DISCUSSION

Breast cancer remains the most prevalent malignancy among women, and screening has been shown to reduce mortality, underscoring the importance of understanding factors that shape women's attitudes toward screening, particularly in high-risk -groups such as those with a family history. Anxiety is a -well-recognized determinant of screening behavior; however, within the familial context, this influence becomes more complex. First-degree relatives not only face heightened genetic risk, which may intensify their screening-related anxiety, but they also frequently assume caregiving roles, making their psychosocial status a pivotal factor in shaping both their own and the patient's attitudes toward screening (19). Consequently, this study aimed to explore the relationship between breast cancer-related anxiety and attitudes toward screening tests among patients and their relatives, and to assess whether patients' attitudes and anxiety were associated with those of their relatives. Our findings demonstrated a positive correlation between patients and their relatives in their attitudes toward screening. In contrast, a negative correlation was noted between patients' anxiety and the relatives' attitudes toward screening.

Positive attitudes toward screening programs are considered an important prerequisite for participation and adherence, given their established health benefits. Unfortunately, compliance rates are low in Türkiye. While many different figures exist for compliance with these programs in Türkiye, some studies indicate that mammography rates range from 15.8% to 54.1% (20-22). According to the recent nationwide data, screening participation is largely driven by socio-demographic factors; i.e.; age, being married, higher education, and social support from a spouse are significant predictors of increased participation, whereas lack of regular contact with family physicians is a barrier (22). However, this nationwide study did not account for family history. Strikingly, despite their elevated risk profile, which necessitates greater vigilance, the participation rate among eligible relatives was 29.1%, lower than that of the general population. This discrepancy underscores the critical need to identify factors that influence attitudes toward screening, particularly among high-risk groups who stand to benefit most from early detection.

Women with a family history of breast cancer are at a higher risk of developing the disease than the general population, making attitudes toward screening programs essential for them (8). Several factors influence screening attitudes, including fear of cancer, lack of knowledge about screening and mammography procedures, privacy concerns, and access to screening (23). Anxiety plays a significant role in screening attitudes, and the literature presents conflicting results on this issue. A review published in 2023, which analyzed 74 articles related to anticipatory anxiety and cancer screenings—specifically for colon, breast, cervical, lung, and prostate cancers—found that anticipatory anxiety regarding a cancer diagnosis was associated with a greater likelihood of attending screenings and an increased intention to undergo them (24). Conversely, a study of breast cancer survivors found that higher levels of anticipatory anxiety were linked to lower participation in mammography (25). Anticipatory anxiety may differentially influence participation in screening programs.

In our study, the median BCWS value was nearly twice that found in a Turkish validation study involving 610 women without breast cancer (14). Based on these results, we hypothesize that both breast cancer patients and their relatives experience higher levels of anxiety than the general population, and that the two groups exhibit similar anxiety levels, as we have demonstrated. Although our results show that patients and their relatives have similar median BCWS scores, we found a negative correlation between patient anxiety and their relatives' screening attitudes: As patient anxiety increased, relatives' attitudes toward screening diminished. This may be due to observing their relatives with cancer being affected by the process and worrying about receiving a negative screening result, which supports the concept of anticipatory anxiety. Thus, our findings suggest an inverse relationship between patient anxiety and the screening attitudes of their relatives, highlighting a potential psychological impact in this high-risk cohort.

The effect of family history on attitudes towards breast cancer screening programs remains unclear. In Türkiye in 2022, a study involving 248 women examined their attitudes towards cancer screening using the ATCS short form questionnaire; the mean cancer screening attitude score was 65, and scores did not differ between women with and without a family history of cancer (26). In contrast, another study conducted in Türkiye found that women with a family history of breast cancer exhibited a more positive attitude. The median screening scale score in our study was 69, which was comparable to scores reported in the literature (26). Scores similar to those reported in the literature and comparable scores between patients and relatives in our study indicate that there is no significant difference among relatives of breast cancer patients, breast cancer patients, and the general population. We have demonstrated a moderate positive correlation between patients and their relatives in scores on the breast cancer screening scale. The patient's and the relative's attitudes are similar; as the patient's attitude increases, the relative's attitude also increases. Lastly, in a subgroup of relatives with available NCI scores, we have also demonstrated a moderate positive correlation between anxiety scores and the lifetime risk of breast cancer. In contrast, no correlation was found between breast cancer risk and attitudes toward breast cancer screening, which is concerning, given that these patients

have increased risk and anxiety without a comparable increase in risk perception. That supports the hypothesis that anticipatory anxiety may be associated with less favorable screening attitudes in this high-risk subgroup. Overall, these results indicate that a structured intervention may be beneficial for relatives of breast cancer patients, a high-risk group, in reducing their anxiety and improving their attitudes toward screening.

Study Limitations

Our study had several limitations. Although the patient population was relatively small, the sample size was determined through power analysis, and participants were recruited and analyzed as patient-relative pairs. Additionally, the use of convenience sampling and the absence of a comparison group from the general population without a family history of breast cancer limit the representativeness of the findings; therefore, they should be viewed as exploratory and hypothesis-generating. Importantly, restricting enrollment to patients accompanied by a relative introduces selection bias toward patients with greater social support and, potentially, more engaged families. Furthermore, although we restricted our screening participation analysis to eligible relatives aged 30 years or older to prevent artificially lowering the observed rates, the inclusion of younger relatives (aged 18-29) in the overall cohort may still introduce structural confounding in risk perception and screening attitudes. In addition, the large age difference between patients and their relatives (median 54 vs. 32 years) could confound screening behaviors and risk perception, yet age adjustment was not feasible given the sample size. We also did not account for the treatment stage, although most patients were in remission, and did not collect data on prior education or knowledge about breast cancer screening, which may be confounding factors for breast cancer anxiety and screening attitudes.

CONCLUSION

We have demonstrated a potential shared dynamic between breast cancer patients and their relatives: Specifically, positive patient attitudes correlate with better screening engagement among relatives, whereas elevated patient anxiety is associated with less favorable attitudes among relatives. Moreover, in a subgroup of first-degree relatives, higher NCI breast cancer risk scores were associated with greater anxiety, whereas no corresponding association was observed between risk and favorable screening attitudes, suggesting a potential mismatch between perceived risk and preventive screening behaviors in this high-risk group. These findings are exploratory and hypothesis-generating, given the limited sample size and methodological constraints; therefore, they should be confirmed by multicenter studies with larger sample sizes. Given that first-degree relatives frequently serve as primary caregivers throughout the diagnostic and surgical trajectory, the perioperative setting may present a unique opportunity not only to identify anxiety but also to integrate family-centered screening and counseling; future research should validate such approaches through evidence-based interventions.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Marmara University Faculty of Medicine Clinical Research Ethics Committee (approval number: 09.2023.111, date: 20.01.2023). This study was conducted per the Declaration of Helsinki and the Research and Publication Ethics, and patient data were anonymized before analysis.

Informed Consent: Informed consent was obtained from all participants and the entire study was conducted in accordance with the Declaration of Helsinki.

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During the preparation of this manuscript, the authors used Gemini (Gemini 3.1 Pro, Google, March 2026), solely for the purpose of language editing to improve the clarity and grammatical accuracy. The use of AI complies with ethical standards regarding confidentiality and data protection. Following the use of this tool, the authors critically reviewed, edited, and validated all content to ensure its accuracy and integrity. The authors take full responsibility for the final content of the manuscript and confirm that no AI tool was used for data collection, statistical analysis, or text generating. An abstract of this study was presented at the European Congress of Internal Medicine (ECIM) 2026 in Vienna, Austria. This presentation was supported by the TÜBİTAK Türkiye through the 2224A-International Scientific Events Participation Support Program.

Footnotes

Author Contributions

Concept - B.K., S.T.D., E.B.S., R.S., A.B.U., N.S., I.V.B., S.H., G.T.; Design - B.K., S.T.D., E.B.S., R.S., A.B.U., N.S., I.V.B., S.H., G.T.; Data Collection or Processing - B.K., S.T.D., E.B.S., R.S., A.B.U., N.S., I.V.B., S.H., G.T.; Analysis or Interpretation - B.K., S.T.D., E.B.S., R.S., A.B.U., N.S., I.V.B., S.H., G.T.; Literature Search - B.K., S.T.D., E.B.S., R.S., A.B.U., N.S., I.V.B., S.H., G.T.; Writing - B.K., S.T.D., E.B.S., R.S., A.B.U., N.S., I.V.B., S.H., G.T.

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ORIGINAL ARTICLE
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Predictive factors of non-invasive follicular thyroid neoplasm with papillary-like nuclear features: A single-center study

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ABSTRACT

Objective: Distinguishing preoperative criteria and postoperative histological features of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) from those of other thyroid tumors with follicular architecture and papillary nuclear features (non-NIFTP) is crucial to prevent overtreatment. In this study, we aim to identify the predictive factors of NIFTP.

Material and Methods: We conducted a retrospective study in which we collected cases of thyroid tumors with follicular architecture and papillary nuclear features diagnosed between 2012 and 2022. Clinicopathological characteristics, therapeutic modalities, and follow-up were compared between NIFTP and non-NIFTP tumors.

Results: Forty cases of NIFTP and 44 cases of non-NIFTP were identified. NIFTP accounted for 8.83% of all PTCs and 33.6% of all thyroid tumors with follicular architecture and papillary nuclear features. NIFTP was associated with younger age (p=0.005), isoechoic nodules on ultrasound (US) (p=0.004), regular contours (p=0.028), absence of microcalcifications (p=0.005), and predominance in European Thyroid Imaging Reporting and Data System 2 and 3 scores (p<0.001). They predominantly exhibited a nuclear score of 2 (p<0.001), focal nuclear abnormalities (p=0.015), and a thin capsule (p=0.004). No case of NIFTP showed distant or lymph node metastases. Multivariate analysis identified a nuclear score of 2, focal nuclear abnormalities, and a thin tumor capsule as independently associated with NIFTP.

Conclusion: Our findings demonstrated the indolent nature of NIFTP and the utility of cervical US in raising preoperative suspicion for this entity. Because findings regarding the Bethesda classification were not available in our study, a prospective multicenter study with a larger sample size and a longer follow-up period is warranted to address this limitation.

Keywords: NIFTP, thyroid cancer, clinical, pathology, follow-up

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common malignant endocrine tumor, with its incidence and prevalence increasing worldwide (1). In Tunisia, it represents 83.2% of differentiated malignant thyroid tumors (2). The follicular variant is the second most common subtype of papillary carcinoma, it accounts for about 20% of thyroid cancers (3). It was traditionally subdivided into a non-encapsulated form that infiltrates the thyroid parenchyma and an encapsulated form. The encapsulated form was further subdivided into two variants: An invasive encapsulated variant (showing capsular and/or vascular invasion) and a non-invasive encapsulated variant (4).

Currently, the new World Health Organization (WHO) 2022 classification considers the invasive encapsulated follicular variant of papillary thyroid carcinoma (IEFVPTC) as a distinct entity among malignant tumors and no longer includes it among PTCs (4,5). In 2016, Nikiforov et al. (6,7) proposed replacing the term "non-invasive encapsulated follicular variant of papillary carcinoma" with the new term NIFTP, meaning "non-invasive follicular thyroid neoplasm with papillary-like nuclear features", because of its indolent nature and favorable prognosis. NIFTP is defined by rigorous diagnostic criteria introduced in 2016 and revised in 2018.

The introduction of NIFTP has had a major impact on therapeutic management. Indeed, the American Thyroid Association (ATA) and French learned societies

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include these nodules among lesions for which conservative management with lobectomy alone is recommended (8,9). There is growing interest in distinguishing the preoperative ultrasound and cytological characteristics of NIFTP from those of other thyroid carcinomas with follicular architecture and papillary-like nuclear features, and in identifying postoperative histological differences. This would help reduce extensive surgery and prevent unnecessary radioactive iodine treatment. This study aimed to identify predictive factors for NIFTP.

MATERIAL and METHODS

Study Design and Population

This single-center retrospective study collected cases of thyroid tumors with follicular architecture and papillary-like nuclear features that were diagnosed in the Department of Pathology between January 2012 and December 2022 and that underwent thyroid surgery in the Department of Otolaryngology-Head and Neck Surgery.

Patients who had other concomitant types of thyroid cancer or those whose clinical records or histological slides were unavailable were excluded from this study.

In this study, two population groups were defined: Patients diagnosed with NIFTP and those with non-NIFTP tumors [namely IEFVPTC, the infiltrative follicular subtype of PTC (IFPTC), and Differentiated High-Grade Thyroid Carcinoma (DHGTC)].

A favourable opinion on the conduct of this study was issued by the Ethics Committee of the Faculty of Stax (decision no: 34/24, date: 10.07.2024) which is in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual patients included in this study for the use of their clinical data. All participants were informed about the purpose of the publication, and their privacy and confidentiality were protected in accordance with ethical standards.

Data Collection and Case Definition

-Clinical, biological and ultrasonography (US) findings: Were collected from medical files and they concerned: Age, sex, personal and family history of malignant thyroid tumors, functional signs, data from clinical examination and indirect laryngoscopy, thyroid function test [free thyroxine (FT4), thyroid-stimulating hormone (TSH)], preoperative neck US data (including the number of nodules, microcalcifications, echogenicity, regular or irregular border, the presence of suspicious lymphadenopathy and the European Thyroid Imaging Reporting and Data System [(EU-TIRADS) classification (10)] and cytological data from preoperative thyroid fine-needle aspiration. Cytological reports were reclassified according to the 2023 Bethesda system (11).

-Type of surgery: The type of thyroid surgery performed with or without lymph node dissection was specified.

-Pathological criteria:

Two pathologists reexamined all pathology reports and archival histology slides in a double-blind review. Cases were reclassified according to the latest WHO 2022 classification (4,5). The diagnosis of NIFTP was made based on diagnostic criteria proposed by Nikiforov et al. (6,7) and validated by the WHO 2022 classification (4,5).

-Pathological data concerned: Tumor size, tumor location, multifocality, histological type, nuclear score [was assessed according to Nikiforov et al. (6,7)], focal or diffuse papillary-like nuclear features, mitotic index [number of mitoses per mm^2 at high magnification (×400)], encapsulated or well-circumscribed nodule, tumor capsule thickness [a capsule is considered thick if it is more than 0.2 mm thick (12)], capsular invasion (was defined as a complete penetration of the capsule), lymphovascular invasion, solid/trabecular/insular growth pattern, psammoma bodies or microcalcifications, colloid appearance, lymphocytic thyroiditis associated and lymph node metastasis.

-Adjuvant treatment and follow-up have been specified: Administration of radioactive iodine treatment or hormonal therapy, and monitoring for tumor recurrence or distant metastasis.

Follow-up duration was calculated from the date of pathological diagnosis to the date of death from any cause or the date of the last available follow-up.

Statistical Analyses

Data were analyzed using SPSS software (version 23.0). Continuous variables were presented as mean ± standard deviation when they were normally distributed and as medians with interquartile ranges when they were not normally distributed. Categorical variables were expressed as numbers and percentages.

Correlation studies to compare characteristics of NIFTP and non-NIFTP groups were performed using Pearson's chi-square test for categorical variables (when the expected value for each cell is five or higher) or Fisher's exact test. For continuous variables, we used the Student's t-test (when normality was confirmed) or the Mann-Whitney U test.

To identify factors associated with NIFTP, a multivariate logistic regression analysis was conducted, incorporating factors identified as significant in the univariate analysis, and 95% confidence intervals (CIs) were calculated.

The threshold of statistical significance was set at 5% (p-value ≤ 0.05).

RESULTS

Case Selection

A total of 84 patients were included in the study. Figure 1 presents a flow chart of our patients.

Diagnosis After Slide Reexamination and NIFTP's Rate

After reexamination of all pathology reports and archival histology slides by two pathologists cases were reclassified as follows: 40 cases of NIFTP (of which 16 were reclassified as NIFTP from 2012 until 2018), 21 cases of IEFVPTC, 22 cases of IFPTC, and one case of DHGTC.

Thus, isolated NIFTP represented 8.83% of all PTC (453 cases of PTC were diagnosed between 2012 and 2022) and 33.6% of all thyroid tumors with follicular architecture and papillary nuclear features.

Comparison of Clinical, Biological and Cytological Characteristics Between NIFTP and Non-NIFTP Groups

The clinical, biological, and cytological variables in the NIFTP and non-NIFTP groups are outlined in Table 1. The two groups differed significantly only in age. The mean age was 40.9 years (±11.4) and 49.48 years (±15.3) in the NIFTP and non-NIFTP groups respectively (p=0.005). The difference was also significant when a threshold of 55 years was used (p=0.026). The mean age of the IFPTC group was 52.59 years, which was significantly different from that of the NIFTP group (p=0.001). The mean age of the IEFVPTC group was 47.57 years (p=0.051).

Preoperative thyroid fine-needle aspiration results were available for five patients in the NIFTP group [benign (category II) in two cases, atypia of undetermined significance (category III) in two cases, and suspicious for malignancy (category V) in one case] and for twelve patients in the non-NIFTP group [malignant (category VI) or suspicious for malignancy (category V) in only 4 cases]. No statistically significant differences in cytological findings were observed between the two groups (p=0.528) (Table 1). However, the limited availability of cytological data precludes a valid comparison using the Bethesda classification.

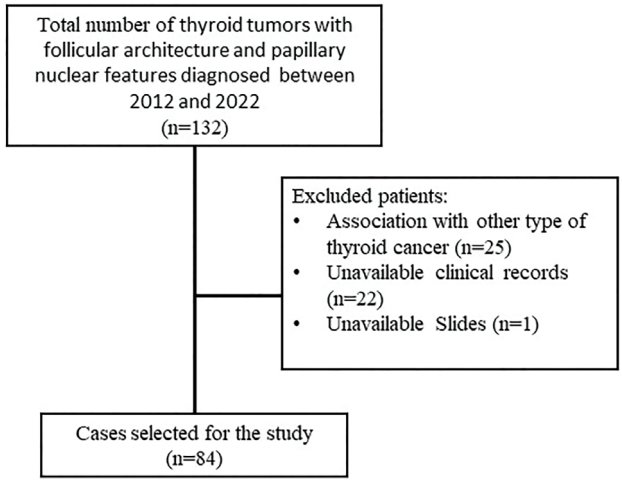

Figure 1. Flow-chart of patient's selection.

Type of Surgery

For the NIFTP group, total thyroidectomy was performed in 27 patients (67.5%) and lobectomy in 13 patients (32.5%). For the non-NIFTP group, total thyroidectomy was performed in 41 cases (93.2%) and lobectomy in 3 cases (6.8%). Seven (17.5%) of NIFTP patients and 33 (75%) of non-NIFTP patients underwent lymph node dissection.

Since the implementation of the 2015 ATA Guidelines recommending conservative management for NIFTP, rates of total thyroidectomy with lymph node dissection have decreased notably. Before 2018, 93.75% of patients with NIFTP underwent total thyroidectomy (15 out of 16 patients), while only 6.25% underwent lobo-isthmectomy (1 out of 16 patients). Lymph node dissection was carried out in 37.5% of cases. After 2018, the rate of total thyroidectomy decreased to 50% (12 out of 24 patients), and lymph node dissection was performed in only 4.2% of cases (1 out of 24 patients).

Comparison of Preoperative Neck Ultrasonographic Characteristics Between NIFTP and Non-NIFTP Groups

A preoperative neck US was performed in all patients in the NIFTP group and in 43 patients in the non-NIFTP group. Only one patient underwent a computed tomography scan to evaluate a plunging goiter. The nodule was solitary in 9 patients with NIFTP and in 11 patients with non-NIFTP.

In the US, NIFTPs were more often isoechoic (55% vs. 25.6%), whereas non-NIFTPs were predominantly very hypoechoic (27.9% vs. 5%) (p=0.004). IFPTC is significantly more often very hypoechoic than NIFTP (42.9% vs. 5%; p=0.001). IEFVPTC is more often hypoechoic than NIFTP (47.6% vs. 22.5%), but this difference is not statistically significant (p=0.63). The presence of irregular contours was significantly greater in the non-NIFTP group (p=0.028). Regular contours were observed in 92.5% of NIFTP cases and 90.5% of IEFVPTC cases. In contrast, irregular contours were observed in only 7.5% of NIFTP cases compared with 42.9% of IFPTC cases; this difference was statistically significant (p=0.002).

A significant association was found between the presence of microcalcifications and the diagnosis of non-NIFTP (p=0.005). No significant difference was observed between the two groups in the presence of suspicious lymphadenopathy on US.

Applying the EU-TIRADS classification, a significant difference between NIFTPs and non-NIFTPs was observed. 67.4% of non-NIFTPs were grouped in scores 4 and 5, and 77.5% of NIFTPs were

Table 1. Clinical, biological and cytological characteristics of NIFTP and non-NIFTP groups				
		NIFTP	**Non-NIFTP**	**p-value**
Age	Mean, years (±SD)	40.9 (±11.4)	49.48 (±15.3)	**0.005**
	≥55 years, n (%)	6 (15)	16 (36.4)	**0.026**
	<55 years, n (%)	34 (85)	28 (63.6)	
Sex	Female, n (%)	34 (85)	37 (84.1)	0.908
	Male, n (%)	6 (15)	7 (15.9)	
Family history of thyroid cancer	Present, n (%)	2 (5)	3 (6.8)	0.546
	Absent, n (%)	38 (95)	41 (93.2)	
Clinical presentation	Nodule, n (%)	36 (90)	34 (77.3)	0.130
	Incidental discovery, n (%)	3 (7.5)	10 (22.7)	
	Hyperthyroidism, n (%)	1 (2.5)	0	
Signs of compression	Present, n (%)	14 (35)	16 (36.4)	0.896
	Absent, n (%)	26 (65)	28 (63.6)	
Thyroid loge examination	Normal, n (%)	3 (7.5)	8 (18.2)	0.328
	Single nodule, n (%)	31 (77.5)	29 (65.9)	
	Multiple nodules, n (%)	6 (15)	7 (15.9)	
Indirect laryngoscopy	Vocal cord paralysis, n (%)	0	2 (5.4)	0.182
	Without abnormality, n (%)	32 (100)	35 (94.6)	
Thyroid function test	Euthyroidism, n (%)	38 (95)	41 (97.6)	0.587
	Hypothyroidism, n (%)	1 (2.5)	1 (2.4)	
	Hyperthyroidism, n (%)	1 (2.5)	0	
Bethesda category	I, II, III and IV, n (%)	4 (80)	8 (66.7)	0.528
	V and VI, n (%)	1 (20)	4 (33.3)	

SD: Standard deviation, NIFTP: Neoplasm with papillary-like nuclear features.

grouped in scores 2 and 3. No non-NIFTP nodule is classified as EU-TIRADS 2 in our series. A single NIFTP nodule was classified as EU-TIRADS 2, and six were classified as EU-TIRADS 5 (Table 2).

Comparison of Histopathological Characteristics Between NIFTP and Non-NIFTP Groups

The histopathological characteristics and differences between NIFTP and non-NIFTP groups are summarized in Table 3. The main differences between NIFTP and IEFVPTC are presented in Table 4, while the key differences between NIFTP and IFPTC are outlined in Table 5.

Nuclear score 3 was significantly more prevalent in the non-NIFTP group (59.1%), whereas NIFTP cases predominantly exhibited nuclear score 2 (87.5%) (p<0.001) (Figure 2a and 2b). Additionally, nuclear abnormalities were diffuse in 59.1% of non-NIFTP cases but focal in 67.5% of NIFTP cases (p=0.015).

Regarding encapsulation, 35 NIFTP and 22 non-NIFTP cases demonstrated encapsulation (21 cases of IEFVPTC and one case of DHGTC). A thin capsule was significantly more common in NIFTP cases (57.1%) than in non-NIFTP cases (18.2%) (p=0.004) (Figure 2c and 2d). Figure 3 illustrates capsular invasion in an IEFVPTC case.

Among the non-NIFTP tumors, ten exhibited lymphovascular invasion (22.7%) (Figure 4). Figure 5 illustrates extrathyroidal extension observed in a case of IEFVPTC.

For the NIFTP group, no lymph node metastases were found in the seven patients who underwent lymph node dissection. In the non-NIFTP group, ten tumors (22.7%) presented lymph node metastases; of these, three cases (30%) had capsular rupture. This difference was statistically significant (p=0.001).

Adjuvant Treatment and Follow-up

Levothyroxine-based hormone therapy was prescribed in 26 cases of NIFTP and 43 cases of non-NIFTP. Radioactive iodine treatment was administered to 12 patients (30%) diagnosed with NIFTP and to 29 patients (65.9%) diagnosed with non-NIFTP tumors. No patient received adjuvant treatment with radioactive iodine after 2018.

For the NIFTP and non-NIFTP groups, the median follow-up durations after surgery were 16 and 25 months, respectively.

None of the NIFTP cases showed distant metastases. Among non-NIFTP cases, metastases were detected in two cases (4.54%). In one case, metastasis occurred in the parotid gland 16 months after diagnosis, while in the second case pulmonary metastasis

developed a decade later. Among the 84 patients in our study, only one patient diagnosed with IFPTC experienced a lymph node relapse with capsular rupture and skin infiltration after a postoperative period of 6 years.

Multivariate Analysis of Parameters Associated with NIFTP

In this analysis, a nuclear score of 2, focal nuclear abnormalities, and a thin tumor capsule were independently related to NIFTP. Age under 55 years and regular border status in the US tended to be statistically significant (Table 6).

DISCUSSION

Our study identified some predictive factors for NIFTP that can guide the preoperative diagnostic approach. Indeed, in young patients with specific cervical US findings (isoechoic nodules, absence of microcalcifications, regular borders, and an EU-TIRADS score of 2 or 3), the diagnosis of NIFTP is strongly suggested. Additionally, the analytical study confirmed the strong association of nuclear grade 2, focal nuclear features, and a thin capsule with the diagnosis of NIFTP. The benign profile of NIFTP was also demonstrated in our series.

After a review of histological slides, we found a rate of 33.6% for thyroid tumors with follicular architecture and papillary nuclear features, and 8.83% for PTC. The global rate reported in the literature varies significantly. According to a meta-analysis, NIFTP accounted for approximately 6% of all PTC, with considerable heterogeneity among included studies (CI: 4.4-8.2). The frequency of NIFTP was higher in North America (9.3%) and Europe (9.6%) compared to Asia (approximately 2.1%) (13). The frequency of NIFTP was 16.9% of all thyroid tumors with follicular architecture and papillary nuclear features and 1.54% of all PTC in the study of Richard et al. (14) covering 40 years. In another meta-analysis including 1563 cases of NIFTP from 29 studies, its frequency among all thyroid tumors with follicular architecture and papillary nuclear features was 43.5% and 4.4% among PTC (15).

These figures reflect changes over time and may vary by study populations and methodologies. Many specimens couldn't be evaluated for capsular invasion because of limitations in slide assessment inherent to the study's retrospective design.

Limited information is available for comparing clinical and biological characteristics between the two groups. In the study of Singh et al. (16) 21 patients with NIFTP were also significantly younger than 153 patients with non-NIFTP (p=0.023).

In other studies, there was no significant disparity in age observed between the two groups of patients (17,18). Female predominance was observed in all studies, including the multi-institutional study by Chereau et al. (19) with 76% of women among 363 NIFTP cases; in the canadian study by Larouche et al. (17) there wasn't a significant difference between the two groups. This aligns with our findings: 85% of cases in the NIFTP group and 84.1% in the non-NIFTP group were women (18,19). The clinical presentation and the laboratory findings of NIFTP are non-specific and similar to those of other thyroid neoplasms (20,21), which explains the absence of significant differences in terms of clinical symptoms and biological analysis between the two study groups.

The aim of comparative studies between these two tumor groups was primarily to highlight the advantages of cytology and cervical US to facilitate preoperative diagnosis of these tumors. The goal is to mitigate the risk of unnecessary surgical procedures.

Table 2. Preoperative neck ultrasonography characteristics of NIFTP and non-NIFTP groups

		NIFTP	Non-NIFTP	p-value
Echogenicity	Hypoechoic, n (%)	9 (22.5)	16 (37.2)	**0.004**
	Strong hypoechogenicity, n (%)	2 (5)	12 (27.9)	
	Isoechoic, n (%)	22 (55)	11 (25.6)	
	Hyperechoic, n (%)	7 (17.5)	4 (9.3)	
Regular border	Present, n (%)	37 (92.5)	32 (74.4)	**0.028**
	Absent, n (%)	3 (7.5)	11 (25.6)	
Microcalcification	Present, n (%)	2 (5)	12 (27.9)	**0.005**
	Absent, n (%)	38 (95)	31 (72.1)	
Suspicious lymphadenopathy	Present, n (%)	6 (15)	9 (20.5)	0.514
	Absent, n (%)	34 (85)	35 (79.5)	
EU-TIRADS	Scores 2 and 3	31 (77.5)	14 (32.6)	**<0.001**
	Scores 4 and 5	9 (22.5)	29 (67.4)	

NIFTP: Neoplasm with papillary-like nuclear features, EU-TIRADS: European Thyroid Imaging Reporting and Data System.

Cervical US is the gold standard for evaluating thyroid nodules, as it enables preoperative nodule characterization and malignancy risk stratification based on the EU-TIRADS classification. Our study revealed significant disparities in US nodule characteristics between the NIFTP and non-NIFTP groups. Similar findings were reported in the study by Hahn et al. (22), which included 34 NIFTPs and 174 non-NIFTPs. Compared with non-NIFTP cases, NIFTPs were more commonly hyperechoic or isoechoic (p=0.043), exhibited regular borders (p=0.001), and lacked calcifications (p=0.031). Similarly, the review by Yang et al. (23), reported that NIFTPs typically exhibited well-circumscribed, oval/round nodules with a hypoechoic rim, often accompanied by hypervascularity on Doppler imaging. In contrast, IEFVPTCs were characterized by hypoechogenicity with irregular or lobulated margins and frequently displayed hypervascularity on Doppler. The US characteristics of IFPTCs included at least one malignant grayscale feature, such as marked hypoechoicity, a taller-than-wide shape, microcalcifications, or blurred margins. Doppler imaging in this group commonly showed avascularity. In a study by Boursier et al. (21), 77% of nodules corresponding to NIFTP were classified as EU-TIRADS 2, 3 or 4, while 84.5% of nodules corresponding to non-NIFTP were classified as EU-TIRADS 5. The difference between the two groups was statistically significant (p<0.001). In our study, 77.5% of NIFTPs had EU-TIRADS scores 2 and 3. However, in a Canadian study, including 44 NIFTP and 159 patients in the non-NIFTP group, there was no statistically

Table 3. Histopathological and clinical characteristics of NIFTP and non-NIFTP groups

		NIFTP	Non-NIFTP	p-value
Tumor size	Mean, mm (±SD)	24.18 (±21.52)	21.90 (±28.36)	0.205
	≥4 cm, n (%)	9 (22.5)	9 (20.5)	0.329
	<4 cm, n (%)	31 (77.5)	35 (79.5)	
Tumor location	Bilateral, n (%)	5 (12.5)	8 (18.2)	0.888
	Right lobe, n (%)	19 (47.5)	21 (47.7)	
	Left lobe, n (%)	15 (37.5)	14 (31.8)	
	Isthmus, n (%)	1 (2.5)	1 (2.3)	
Multifocality	Present, n (%)	7 (17.5)	10 (22.7)	0.551
	Absent, n (%)	33 (82.5)	36 (77.3)	
Nuclear score	Score 2, n (%)	35 (87.5)	18 (40.9)	**<0.001**
	Score 3, n (%)	5 (12.5)	26 (59.1)	
Nuclear features	Diffuse, n (%)	13 (32.5)	26 (59.1)	**0.015**
	Focal, n (%)	27 (67.5)	18 (40.9)	
Mitosis	Present, n (%) Range/2 mm^2	12 (30) 0-2	11 (25) 0-6	0.608
	Absent, n (%)	28 (70)	33 (75)	
Tumor capsule thickness	Thin, n (%)	20 (57.1)	4 (18.2)	**0.004**
	Thick, n (%)	15 (42.9)	18 (81.8)	
Solid/trabecular/insular growth pattern	Present, n (%)	6 (15)	8 (18.2)	0.696
	Absent, n (%) % of the nodule	34 (85) 5-10%	36 (81.8) 5-40%	
Dense colloid	Present, n (%)	29 (72.5)	30 (68.2)	0.666
	Absent, n (%)	11 (27.5)	14 (31.8)	
Lymphocytic thyroiditis associated	Present, n (%)	8 (20)	14 (31.8)	0.219
	Absent, n (%)	32 (80)	30 (68.2)	
Lymph node metastasis	Present, n (%)	0	10 (22.7)	**0.001**
	Absent, n (%)	7 (100)	34 (77.3)	
Type of surgery	Total thyroidectomy, n (%)	27 (67.5%)	41 (93.2%)	**0.003**
	Lobo-isthmectomy	13 (32.5%)	3 (6.8%)	
Lymph node dissection		7 (17.5%)	33 (75%)	**<0.001**

SD: Standard deviation, NIFTP: Neoplasm with papillary-like nuclear features.

Table 4. Comparison of characteristics between NIFTP and IEFVPTC				
		NIFTP	**IEFVPTC**	**p-value**
Echogenicity	Hypoechoic, n (%)	9 (22.5%)	10 (47.6%)	0.063
	Strong hypoechogenicity, n (%)	2 (5%)	3 (14.3%)	
	Isoechoic, n (%)	22 (55%)	7 (33.3%)	
	Hyperechoic, n (%)	7 (17.5%)	1 (4.8%)	
EU-TIRADS	Scores 2 and 3	31 (77.5%)	7 (33.3%)	0.001
	Scores 4 and 5	9 (22.5%)	14 (66.7%)	
Microcalcifications	Present, n (%)	2 (5%)	6 (28.6%)	0.016
	Absent, n (%)	38 (95%)	15 (71.4%)	
Nuclear score	Score 2, n (%)	35 (87.5%)	13 (61.9%)	0.045
	Score 3, n (%)	5 (12.5%)	8 (38.1%)	
Nuclear features	Diffuse, n (%)	13 (32.5%)	10 (47.6%)	0.247
	Focal, n (%)	27 (67.5%)	11 (52.4%)	
Tumor capsule thickness	Thin, n (%)	25 (62.5%)	4 (19%)	0.001
	Thick, n (%)	15 (37.5%)	17 (81%)	
Lymph node metastasis	Present, n (%)	0	3 (14.3%)	0.037
	Absent, n (%)	40 (100%)	18 (85.7%)	

NIFTP: Neoplasm with papillary-like nuclear features, EU-TIRADS: European Thyroid Imaging Reporting and Data System, IEFVPTC: Invasive encapsulated follicular variant of papillary thyroid carcinoma.

Table 5. Comparison of characteristics between NIFTP and IFPTC				
		NIFTP	**IFPTC**	**p-value**
Echogenicity	Hypoechoic, n (%)	9 (22.9%)	6 (28.6%)	**0.001**
	Strong hypoechogenicity, n (%)	2 (5%)	9 (42.9%)	
	Isoechoic, n (%)	22 (55%)	4 (19%)	
	Hyperechoic, n (%)	7 (17.5%)	2 (9.5%)	
EU-TIRADS	Scores 2 and 3	31 (77.5%)	6 (28.6%)	**0.000**
	Scores 4 and 5	9 (22.5%)	15 (71.4%)	
Microcalcifications	Present, n (%)	2 (5%)	6 (28.6%)	**0.016**
	Absent, n (%)	38 (95%)	15 (71.4%)	
Nuclear score	Score 2, n (%)	35 (87.5%)	4 (18.2%)	**0.000**
	Score 3, n (%)	5 (12.5%)	18 (81.8%)	
Nuclear features	Diffuse, n (%)	13 (32.5%)	16 (72.7%)	**0.002**
	Focal, n (%)	27 (67.5%)	6 (27.3%)	
Lymph node metastasis	Present, n (%)	0	7 (31.8%)	**0.000**
	Absent, n (%)	40 (100%)	15 (68.2%)	

NIFTP: Neoplasm with papillary-like nuclear features, EU-TIRADS: European Thyroid Imaging Reporting and Data System, IFPTC: Infiltrative follicular subtype of PTC, PTC: Papillary thyroid carcinoma.

significant difference when comparing US characteristics between the two study groups (17).

Cytological findings are also informative in thyroid pathology, but they remain insufficient for a definitive diagnosis and for distinguishing NIFTP from other thyroid tumors with follicular architecture and papillary nuclear features. In a study conducted by Boursier et al. (21), a notable distinction was observed between the two groups: NIFTP cases were mainly classified according to the Bethesda classifications III (27.3%), IV (18.2%), and V (36.4%). Conversely, most of the non-NIFTP cases fell into categories V (49%) and VI (28.6%) of the Bethesda classification system (p=0.004). In the study of Jang et al. (24) both the NIFTP

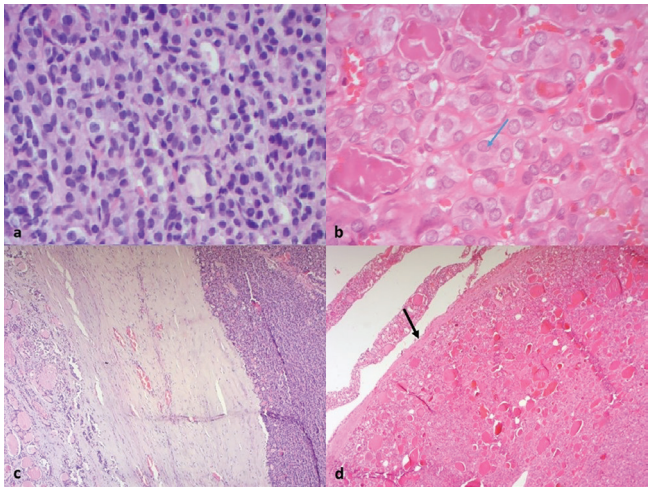

Figure 2. a: NIFTP tumor with nuclear score 2 (HE*200), b: NIFTP tumor with nuclear score 3 (HE*400, note: pseudo-inclusion in blue arrow), c: Thick capsule in a NIFTP tumor (HE*50), d: Thin capsule in a NIFTP tumor (black arrow) (HE*50).

NIFTP: Neoplasm with papillary-like nuclear features, HE: Hematoxylin and eosin.

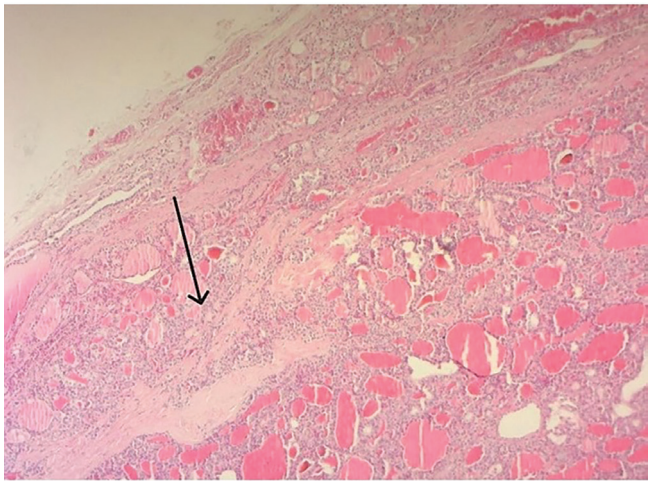

Figure 3. Capsular invasion in IEFVPTC (black arrow) (HE*50).

IEFVPTC: Invasive encapsulated follicular variant of papillary thyroid carcinoma, HE: Hematoxylin and eosin.

and IEFVPTC groups exhibited relatively benign characteristics, with a majority of patients categorized under Bethesda category III [(25.8% and 25.6%, respectively) or IV (34.8% and 30.2%, respectively)]; in contrast, the IFPTC group demonstrated more malignant features, with a higher proportion of patients falling into category V (28.6%) or VI (47.6%) ($p<0.001$) (24). Ruanpeng et al.'s (15) meta-analysis revealed that the majority of NIFTP cases reported in the literature are identified within the III (34.2%), IV (22.7%), and V (22.4%) categories. In other studies, there was no significant difference in Bethesda categories between NIFTPs and non-NIFTPs (17). As in our study, this result was observed, likely because of the low number of cytology tests performed.

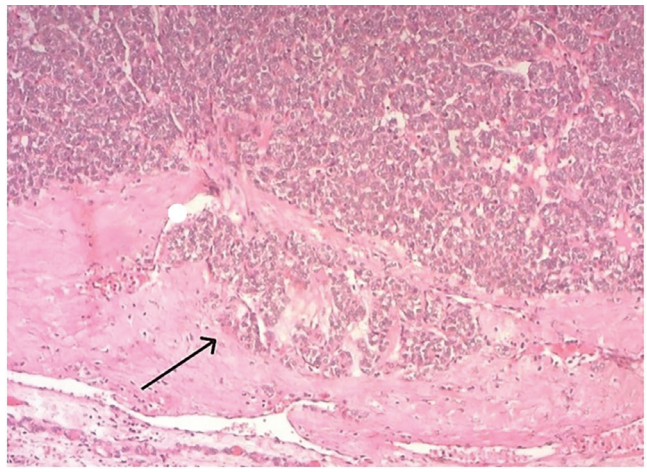

Figure 4. Angioinvasion in IEFVPTC (HE*100).

IEFVPTC: Invasive encapsulated follicular variant of papillary thyroid carcinoma, HE: Hematoxylin and eosin.

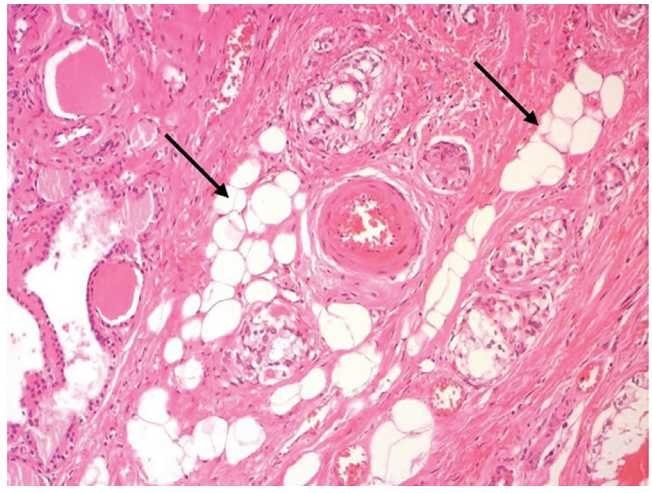

Figure 5. Extrathyroid extension in IEFVPTC (black arrows indicating adipocytes) (HE*100).

IEFVPTC: Invasive encapsulated follicular variant of papillary thyroid carcinoma, HE: Hematoxylin and eosin.

Focusing on histopathological characteristics that could predict the diagnosis of NIFTP is crucial to avoid subjectivity in the analysis of thyroid nodules. In 2022, in an Italian study conducted by Vignali et al. (25) including 451 NIFTP cases, 85.4% of these lesions exhibited a nuclear score of 2, while only 14.6% had a nuclear score of 3. Moreover, a review suggests that the papillary-like nuclear features of NIFTP are generally more subtle than those of PTC and can present as focal, diffuse, or multifocal. These nuclear features tend to be more pronounced at the periphery of the tumor, especially in the subcapsular area and in the more cellular or microfollicular zones. Intranuclear inclusions are also inconspicuous and rare in NIFTP (26).

Table 6. Multivariable logistic regression adjusted odds ratios for NIFTP			
Variable	**Odds ratio**	**95% CI**	**p-value**
Age <55 years-old	6.633	(0.826-53.273)	0.075
Echogenicity	1.061	(0.122-9.211)	0.957
Regular border	0.067	(0.004-1.184)	0.065
Microcalcification	6.030	(0.399-91.137)	0.195
EU-TIRADS score 2 or 3	0.000	(0.000-0)	0.999
Nuclear score 2	0.018	(0.002-0.175)	**<0.001**
Focal nuclear features	0.106	(0.020-0.558)	**0.008**
Thin tumor capsule	15.342	(2.134-110.286)	**0.007**
Lymph node metastasis	0.000	(0.000-0)	1.000
CI: Confidence interval, EU-TIRADS: European Thyroid Imaging Reporting and Data System, NIFTP: Neoplasm with papillary-like nuclear features.			

The revised criteria by Nikiforov et al. (6,7) emphasize that NIFTP is often characterized by moderately expressed papillary-like nuclear features (nuclear score 2). A nuclear score of 3 should raise concerns about the diagnosis of NIFTP and may suggest a variant of papillary carcinoma. It is recommended to thoroughly examine the entire tumor capsule in cases with pronounced papillary-like nuclear features (nuclear score 3) and to assess the whole tumor to rule out the presence of papillary structures (7,27). In a study conducted by French et al. (12) that included 92 lesions, 39 NIFTPs, 15 non-invasive EFVPTCs, and 38 IEFVPTCs, a statistically significant difference in capsular thickness was noted among these neoplasms. The tumor capsule was significantly thinner in NIFTPs, with a mean thickness of 0.08 mm (p=0.022), and significantly thicker in IEFVPTCs, with a mean thickness of 0.53 mm (p=0.0006). This study concluded that a capsule thickness greater than 0.2 mm should raise suspicion of encapsulated FVPTC and prompt a more meticulous evaluation of the tumor by conducting additional section levels to ensure that a small focus of invasion was not overlooked before considering a diagnosis of NIFTP (12).

In our study, none of the NIFTP cases exhibited lymph node metastases, whereas 22.7% of non-NIFTP cases demonstrated metastases—findings that align with several previous reports (28-30). This indolent behavior extended into our follow-up period, during which no NIFTP cases showed distant metastases, in contrast to two in the non-NIFTP group. While the majority of literature supports this low-risk clinical course (15,19,30), controversies regarding the non-malignant behavior of these tumors persist. Some studies have documented lymph node involvement in NIFTP patients (24,31,32), and Parente et al. (31) reported that among 102 cases, one patient developed pulmonary metastasis and five were diagnosed with nodal metastasis over an average follow-up of 5.7 years.

According to Rosario and Mourão (33), the presence of these metastases does not necessarily confirm potential for dissemination and may be attributable to various factors. It could result from insufficient sampling of the entire tumor and capsule in some retrospective studies. Secondly, microcarcinomas that went undetected by US examination of the remaining lobe in lobectomy patients or that were missed on histological slides might contribute to these metastases. Additionally, another possibility could be the regression of the microcarcinoma after the formation of metastases (33).

After the histopathological diagnosis of NIFTP, completion thyroidectomy or radioactive iodine treatment is not necessary (34). In a study by You et al. (35), total thyroidectomy was less frequently performed for NIFTP compared to non-NIFTP cases (48.9% versus 69.1%). This trend can be attributed to the findings of fine needle aspiration, which often falls into the Bethesda categories III and IV, as well as the absence of preoperative lymph node metastases, directing the therapeutic approach towards lobectomy.

To our knowledge, this is the first study in our country to identify the clinical, US, cytological, and histopathological predictive factors for NIFTP and to compare its characteristics with those of other thyroid tumors with follicular architecture and papillary nuclear features. A double-blind re-evaluation of all histological slides from cases presenting vesicular architecture with papillary-type nuclear atypia over an 11-year period was performed by two pathologists. These cases were reclassified according to the latest WHO classification of 2022. We conducted a univariate statistical analysis supplemented by a multivariate analysis, which yielded important results that can guide clinicians and pathologists in the management of these tumors.

Study Limitations

However, our study is subject to several limitations due to its retrospective design. There may be uncertainty regarding the inclusion of all tumors presenting the characteristics of NIFTP before the introduction of this entity. Additionally, the relatively small number of patients included and the missing data further contribute to the limitations of our study. The relatively short

follow-up period, compared to other studies, is a limitation of our study and limits the evaluation of long-term survival data.

CONCLUSION

O ur study reaffirms the indolent nature of NIFTP. Furthermore, we demonstrated the usefulness of cervical US in suspecting NIFTP preoperatively and in guiding therapeutic decisions. However, our study did not yield significant results regarding the Bethesda classification; a prospective multicenter study with a larger sample size and a longer follow-up period is needed.

Ethics

Ethics Committee Approval: A favourable opinion on the conduct of this study was issued by the Ethics Committee of the Faculty of Stax (decision no: 34/24, date: 10.07.2024) which is in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual patients included in this study for the use of their clinical data.

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Footnotes

Author Contributions

Concept - S.M., R.K., T.S.B.; Design - S.M., R.K., T.S.B.; Data Collection or Processing - Y.L.; Analysis or Interpretation - Y.L.; Literature Search - Y.L.; Writing - S.M., M.T., M.Z., F.K., N.G., T.S.B., I.C., M.M.

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ORIGINAL ARTICLE
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The ergonomic impact of robotic vs. laparoscopic surgery on operating room nurses: A multicenter survey analysis

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ABSTRACT

Objective: Robotic surgery is increasingly used across specialties, yet its ergonomic impact on operating room nurses remains underexplored. This multicenter study aimed to evaluate the ergonomic challenges and musculoskeletal discomfort among scrub nurses during robotic surgery and to compare these outcomes with laparoscopic procedures, with additional analysis based on years of robotic surgery experience.

Material and Methods: This cross-sectional, multicenter, questionnaire-based study was conducted between January and February 2025, among scrub nurses with experience in robotic surgery from multiple centers. Ergonomic perceptions, physical strain, musculoskeletal discomfort, and comparisons between robotic and laparoscopic surgery were assessed. Nurses were stratified into less than and more than 5 years of robotic surgery experience, and comparative statistical analyses were performed.

Results: Most nurses rated the robotic operating environment as comfortable (69.6%), and 56.4% reported reduced workload compared with laparoscopy. Physical strain was reported by 30.9%, most commonly during instrument exchange. Musculoskeletal discomfort predominantly affected the neck, back, and shoulders. Shoulder pain was significantly more common among nurses with >5 years of experience (70% vs. 33.3%, p=0.008). Although 71.4% reported ergonomic support from robotic systems, 85.7% had not received ergonomic training.

Conclusion: Robotic surgery is perceived by scrub nurses as ergonomically more favorable than laparoscopic surgery; however, substantial musculoskeletal discomfort persists, particularly among more experienced nurses and in the absence of ergonomic training. These findings suggest a potential cumulative ergonomic burden and highlight the need for structured ergonomic education and system-level interventions.

Keywords: Ergonomics, robotic surgery, scrub nurses, laparoscopy

INTRODUCTION

The rapid evolution of robotic surgery has fundamentally transformed operating room dynamics, offering ergonomic advantages primarily tailored to console surgeons. Seated posture, wrist supports, and intuitive control systems have been shown to reduce musculoskeletal strain and workload during complex procedures (1,2). Robot-assisted procedures demonstrated reduced postoperative shoulder and hand discomfort and lower physical demand when compared with conventional laparoscopy in surgical trainees and surgeons, with objectively lower muscle activity in upper limb musculature during robotic procedures (3). However, these improvements do not necessarily extend to all members of the surgical team, particularly scrub nurses, who remain physically engaged at the sterile field throughout the operation.

Unlike the console surgeon, the scrub nurse must maneuver within a constrained space, often working around bulky robotic arms with limited visual feedback or direct communication. These conditions may lead to prolonged static postures, awkward joint angles, and increased risk of musculoskeletal discomfort (4,5). In laparoscopic settings, scrub nurses have been shown to experience significant neck, back, and upper extremity discomfort, attributable to awkward positioning and extended reach for instruments outside the central surgical area (6).

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While previous research has acknowledged the ergonomic challenges faced by scrub nurses in robotic surgery, most studies have been limited to small samples, single institutions, or specific subspecialties such as urology and gynecology, and there remains a paucity of multicenter data assessing ergonomic perceptions and musculoskeletal pain among scrub nurses (7). Moreover, few have directly compared the ergonomic demands of robotic and laparoscopic surgery from the scrub nurse's perspective, even though these professionals often alternate between both modalities in routine practice.

In Türkiye, where robotic surgery is increasingly adopted across diverse clinical settings, there is a notable lack of multicenter data on scrub nurse ergonomics. Addressing this gap is critical for developing more inclusive intraoperative ergonomics protocols that account for the physical demands placed on all members of the surgical team.

In addition to describing overall ergonomic perceptions, this study specifically explores whether years of experience in robotic surgery influence ergonomic outcomes among scrub nurses. By comparing responses from nurses with more than 5 years and less than 5 years of robotic surgery experience, we aim to assess the potential cumulative ergonomic burden associated with long-term exposure to robotic procedures. This experience-based comparison provides further insight into how ergonomic challenges evolve over time within the robotic operating room environment.

MATERIAL and METHODS

Study Population

This cross-sectional, multicenter, survey-based study was conducted between January 1, 2025, and February 28, 2025. Eligible participants included nurses from multiple centers actively involved as surgical assistants in robotic procedures, with varying levels of experience and exposure to different surgical specialties, such as general surgery, urology, gynecology, and colorectal surgery. Participation was voluntary, and written informed consent was obtained from all respondents. The sample size of the study was determined based on the number of eligible scrub nurses actively involved in robotic surgery across the participating centers during the study period. A total of 12 tertiary care centers with established robotic surgery programs and high procedural volumes, where robotic surgery is routinely performed, contributed to the study, and all eligible and consenting participants were included. Due to the exploratory and descriptive nature of the study, and the limited number of specialized robotic scrub nurses in each center, a formal a priori sample size calculation was not performed. The study was approved by the Ethics Committee of Acıbadem Mehmet Ali Aydınlar University (ID: 2025-12/98, date: 10.07.2025, decision number: 2025-11/419).

Inclusion and Exclusion Criteria

Nurses were eligible for inclusion if they had participated in robotic surgical procedures as scrub nurses within the previous year and had experience with both robotic and laparoscopic surgery. Nurses without direct intraoperative involvement in robotic surgery, those exclusively working in non-robotic settings, and incomplete survey responses were excluded from the analysis.

Survey and Data Collection

The survey collected data on nurses' ergonomic perceptions, levels of physical discomfort, and their comparisons of robotic and laparoscopic surgical approaches. The responses were analyzed to identify common ergonomic issues, physical strain, and factors influencing the working environment.

The questionnaire was developed based on a review of the literature on surgical ergonomics and previously published survey-based studies evaluating ergonomic strain among surgical team members in minimally invasive and robotic surgery. Prior studies assessing first assistants and perioperative staff have commonly utilized structured questionnaires and subjective assessment tools to evaluate physical strain, musculoskeletal discomfort, and workflow-related factors (7,8). Prior to distribution, the questionnaire was reviewed by experienced surgeons and scrub nurses to ensure content validity and clinical relevance. A pilot test was conducted on a small group of nurses to assess clarity and feasibility, and minor revisions were made accordingly.

Participants completed the survey electronically. The survey required approximately 15 minutes to complete. The questionnaire consisted of 23 items organized into six main sections: demographic information, working environment and positioning, physical strain, communication and workflow, technological and ergonomic support, and overall health and well-being. Both multiple-choice and open-ended questions were included to assess physical discomfort, ergonomic challenges, perceived workload, and comparisons between robotic and laparoscopic surgery.

Participants were asked about their frequency of musculoskeletal pain, ability to reposition during surgery, physical difficulty associated with specific tasks (e.g., instrument exchange), and the impact of ergonomic conditions on job satisfaction. Perceptions of intraoperative communication, clarity of responsibilities, and adequacy of ergonomic training were also assessed.

All responses were collected anonymously and analyzed to identify common patterns and concerns related to physical strain, communication, and workflow disruptions during robotic surgery. Comparisons between robotic and laparoscopic procedures were also assessed based on perceived ergonomic advantages and workload impact.

Primary outcomes included nurses' perceived ergonomic challenges, reported musculoskeletal discomfort in various body regions, and subjective assessments of workload associated with robotic versus laparoscopic surgery. Secondary outcomes involved identifying factors influencing ergonomic strain and workplace satisfaction.

Statistical Analysis

To minimize response bias, anonymity was ensured, and no personal identifiers were collected. Categorical variables were summarized as frequencies and percentages. In addition to descriptive analyses, a comparative statistical analysis was performed between nurses with ≤5 years and >5 years of robotic surgery experience to evaluate potential differences related to cumulative exposure. Group comparisons were conducted using the chi-square test. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using R statistical software (version 4.3.1).

RESULTS

A total of 56 scrub nurses participated in the survey, with a mean age of 30 years; 36 participants (64.3%) were female. Most nurses had less than 5 years of experience in robotic surgery (64.3%), while 35.7% reported more than 5 years of experience. Nearly half of the participants (47.3%) reported assisting in more than 50 robotic procedures annually. The most frequently represented surgical fields were urology (67.9%), colorectal surgery (60.7%), and gynecology (55.4%). Demographic characteristics and professional experience stratified by years of robotic surgery experience are summarized in Table 1.

Regarding the ergonomic conditions of the robotic operating environment, 39 nurses (69.6%) rated their working environment as comfortable, whereas 12.5% described it as uncomfortable. Most participants (67.9%) reported having adequate opportunities to change position during robotic surgery. No significant differences were observed between nurses with less than and more than 5 years of experience in perceived comfort or positional flexibility (Table 1).

Musculoskeletal discomfort during or following surgical procedures was commonly reported. The most frequently affected body regions were the neck (67.9%), back (58.9%), and shoulders (46.4%). Shoulder discomfort was significantly more common among nurses with more than 5 years of experience compared with those with less than 5 years (70% vs. 33.3%, p=0.008), while no statistically significant differences were observed for other body regions (Table 1). Overall, 42.9% of nurses reported frequently experiencing back, neck, or shoulder pain during surgical procedures.

Seventeen nurses (30.9%) reported experiencing physical strain during robotic instrument placement or exchange. Instrument change was identified as the most physically demanding task (35.7%), followed by surgical field organization (33.9%) and coordination with the surgical console (30.4%). These findings were consistent across experience groups, with no statistically significant differences observed (Table 1).

Most participants (71.4%) stated that the technology used during robotic surgery supported ergonomic practice. Communication and coordination within the surgical team were rated as very good by 78.6% of respondents, and 80.4% reported no factors negatively affecting workflow during robotic procedures. Clearly defined roles and responsibilities were reported by 66.1% of nurses, with no significant differences based on experience level.

A notable finding was the lack of formal ergonomic training: 48 nurses (85.7%) reported not having received any training aimed at improving ergonomics in robotic surgery. Nurses without ergonomic training reported higher levels of physical discomfort, although this did not reach statistical significance between experience groups (Table 1).

When comparing robotic and laparoscopic surgery, 79.6% of nurses perceived robotic surgery as less physically demanding, while 10.2% reported greater strain and 10.2% perceived no difference. Nearly half of the participants (49.1%) indicated that laparoscopic surgery posed greater difficulty in terms of instrument use and exchange. Robotic surgery was perceived to offer a better ergonomic working environment by 62% of nurses and to decrease workload by 56.4%, whereas 27.3% reported increased workload and 16.4% reported no change. No significant differences were observed between experience groups in comparative assessments (Table 1).

DISCUSSION

This multicenter survey provides a comprehensive perspective on the ergonomic challenges experienced by scrub nurses during robotic surgery, a population that has been relatively underrepresented in ergonomic research, which has traditionally focused on console surgeons. In minimally invasive and robotic surgery, scrub nurses have evolved from passive assistants to active members of the surgical team, requiring a detailed understanding of surgical steps and instrument management, which may contribute to increased physical and cognitive demands (9). Although most nurses perceived robotic surgery as ergonomically more favorable than laparoscopy, a considerable proportion reported persistent musculoskeletal discomfort, particularly in the neck, back, and shoulders. These findings are consistent with previous reports indicating that the ergonomic advantages of robotic platforms may not extend uniformly to all members of the surgical team (4).

Robotic systems are well known to reduce physical fatigue for surgeons by enabling seated operation, wrist support,

Table 1. Demographic characteristics, ergonomic perceptions, musculoskeletal discomfort, and comparison of robotic versus laparoscopic surgery among scrub nurses, stratified by years of robotic surgery experience				
	Total	**≤5 years**	**>5 years**	**p-value**
Gender				
Male	20 (35.7)	7 (35)	13 (36.1)	0.934
Female	36 (64.3)	13 (65)	23 (63.9)	
Years of experience working as a bedside nurse in robotic surgery				
0-1	14 (25)			
2nd May	22 (39.3)			
10+	8 (14.3)			
6th Oct	12 (21.4)			
Experience (years)				
>5	20 (35.7)			
≤5	36 (64.3)			
Field of working in robotic surgery				
Bariatric	14 (25)	8 (22.2)	6 (30)	0.52
Colorectal	34 (60.7)	19 (52.8)	15 (75)	0.103
Urology	38 (67.9)	22 (61.1)	16 (80)	0.147
Upper GI	21 (37.5)	13 (36.1)	8 (40)	0.773
Gynecology	31 (55.4)	18 (50)	13 (65)	0.279
The ergonomics of your current working environment during robotic surgery				
Comfortable	39 (69.6)	23 (63.9)	16 (80)	0.191
Neither comfortable nor uncomfortable	10 (17.9)	9 (25)	1 (5)	
Uncomfortable	7 (12.5)	4 (11.1)	3 (15)	
Musculoskeletal pain in the back, neck, or shoulder regions while working during surgical procedures				
Frequently	24	0.429		
Sometimes	17	0.304		
Rarely	10	0.179		
No	5	0.089		
The body regions you experience discomfort during or following surgical procedures				
Neck	38 (67.9)	25 (69.4)	13 (65)	0.733
Shoulder	26 (46.4)	12 (33.3)	14 (70)	0.008
Back	33 (58.9)	22 (61.1)	11 (55)	0.656
Arm	6 (10.7)	4 (11.1)	2 (10)	>0.999
Leg	20 (35.7)	16 (44.4)	4 (20)	0.086
Foot	12 (21.4)	9 (25)	3 (15)	0.506
Adequate opportunity to change position during robotic surgery				
Yes	38 (67.9)	22 (61.1)	16 (80)	0.233
No	18 (32.1)	14 (38.9)	4 (20)	
Pysical strain when placing or exchanging surgical instruments during robotic surgery				
Yes	17 (30.9)	13 (36.1)	4 (21.1)	0.36
No	38 (69.1)	23 (63.9)	15 (78.9)	

Table 1. Continued				
	Total	**≤5 years**	**>5 years**	**p-value**
Activities physically most demanding during robotic surgery				
Instrument change	20 (35.7)	15 (41.7)	5 (25)	0.256
Positioning of the camera	12 (21.4)	7 (19.4)	5 (25)	0.737
Organisation of surgical field	19 (33.9)	13 (36.1)	6 (30)	0.772
Coordination with the surgeon at the console	17 (30.4)	10 (27.8)	7 (35)	0.762
Level of communication and coordination within the surgical team				
Very poor	2 (3.6)	2 (5.6)	0 (0)	0.638
Neutral	10 (17.9)	7 (19.4)	3 (15)	
Very good	44 (78.6)	27 (75)	17 (85)	
Any factors that negatively affect workflow during robotic surgery				
Yes	11 (19.6)	7 (19.4)	4 (20)	>0.999
No	45 (80.4)	29 (80.6)	16 (80)	
Clearly defined roles and responsibilities during robotic surgery				
Yes	37 (66.1)	23 (63.9)	14 (70)	0.644
No	19 (33.9)	13 (36.1)	6 (30)	
The technology used during robotic surgical procedures supports ergonomic practice				
Yes	40 (71.4)	25 (69.4)	15 (75)	0.659
No	16 (28.6)	11 (30.6)	5 (25)	
Physical strain experienced during robotic surgical procedures affects overall health				
Yes	25 (44.6)	15 (41.7)	10 (50)	0.548
No	31 (55.4)	21 (58.3)	10 (50)	
Any received formal training aimed at enhancing ergonomics in robotic surgery				
Yes	8 (14.3)	4 (11.1)	4 (20)	0.437
No	48 (85.7)	32 (88.9)	16 (80)	
Ergonomics of robotic surgery affecting overall job satisfaction				
Yes, positively affects	23 (41.1)	15 (41.7)	8 (40)	>0.999
Neutral	27 (48.2)	17 (47.2)	10 (50)	
No, negatively affects	6 (10.7)	4 (11.1)	2 (10)	
Comparison of laparoscopic and robotic surgical procedures in terms of physical strain				
Robotic surgery is associated with less physical strain	39 (79.6)	24 (77.4)	15 (83.3)	0.869
Robotic surgery is associated with more physical strain	5 (10.2)	4 (12.9)	1 (5.6)	
Robotic surgery is equally physically demanding as laparoscopic surgery	5 (10.2)	3 (9.7)	2 (11.1)	
Which surgical approach poses greater difficulty in terms of instrument use and exchange				
Both are similar	9 (17)	7 (20.6)	2 (10.5)	0.509
Laparoscopic surgery	26 (49.1)	17 (50)	9 (47.4)	
Robotic surgery	18 (34)	10 (29.4)	8 (42.1)	
Which surgical approach offers a better ergonomic working environment for bedside nurses				
Both are similar	12 (24)	10 (33.3)	2 (10)	0.167
Laparoscopic surgery	7 (14)	4 (13.3)	3 (15)	
Robotic surgery	31 (62)	16 (53.3)	15 (75)	

Table 1. Continued				
	Total	**≤5 years**	**>5 years**	**p-value**
Robotic surgical systems reduce or increase workload when compared with laparoscopic procedures				
No change	9 (16.4)	8 (22.9)	1 (5)	0.234
Increases workload	15 (27.3)	9 (25.7)	6 (30)	
Decreases workload	31 (56.4)	18 (51.4)	13 (65)	
GI: Gastrointestinal.				

improved visualization, and enhanced dexterity (1,2). However, scrub nurses remain physically active at the bedside, frequently working in spatially constrained environments around rigid robotic arms. Prior studies have shown that assistants are exposed to prolonged static postures and awkward joint positions during minimally invasive surgery (6). van't Hullenaar et al. (7) demonstrated that first assistants, who perform tasks comparable to those of scrub nurses, frequently assume high-risk ergonomic postures during robot-assisted surgery, particularly during instrument exchange and intraoperative coordination. In accordance with these findings, more than one-third of nurses in our study identified instrument exchange as the most physically demanding task, followed by surgical field organization and coordination with the surgical console.

A key strength of the present study is the experience-based subgroup analysis. Shoulder discomfort was significantly more common among nurses with more than five years of robotic surgery experience compared with those with less experience, suggesting a potential ergonomic burden associated with long-term exposure. This observation adds a novel dimension to the existing literature, which has largely relied on descriptive survey data without examining the impact of cumulative experience on ergonomic outcomes among scrub nurses.

Task-specific strain emerged as an important contributor to musculoskeletal discomfort. Activities such as instrument exchange, organization of the surgical field, and coordination with the console require sustained upper-body engagement, repetitive reaching, and continuous attention, all of which are recognized risk factors for work-related musculoskeletal disorders in perioperative personnel (3,5). These findings highlight that ergonomic risk in robotic surgery is not solely technology-related but also task-driven, emphasizing the need for workflow-oriented ergonomic interventions.

Another striking finding was the lack of formal ergonomic training, with 85.7% of participants reporting no education aimed at improving ergonomic practice in robotic surgery. Previous studies have demonstrated that structured ergonomic education can reduce musculoskeletal symptoms by improving posture awareness, task modification, and early recognition of strain-related risks (10,11). A recent systematic review by Møller et al. (12) further emphasized that ergonomic training programs tailored to nurses involved in robotic surgery can significantly mitigate physical discomfort and improve occupational well-being. The absence of such training in our cohort may partly explain the persistence of musculoskeletal complaints despite favorable perceptions of robotic systems.

Beyond individual-level interventions, organizational and system-level strategies play a crucial role in mitigating ergonomic strain. Adjustable-height operating tables, optimized monitor placement, anti-fatigue mats, and scheduled intraoperative microbreaks have all been associated with reductions in physical strain and improved team performance (13,14). Although more than 70% of nurses in our study acknowledged that robotic systems supported ergonomic practice, the persistence of discomfort suggests that environmental design alone is insufficient without structured ergonomic implementation. The establishment of dedicated roles, such as the perioperative robotics nurse specialist, has been proposed as a means of institutionalizing ergonomic standards and ensuring consistency in education and practice (15).

At a broader level, these findings underscore the importance of integrating ergonomic considerations into institutional policies and surgical quality frameworks. Incorporating ergonomic risk assessments into robotic surgery programs and accreditation processes may help recognize musculoskeletal strain as an occupational hazard and promote nurse well-being (16). Furthermore, interdisciplinary collaboration between surgeons, nurses, biomedical engineers, and ergonomists is essential to guide the development of more user-centered robotic systems. Emerging innovations, including modular robotic arms, real-time posture monitoring, and ergonomically adaptive system design, hold promise for reducing physical workload across the surgical team (17).

Study Limitations

This study has several limitations. First, ergonomic strain and musculoskeletal discomfort were assessed exclusively using self-reported measures, without the use of objective ergonomic assessment tools such as RULA, REBA, or electromyography. This may limit the objectivity and precision of the findings. The sample size was modest (n=56), reflecting the limited number of scrub nurses actively involved in robotic surgery across

participating centers, which may restrict the generalizability of the findings.

In addition, direct statistical comparison between robotic and laparoscopic surgery groups was not feasible due to the study design. However, we performed a comparative statistical analysis between nurses with less than 5 years and more than 5 years of robotic surgery experience, which adds analytical depth and addresses cumulative exposure effects. Potential confounders such as procedure duration, case complexity, and operating room layout could not be controlled. Despite these limitations, the experience-based subgroup analysis provides novel insight into ergonomic strain among scrub nurses and strengthens the contribution of this study to existing literature.

CONCLUSION

In summary, while robotic surgery is generally perceived by scrub nurses to offer ergonomic advantages over laparoscopy, persistent musculoskeletal challenges remain, particularly among more experienced nurses and in the absence of ergonomic training. Addressing these issues through structured education, workflow optimization, and system-level ergonomic interventions is essential to ensure that the benefits of robotic surgery extend to all members of the surgical team and support sustainable surgical practice.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Acıbadem Mehmet Ali Aydınlar University (ID: 2025-12/98, date: 10.07.2025, decision number: 2025-11/419).

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

Footnotes

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Author Contributions

Concept - Ö.B., İ.A.B., İ.V., S.G., B.B.; Design - Ö.B., İ.A.B., İ.V., S.G., B.B.; Data Collection or Processing - N.R., İ.A.B., D.A., A.U.M., İ.V., S.G., M.A.B.; Analysis or Interpretation - Ç.B., D.A., B.B.; Literature Search - Ç.B., N.R., İ.V., S.G.; Writing - Ç.B., N.R., İ.A.B., M.A.B., B.B.

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ORIGINAL ARTICLE
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Lemmel syndrome: A single-center cohort and diagnostic considerations

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ABSTRACT

Objective: Lemmel syndrome is an uncommon cause of obstructive jaundice resulting from extrinsic compression of the common bile duct by a periampullary duodenal diverticulum (PAD) in the absence of choledocholithiasis. Due to its non-specific clinical presentation, diagnosis may be delayed or misinterpreted.

Material and Methods: A retrospective review was conducted on 12 patients diagnosed with Lemmel syndrome at a single tertiary center between 2022 and 2024. Demographic characteristics, clinical presentation, laboratory findings, imaging modalities [ultrasonography (USG), computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP)], endoscopic interventions, and outcomes were analyzed descriptively.

Results: The cohort included 12 patients with a mean age of 70±9 years. All patients presented with clinical or biochemical evidence of obstructive jaundice. USG frequently failed to establish the diagnosis, whereas CT and particularly MRCP demonstrated the anatomical relationship between the PAD and the biliary tree. Endoscopic retrograde cholangiopancreatography served both diagnostic and therapeutic purposes, with biliary stenting performed when indicated. Most patients improved with conservative and/or endoscopic management.

Conclusion: Lemmel syndrome should be considered in elderly patients with unexplained obstructive jaundice. Cross-sectional imaging, particularly MRCP, plays a key role in diagnosis, while endoscopic intervention remains central to management.

Keywords: Lemmel syndrome, periampullary duodenal diverticulum, obstructive jaundice

INTRODUCTION

Lemmel syndrome is an uncommon clinical presentation characterized by extrinsic compression of the common bile duct and obstructive jaundice secondary to a periampullary duodenal diverticulum (PAD) in the absence of choledocholithiasis (1). First described by Lemmel in 1934, this syndrome has increasingly been reported in the literature through case reports and case series, particularly with the widespread use of advanced cross-sectional imaging (2). Its nonspecific clinical presentation and frequent occurrence in elderly patients with multiple comorbidities may lead to diagnostic delay or misinterpretation rather than true epidemiological rarity.

PADs are mucosal outpouchings located around the second part of the duodenum, particularly near the ampulla of Vater (major papilla) (3). Autopsy and endoscopic studies have reported PAD prevalence ranging from 2% to 27%, suggesting the true prevalence may be higher since many cases are asymptomatic (4). Although PADs are relatively common anatomical findings, only a small proportion of patients develop clinically significant complications such as cholangitis, pancreatitis, bleeding, or biliary obstruction, which are reported in approximately 5% of cases (5,6). Lemmel syndrome represents an uncommon complication of this common anatomical entity rather than an intrinsically rare disease. Differential diagnoses for Lemmel syndrome include choledocholithiasis, periampullary tumors, and Mirizzi syndrome (7). PADs can also be classified according to their anatomical relationship with the major papilla (e.g., periampullary or juxtapapillary types), a distinction that may influence endoscopic accessibility and technical success during endoscopic retrograde cholangiopancreatography (ERCP).

For diagnostic evaluation, ultrasonography (USG) is commonly used due to its accessibility and ability to detect bile duct dilatation. However, USG is often insufficient in identifying PADs due to intestinal gas and anatomical variations (8).

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Computed tomography (CT) provides more detailed visualization of the periampullary region, while magnetic resonance cholangiopancreatography MRCP offers superior diagnostic accuracy, especially in suspected cases of Lemmel syndrome. MRCP is crucial for delineating the three-dimensional anatomical relationship between the PAD and the bile/pancreatic ducts. ERCP remains the gold standard, serving both diagnostic and therapeutic purposes, including stone removal and stent placement (9).

In this study, the demographic, clinical, and radiological characteristics, as well as endoscopic findings, of 12 patients diagnosed with Lemmel syndrome in our clinic were retrospectively evaluated. This case series aimed to contribute additional observational data to the existing literature on Lemmel syndrome, with a particular focus on diagnostic evaluation and management in elderly patients. Specifically, it aimed to clarify diagnostic challenges, evaluate the efficacy of imaging and endoscopic modalities, and identify practical therapeutic strategies to improve patient outcomes.

MATERIAL and METHODS

This retrospective descriptive case series was conducted on patients diagnosed with Lemmel syndrome at University of Health Sciences Türkiye, Ankara Etlik City Hospital, between 2022 and 2024, in accordance with the surgical case report 2023 guidelines (10). The study population consisted of individuals who presented with obstructive jaundice and were subsequently found to have extrinsic common bile duct compression secondary to a PAD in the absence of choledocholithiasis or malignancy. A total of 12 patients met these criteria and were included after a thorough review of hospital data storage and patient files.

This study was approved by the Ethics Committee of University of Health Sciences Türkiye, Ankara Etlik City Hospital (approval no: AEŞH-BADEK-2024-1240, date: 18.12.2024), and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Demographic data, including age, sex, and relevant comorbidities, such as hypertension, diabetes mellitus, and cardiac conditions, were obtained from medical records. Additionally, clinical symptoms associated with jaundice, including right upper quadrant pain, nausea, vomiting, and changes in urine and stool color, were documented. Laboratory parameters, including total, direct, and indirect bilirubin levels, as well as liver enzyme levels [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], were analyzed to assess cholestatic liver injury. Imaging modalities such as USG, CT, and MRCP were meticulously evaluated to confirm bile duct compression due to a PAD.

The therapeutic approach varied depending on clinical presentation and imaging findings. Patients were managed conservatively, with symptomatic treatment including proton pump inhibitors, antiemetics, and intravenous fluid support. In cases where endoscopic intervention was required, ERCP was performed to relieve biliary obstruction, often through the placement of a biliary stent. Procedural details, including the type of intervention performed and any associated complications such as bleeding or perforation, were retrospectively reviewed from patient records. The duration of hospital stay and follow-up period were also recorded.

Patients were included in the study based on the presence of obstructive jaundice supported by elevated serum bilirubin (predominantly direct bilirubin) and liver enzyme abnormalities (ALT and AST), along with imaging or endoscopic confirmation of extrinsic bile duct compression by a PAD. They were excluded if other causes of biliary obstruction, such as Mirizzi syndrome, gallbladder carcinoma, or pancreaticoduodenal tumors, were identified. Additionally, those with incomplete medical records or asymptomatic individuals with incidental PADs were not included in the study.

Imaging modalities were considered "sufficient" when they provided clear visualization of the PAD and its anatomical relationship to the common bile duct, allowing for confident diagnosis of Lemmel syndrome. "Insufficient" imaging lacked adequate resolution or anatomical clarity to establish this relationship.

Statistical Analysis

For statistical analysis, numerical variables were expressed as the mean ± standard deviation or median with minimum and maximum values, while categorical variables were presented as frequencies and percentages. Due to the small sample size, advanced statistical comparisons were not performed, and data analysis was primarily descriptive.

RESULTS

Demographic data and clinical presentation are shown in Table 1. Jaundice was the most common presenting symptom on clinical presentation, observed in all patients (100%), accompanied by scleral icterus and yellowish skin discoloration. Five patients had a history of non-malignant cholangitis or cholecystitis episodes.

Laboratory findings at initial presentation revealed a cholestatic pattern of liver function test abnormalities in all patients (Table 2). The median PAD diameter measured on cross-sectional imaging was 35 mm (range: 20-48 mm). Four patients (33%) had PADs measuring ≥40 mm.

Radiological and endoscopic evaluations played a crucial role in diagnosis. All patients underwent at least one imaging modality, and their diagnostic contributions were categorized as "sufficient" or "insufficient" (Table 3).

All patients initially received medical management, including proton pump inhibitors, antiemetics, and intravenous fluid support. ERCP was considered for those with significant biliary obstruction, particularly those with elevated bilirubin levels. Among the five patients who underwent stenting, three demonstrated significant clinical and biochemical improvement, whereas two elderly patients with multiple comorbidities showed only partial resolution of the symptoms. The mean duration of hospital stay was 12±6 days (range: 2-56), and the average follow-up duration was 8 months.

Table 1. Demographic and clinical characteristics of the study population (n=12)

Variable	Value
Age, mean ± SD (range), years	70±9 (43-87)
Sex, n (%)	
Female	7 (58.3%)
Male	5 (41.7%)
Comorbidities, n (%)	
Hypertension	9 (75%)
Diabetes mellitus	6 (50%)
Cardiovascular disease	7 (58.3%)
Chronic obstructive pulmonary disease	2 (16.7%)
Myeloma	1 (8.3%)
Bullous pemphigoid	1 (8.3%)
Presenting symptoms, n (%)	
Jaundice	12 (100%)
Right upper quadrant pain	6 (50%)
Dyspepsia	10 (83.3%)
History of cholangitis/cholecystitis	5 (41.7%)

SD: Standard deviation.

Table 2. Laboratory findings at presentation

Parameter	Median [min-max], n=12
Total bilirubin (mg/dL)	3.05 [0.31-9.6]
Direct bilirubin (mg/dL)	1.7 [0.12-5.5]
ALT (U/L)	166.5 [11-419]
AST (U/L)	161 [13-471]

ALT: Alanine aminotransferase, AST: aspartate aminotransferase.

One patient with a known history of advanced gastric malignancy and multiple systemic comorbidities died during the follow-up period. Mortality was attributed to progression of the underlying malignancy and sepsis and was not considered to be directly related to Lemmel syndrome or to any diagnostic or therapeutic endoscopic intervention performed during hospitalization. The remaining patients were discharged after resolution of the obstructive jaundice, with no major complications noted during outpatient follow-up.

DISCUSSION

This case series adds further observational data to the expanding literature on Lemmel syndrome, particularly in an elderly and comorbid patient population. The findings corroborate previously reported diagnostic challenges, imaging characteristics, and outcomes of endoscopic management in routine clinical practice. Lemmel syndrome may be overlooked in elderly patients with nonspecific presentations and multiple comorbidities; careful integration of clinical findings with appropriate cross-sectional imaging and endoscopic evaluation remains essential for accurate diagnosis and effective management.

PADs are generally asymptomatic and are often detected incidentally during endoscopic or radiological imaging. However, their anatomical proximity to the common bile duct or pancreatic duct may lead to severe clinical conditions such as obstructive jaundice, cholangitis, or pancreatitis (11). In the current series, elevations in liver enzymes in addition to hyperbilirubinemia can be adequately explained by biliary obstruction and, in some cases, associated cholangitis, which are well-recognized biochemical manifestations of extrahepatic biliary compression. These non-specific symptoms, especially in patients with multiple comorbidities, may mimic malignancy or choledocholithiasis, leading to misdiagnosis and inappropriate initial work-up. Previous studies have emphasized that Lemmel syndrome can present with atypical symptoms and is often misdiagnosed as malignancy, choledocholithiasis, or Mirizzi syndrome (12). Similarly, in the present series, several patients presented with dyspeptic complaints and non-specific

Table 3. Diagnostic performance of the imaging and endoscopic modalities (n=2)

Modalities	Patients evaluated, n	Sufficient, n (%)	Insufficient, n (%)	Not performed, n (%)
USG	11	3 (27.3)	7 (63.6)	1 (8.3%)
CT	10	5 (50)	5 (50)	2 (16.7%)
MRCP	9	6 (66.7)	3 (33.3)	3 (25%)
EGD	12	8 (66.7)	4 (33.3)	0 (0%)
ERCP	7	5 (71.4)	2 (28.6)	5 (41.7%)
EUS	4	4 (100)	0 (0%)	8 (66.7%)

USG: Ultrasonography, CT: Computed tomography, MRCP: Magnetic resonance cholangiopancreatography, EGD: Gastroduodenoscopy, ERCP: Endoscopic retrograde cholangiopancreatography, EUS: Endoscopic ultrasound.

abdominal pain in addition to jaundice, which may further complicate USG diagnostic evaluation.

Despite its widespread use as an initial diagnostic modality, demonstrated limited sensitivity in detecting PAD-related extrinsic compression in most cases. This finding aligns with prior literature, where even large PADs may be overlooked due to interference from bowel gas and anatomical overlap. Conversely, CT can visualize mass-like lesions or diverticular extensions in the periampullary region, yet it may present difficulties in differential diagnosis (Figure 1) (8). The current findings indicated that MRCP played a crucial role in establishing the diagnosis (Figure 2). By providing a three-dimensional assessment of the relationship between PADs and the biliary and pancreatic ducts, MRCP may be essential in differentiating Lemmel syndrome from choledocholithiasis and malignancies. These findings support the consideration of early MRCP evaluation, particularly in elderly patients with obstructive jaundice of unclear etiology. Given its non-invasive nature and superior anatomical resolution, MRCP should be considered early in the diagnostic algorithm for elderly patients with unexplained biliary obstruction.

Endoscopic interventions, including gastroduodenoscopy (EGD) and ERCP, represent the cornerstone of both diagnostic and therapeutic approaches in Lemmel syndrome (12). In the present series, gastroduodenoscopy was performed in all patients to identify the position of the major papilla within or adjacent to the PAD (Figure 3). In some cases, assessment was technically challenging due to large size of the PAD and altered periampullary anatomy. ERCP facilitated both anatomical clarification and therapeutic biliary stenting, effectively resolving obstructive jaundice (13). However, technical difficulty was encountered in two cases with massive PADs, where complete ERCP procedures could not be performed.

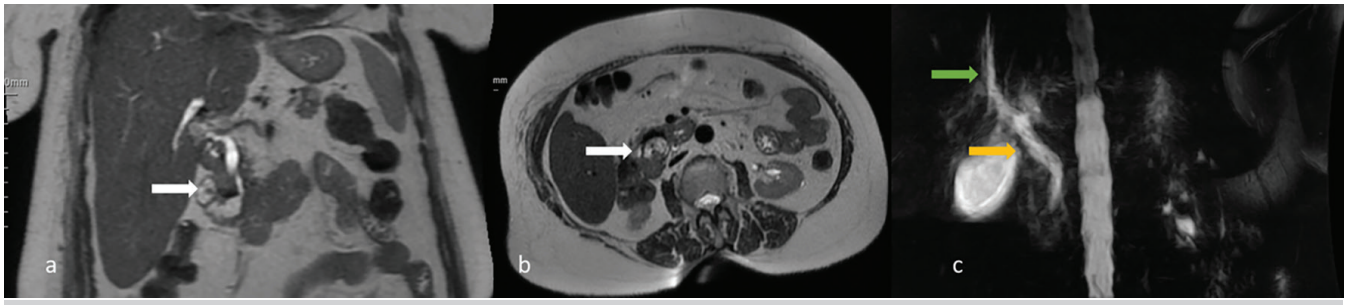

Figure 1. Upper abdominal magnetic resonance imaging: coronal and axial T2 sections showed a periampullary duodenal diverticulum (PAD) (white arrows) (**a, b**). Magnetic resonance cholangiopancreatography: Biliary sequence showing a PAD causing dilatation of the common bile duct (yellow arrow) and the proximal part of intrahepatic bile duct dilatation (green arrow) (**c**).

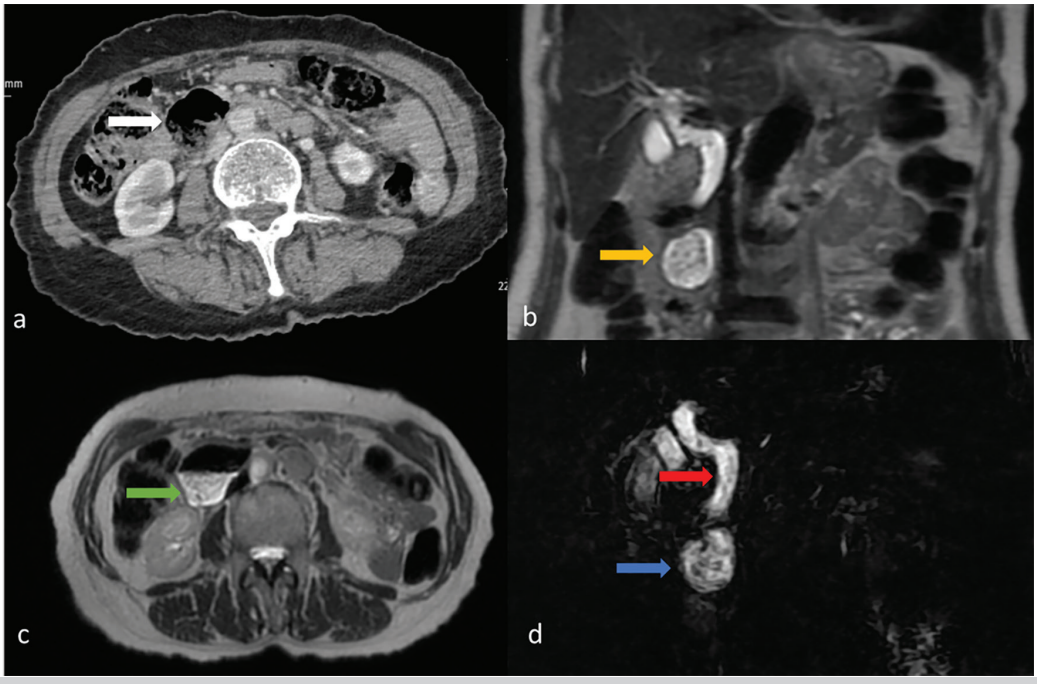

Figure 2. Abdominal computed tomography scan demonstrating a periampullary duodenal diverticulum (PAD) (white arrow) with resultant upstream dilatation of the common bile duct (**a**). Magnetic resonance cholangiopancreatography: Coronal (**b**) and axial (**c**) T2 sections showing a PAD of the same patient (yellow and green arrows). 3D biliary sequence showing a PAD (blue arrow) causing dilatation of the common bile duct (red arrow) (**d**).

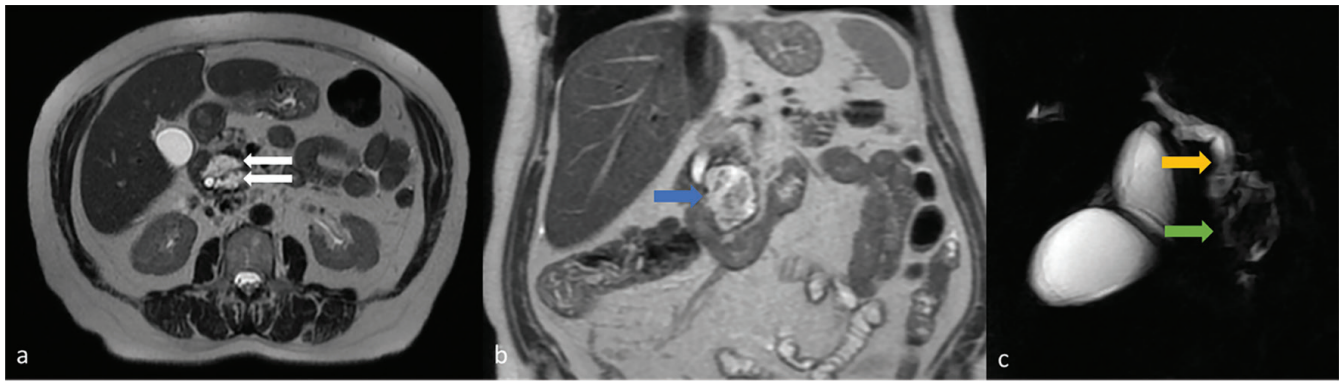

Figure 3. Magnetic resonance cholangiopancreatography: Axial T2 sections showing two periampullary duodenal diverticulum (PAD) adjacent to each other (white arrows) (**a**) and coronal T2 sections showing a PAD (blue arrow) (**b**). 3D biliary sequence showing a PAD (green arrow) causing dilatation of the common bile duct (yellow arrow) (**c**).

Endoscopic ultrasound (EUS) was utilized in four patients and contributed to the diagnostic evaluation.

As reported in previous literature, EUS offers detailed visualization of extraluminal structures and may serve as a valuable adjunctive modality when ERCP is technically challenging (12). Nevertheless, EUS remains operator-dependent, and its diagnostic performance may vary according to institutional expertise.

The presence of advanced age and multiple systemic comorbidities in most patients in our study added complexity to the management of Lemmel syndrome. Coexisting conditions, such as cardiovascular, endocrine, or respiratory diseases, not only contributed to diagnostic delays but also complicated treatment planning. In patients with significant comorbidities, conservative or endoscopic management was prioritized over radical surgical interventions. However, in cases where conservative treatment was inadequate, surgical options were considered. In our series, one patient who exhibited persistent symptoms and recurrent clinical episodes despite medical treatment underwent gastrojejunostomy with Braun anastomosis, which was successfully performed. Postoperative follow-up revealed no additional complications. However, our experience suggests that conservative or endoscopic management may be appropriate as an initial approach in clinically stable patients.

Study Limitations

This study had several limitations, including its single-center, retrospective design and small sample size, which precluded comparative statistical analysis. Although the PAD size measurements were available, the limited sample size also restricted meaningful assessment of potential correlations between the PAD diameter and biochemical parameters. Additionally, some diagnostic procedures (e.g., USG, ERCP) are operator-dependent, introducing variability in diagnostic accuracy. Despite these constraints, the series contributes additional descriptive data within the context of a relatively uncommon clinical presentation.

In conclusion, clinicians should maintain a high index of suspicion for Lemmel syndrome in elderly patients presenting with unexplained obstructive jaundice. A structured diagnostic pathway—initiating with MRCP and supplemented by endoscopy—may reduce delays and optimize outcomes. Given the rarity of the condition and the lack of standardized protocols, larger multicenter studies are warranted to validate these observations and refine treatment strategies.

CONCLUSION

Lemmel syndrome should be considered in elderly patients presenting with obstructive jaundice, as its clinical presentation can often mimic other causes of biliary obstruction. Diagnosis and management rely primarily on advanced imaging and endoscopic techniques, particularly MRCP and ERCP, with EUS serving as a complementary tool when needed. Given the complexity of the condition, a multidisciplinary approach involving gastroenterologists, surgeons, and radiologists is essential to ensure optimal patient outcomes and to tailor individualized treatment strategies.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences Türkiye, Ankara Etlik City Hospital (approval no: AEŞH-BADEK-2024-1240, date: 18.12.2024), and was conducted in accordance with the Declaration of Helsinki.

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

Footnotes

Author Contributions

Surgical and Medical Practices - E.E., S.D., M.S.S., Ş.B.; Concept - E.E.; Design - E.E., S.D.; Data Collection or Processing - E.E., S.D., Ş.E.; Analysis or Interpretation - E.E., S.D., M.S.S.; Literature Search - E.E., S.D.; Writing - E.E., S.D.

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ORIGINAL ARTICLE
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Surgeons' preferences in the management of recurrence after laparoscopic inguinal hernia repair: A nationwide survey

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ABSTRACT

Objective: This study aimed to evaluate contemporary surgical approaches and decision-making patterns of general surgeons in the management of recurrent inguinal hernia following laparoscopic inguinal hernia repair (LIHR), with particular emphasis on recurrence timing, surgeon experience, and annual laparoscopic case volume.

Material and Methods: The questionnaire consisted of 26 items, including both multiple-choice and short-answer questions, and was designed to assess demographic characteristics, surgical experience, preferred surgical techniques, preoperative evaluation strategies, and management approaches for recurrent inguinal hernia following LIHR. Recurrences were classified as early (≤2 years) or late (>2 years) based on the postoperative time interval.

Results: A total of 179 surgeons participated in the survey. Most respondents were male and had ≤10 years of surgical experience. Surgeons with higher annual laparoscopic hernia repair volumes were significantly more likely to prefer re-laparoscopic posterior approaches for both early and late recurrences, whereas surgeons with lower case volumes predominantly favored open anterior repair techniques ($p<0.05$). Surgical preferences also varied in female patients and according to the initial repair technique (transabdominal preperitoneal or total extraperitoneal). Nearly two-thirds of participants reported insufficient or only partially sufficient training in recurrent hernia repair, while the majority strongly agreed on the need for national or international clinical guidelines.

Conclusion: Surgeon experience and annual laparoscopic case volume significantly influence the management of recurrent inguinal hernia following LIHR. As laparoscopic expertise increases, re-laparoscopic approaches are more frequently adopted. These findings highlight the need for standardized training programs and evidence-based guidelines to optimize the management of recurrent inguinal hernia after laparoscopic repair.

Keywords: Laparoscopic, hernia, recurrence, surgeon decision

INTRODUCTION

Inguinal hernia is among the most prevalent surgical conditions in general surgery, particularly in the older population. It constitutes a substantial health issue in both developed and developing nations (1). Numerous approaches for open and laparoscopic inguinal hernia repair (LIHR) have been documented for its management. The open surgical approaches include Lichtenstein, Shouldice, anterior preperitoneal, Kugel, and Rives-Stoppa methods; the predominant laparoscopic techniques are total extraperitoneal (TEP), transabdominal preperitoneal (TAPP), and extended TEP (e-TEP) repairs (2,3).

Laparoscopic hernia repair has gained popularity in recent years owing to its benefits, including less postoperative pain, abbreviated hospital stays, expedited resumption of normal activities, and superior cosmetic results. etheless, despite the numerous benefits of minimally invasive approaches, studies indicate that recurrence rates following laparoscopic repairs are comparable to those observed after open surgical procedures (4,5).

The selection of surgical method for recurrent inguinal hernias primarily hinges on the original repair technique employed. Traditionally, posterior approaches (laparoscopic or Rives-Stoppa) are advised for recurrences of anterior open repairs, whereas anterior open surgical techniques are suggested for recurrences of LIHR (6,7). Advancements in laparoscopic and robotic technologies, enhanced surgeon expertise, and the introduction of novel mesh materials have redefined surgical techniques for recurring patients (8). Recent investigations indicate that laparoscopic

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repair is both feasible and safe for recurring instances following first laparoscopic surgery, contingent upon suitable patient selection (9,10). Given these advances, it is essential to evaluate surgeons' contemporary trends and methodologies in the therapy of recurrent inguinal hernias.

In this study, we sought to assess the contemporary surgical techniques employed by general surgeons in instances of recurrence after LIHR. We hypothesize that the frequency of re-laparoscopic operations has risen in recent years following recurrence after laparoscopic repair.

MATERIAL and METHODS

Study Design and Ethical Approval

This study was designed as a cross-sectional, questionnaire-based descriptive research. Ethical approval was obtained from the Local Ethics Committee of Kahramanmaraş Sütçü İmam University on September 22, 2025 (approval no: 24 following approval, the survey was conducted between October 1 and October 15, 2025). Informed consent was obtained from patients.

Study Population

The study population consisted of 300 general surgeons working in 25 healthcare centers across different regions of Türkiye. Participation was entirely voluntary, and no incentives were offered. The inclusion criterion was being a general surgeon who had completed specialty training in general surgery and was actively performing hernia repair surgery.

Data Collection Tool

Data were collected using a structured electronic questionnaire developed via Google forms (Google LLC, California, USA). The questionnaire link was distributed to participants through WhatsApp communication groups of general surgeons. Each participant could complete the survey only once, as the form was configured to prevent duplicate responses.

Before accessing the questionnaire, participants read an informed consent form outlining the study's aim, data confidentiality, and voluntariness. Clicking the participation link and submitting the form indicated consent to participate. No personal identifiers other than initials and e-mail address (for consent verification only) were collected, ensuring full anonymity.

Questionnaire Structure

The questionnaire consisted of 26 items, including both multiple-choice and short-answer questions. It was designed to evaluate surgeons' demographic characteristics, professional experience, preferred surgical techniques, and management approaches in recurrent inguinal hernia cases following laparoscopic repair.

The content of the questionnaire was structured under four main sections:

1. Demographic and professional information — gender, age, surgical experience, preferred repair technique, and annual number of laparoscopic repairs performed.

2. Decision-making and clinical practice — factors influencing the choice of surgical approach, preoperative evaluations, and perceived intraoperative challenges.

3. Surgical management of recurrent Hernia — approach selection based on recurrence type (early vs. late), previous technique (TAPP vs. TEP), and patient factors such as gender and prior abdominal surgery.

4. Education and guideline needs — surgeons' self-assessment of training sufficiency and opinions regarding the necessity of national/international guidelines.

In the questionnaire, recurrence was presented as a standardized clinical scenario rather than a confirmed patient diagnosis. The survey aimed to evaluate surgeons' decision-making preferences; therefore, no specific diagnostic modality (clinical examination, imaging, or patient-reported symptoms) was imposed. Participants were asked to consider a clinically established recurrence after previous LIHR. Unless otherwise specified, the scenario referred to ipsilateral recurrence at the previously repaired side.

Recurrence timing was categorized as early or late based on the postoperative interval. Early recurrence was defined as recurrence occurring within 2 years after the initial LIHR, whereas late recurrence was defined as recurrence occurring beyond 2 years. This cut-off was selected in accordance with previous studies demonstrating that most recurrences following LIHR occur within the first 1-2 years postoperatively and are more likely related to technical or procedure-dependent factors, while later recurrences may reflect patient-related or progressive tissue factors (11,12).

Statistical Analysis

Descriptive statistics are presented with frequency, percentage, mean, standard deviation, minimum, and maximum values. In the analysis of categorical data, Fisher's-Freeman-Halton test (for nXn tables) was used if the percentage of cells with an expected value less than 5 was greater than 20%, and Pearson's chi-square test was used if it was less than 20%. Analyses were performed using the SPSS 23.0 programmed. $P<0.05$ was considered statistically significant.

RESULTS

A total of 179 surgeons engaged in the survey. The majority were male, and most possessed between 0 and 10 years of surgical experience. TAPPP (TEP) repair was the predominant procedure employed in routine surgery, succeeded by open anterior repair and TAPP repair. About fifty percent of the participants

conducted over 50 LIHRs each year. The majority of surgeons indicated that they actively address recurrent inguinal hernia patients in their clinical practice, but a lesser percentage opted to operate just on specific cases (Table 1). Regarding preoperative assessment, physical examination and ultrasonography were routinely used by most respondents. Computed tomography was applied selectively, while magnetic resonance imaging was rarely preferred in routine evaluation (Table 2).

Because participants were allowed to select more than one surgical difficulty, separate binary variables (present/absent) were created for each reported difficulty, and their associations with annual laparoscopic hernia repair volume groups were analyzed. The reporting rate of "distortion of anatomical planes" decreased with increasing case volume (<10: 90.9%; 10-50: 89.4%; 51-100: 78%; >100: 61.9%), with a statistically significant difference between groups (p=0.012).

In contrast, the reporting rate of "mesh migration" increased with higher case volume (<10: 18.2%; 10-50: 18.2%; 51-100: 40.7%; >100: 38.1%), and the difference between groups was statistically significant (p=0.011). Difficulty in accessing the previously placed mesh also differed significantly across volume groups (p=0.015). However, the reporting rates of "dense fibrosis" were similar among volume groups (p=0.376) (Figure 1).

Although a proportion of surgeons considered their training in recurrent hernia repair to be adequate, nearly half reported only partial adequacy, and a notable minority indicated insufficient training. In contrast, there was a strong consensus regarding the need for national or international clinical guidelines for the management of recurrences following LIHR (Table 3).

Table 1. Demographic characteristics of the physicians participating in the study

	Frequency (n)	Percentage (%)
Gender		
Male	152	84.9
Female	27	15.1
Surgical experience		
0-5 years	64	35.7
6-10 years	67	37.4
11-20 years >20 years	36 12	20.1 6.7
Which surgical technique do you most frequently use in your practice?		
TEP	78	43.6
TAPP	44	24.6
Lichnestein open repair technique	54	30.2
e-TEP	3	1.7
How many laparoscopic hernia repairs do you perform per year?		
<10	33	18.4
10-50	66	36.9
51-100	59	33
>100	21	11.7
Do you prefer to take on recurrent inguinal hernia cases in your surgical practice?		
Yes, I actively follow up and operate on them	128	72.7
Yes, but only in selected cases	45	25.6
No, I refer such cases to another surgeon	3	1.7

TEP: Total extraperitoneal, TAPP: Transabdominal preperitoneal, e-TEP: Extended TEP.

Table 2. Routine assessments routinely performed on patients prior to recurrence repair

Which assessments do you routinely perform on the patient before recurrence repair?	Frequency (n)	Percentage (%)
Physical examination		
No	16	8.9
Yes	163	91.1
Ultrasonography		
No	36	20.1
Yes	143	79.9
CT scan		
No	120	67
Yes	59	33
MRI		
No	171	95.5
Yes	8	4.5

Because this question allows selecting multiple options, the sum of the percentages can exceed 100.
CT: Computed tomography, MRI: Magnetic resonance imaging.

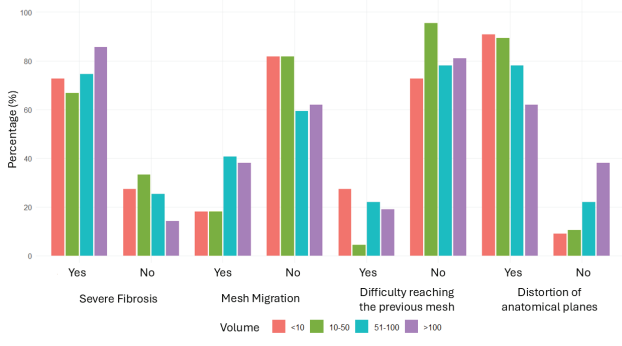

Figure 1. The most common surgical challenges in recurrent cases.

Table 3. Opinions regarding training adequacy and guideline requirements for recurrent hernia repair		
Do you think you have received sufficient training on hernia recurrence repair?	**Frequency (n)**	**Percentage (%)**
Yes	61	34.1
Partially	89	49.7
No	29	16.2
Do you think there is a need for a national/international surgical guideline on the management of recurrence after laparoscopic inguinal hernia repair?		
I definitely agree	54	30.2
I agree	99	55.3
I am undecided	15	8.4
I disagree	11	6.1

Annual laparoscopic hernia repair volume was significantly associated with surgical preferences in after laparoscopic recurrent cases. In early recurrences (≤2 years), surgeons with higher annual case volumes were more likely to prefer advanced laparoscopic approaches, whereas those with lower volumes more frequently opted for open anterior repair techniques. A similar pattern was observed in late recurrences (>2 years), with high-volume surgeons predominantly favoring laparoscopic strategies.

In female patients with recurrent hernia, surgical preference also varied according to annual laparoscopic volume. Surgeons with lower case volumes more commonly preferred open techniques specifically addressing the femoral canal, whereas surgeons with moderate to high volumes more frequently opted for repeat laparoscopic approaches or individualized decision-making strategies (Table 4).

When recurrence occurred after an initial TAPP or TEP repair, surgical volume remained a significant determinant of the chosen strategy. High-volume surgeons were more likely to adopt repeat laparoscopic repair or to base their decision on additional imaging, while lower-volume surgeons predominantly favored open anterior repair techniques. All observed associations between annual surgical volume and treatment preference were statistically significant (Table 5).

A statistically significant relationship was found between the annual volume of laparoscopic hernia repairs and the most commonly used surgical technique in practice (p<0.001) (Table 6).

Due to the small number of observations, the e-TEP category was excluded from the analysis, and TEP and TAPP were combined and defined as the "relaparoscopic" category (1), whereas Lichtenstein open repair was defined as (0). In the multivariable

Table 4. Comparison of the annual rates of laparoscopic hernia repairs performed according to surgical preferences in early-stage, late-stage, and female patients with laparoscopic recurrence					
	Early-stage recurrent (≤2 years)				
Number of laparoscopic hernia repairs performed annually	**TEP n (%)**	**TAPP n (%)**	**Open ant repair tech. n (%)**	**e-TEP n (%)**	**p**
<10	6 (18.8)	12 (27.3)	15 (15.6)	0 (0)	0.006
10-50	12 (37.5)	13 (29.5)	41 (42.7)	0 (0)	
51-100	7 (21.9)	16 (36.4)	33 (34.4)	3 (42.9)	
>100	7 (21.9)	3 (6.8)	7 (7.3)	4 (57.1)	
	Late-stage recurrent (>2 years)				
	TEP n (%)	**TAPP n (%)**	**Open ant. repair tech. n (%)**	**e-TEP n (%)**	**p**
<10	3 (12)	9 (21.4)	21 (19.4)	0 (0)	<0.001
10-50	12 (48)	7 (16.7)	47 (43.5)	0 (0)	
51-100	7 (28)	19 (45.2)	33 (30.6)	0 (0)	
>100	3 (12)	7 (16.7)	7 (6.5)	4 (100)	
	Female				
	Open ant. repair tech. n (%)	**It depends on the situation n (%)**	**Open repair n (%)**	**Again TAP n (%)**	**p**
<10	12 (11.5)	9 (23.7)	9 (60)	3 (13.6)	0.001
10-50	44 (42.3)	9 (23.7)	6 (40)	7 (31.8)	
51-100	34 (32.7)	16 (42.1)	0 (0)	9 (40.9)	
>100	14 (13.5)	4 (10.5)	0 (0)	3 (13.6)	

The column totals are provided. Fisher's-Freeman-Halton test was used for all of them.
TEP: Total extraperitoneal, TAPP: Transabdominal preperitoneal, e-TEP: Extended TEP.

Table 5. Comparison of the rates of annual laparoscopic hernia repair according to surgical preferences in recurrences repaired with TAPP and TEP

	Surgical preference when recurrence develops in a patient repaired with TAPP				
Number of laparoscopic hernia repairs performed annually	**Lichnestein repair n (%)**	**TEP n (%)**	**Again TAPP n (%)**	**Decide based on the outcome n (%)**	**p**
<10	33 (20.6)	0 (0)	0 (0)	0 (0)	<0.001
10-50	63 (39.4)	3 (50)	0 (0)	0 (0)	
51-100	47 (29.4)	3 (50)	6 (100)	3 (42.9)	
>100	17 (10.6)	0 (0)	0 (0)	4 (57.1)	
	Lichnestein repair n (%)	**TAPP n (%)**	**Again TEP n (%)**	**Decide based on the outcome n (%)**	
<10	18 (14.1)	9 (28.1)	6 (40)	0 (0)	<0.001
10-50	60 (46.9)	6 (18.8)	0 (0)	0 (0)	
51-100	40 (31.3)	10 (31.3)	9 (60)	0 (0)	
>100	10 (7.8)	7 (21.9)	0 (0)	4 (100)	

The column totals are provided. Fisher's-Freeman-Halton test was used for all of them.
TEP: Total extraperitoneal, TAPP: Transabdominal preperitoneal, e-TEP: Extended TE preperitoneal.

Table 6. Relationship between surgical preference and annual laparoscopic preference

	Surgical preference			
	Lichnestein n (%)	**Relaparoscopic n (%)**	**Total n (%)**	**p**
How many laparoscopic hernia repairs do you perform per year?				
<10	24 (44.4)	9 (7.4)	33 (18.8)	<0.001
Between 10 and 50	30 (55.6)	36 (29.5)	66 (37.5)	
Between 51 and 100	0 (0)	56 (45.9)	56 (31.8)	
>100	0 (0)	21 (17.2)	21 (11.9)	
Total	54 (100)	122 (100)	176 (100)	

The Pearson chi-square test was applied.

logistic regression analysis, the presence of prior laparoscopic experience was independently associated with a relaparoscopic preference (p=0.021). Surgeons with such experience were 2.69 times more likely to prefer a relaparoscopic approach than those without experience.

Availability of information regarding the previous operation type and details was inversely associated with relaparoscopic preference (p=0.002). When prior operative information was available, the likelihood of choosing a relaparoscopic (TEP/TAPP) approach was 74% lower compared with cases in which such information was unavailable (1-0.260).

Years of surgical experience were not independently significant in the multivariable model (p=0.380). When annual laparoscopic repair volume was entered into the model, the absence of open repair choices in certain volume categories resulted in unstable coefficient estimates in standard logistic regression. Therefore, this variable was not included in the final multivariable model (Table 7).

DISCUSSION

The emergence of novel surgical techniques has continuously reshaped the management of recurrences following LIHR. While conventional open repair approaches have traditionally been favored in revision surgery, recent studies demonstrate an increasing preference for posterior repair using a re-laparoscopic

Table 7. Multivariate logistic regression analysis for laparoscopic preference

	B	**S.E.**	**Wald**	**p**	**Exp(B)**	**95% CI for Exp(B)**	
						Lower	**Upper**
Surgical experience			1.934	0.38			
0-5 years vs. 11-20 years	-0.568	0.453	1.576	0.209	0.567	0.233	1.376
6-10 years vs. 11-20 years	-0.103	0.441	0.055	0.815	0.902	0.38	2.139
Previous surgery type and details (Present vs. Absent)	-1.346	0.434	9.636	0.002	0.26	0.111	0.609
The surgeon's previous experience (Yes vs. No)	0.993	0.431	5.319	0.021	2.699	1.161	6.276
Constant	0.64	0.41	2.436	0.119	1.896		

-2LL=205,184; Hosmer Lemeshow p=0.194; Nagelkerke R^2=0.092, S.E.: Standard error, CI: Confidence interval.

approach (13). With growing surgical experience, complications encountered during LIHR can also be effectively managed under laparoscopic guidance (14).

Our findings indicate that increasing laparoscopic expertise among surgeons is associated with a greater tendency to perform repeat laparoscopic posterior repairs in cases of recurrence following LIHR. At the same time, there is a prevailing perception among surgeons in our country that current surgical training provides insufficient preparation for the management of recurrent hernias after LIHR. Accordingly, the vast majority of respondents emphasized the need for national and international guidelines to standardize the management of such recurrences.

In recurrent cases following LIHR, the traditional anterior approach appears to be increasingly replaced by laparoscopic posterior repair techniques (15). Van den Heuvel and Dwars (16) demonstrated that the TAPP approach is a safe and effective option for the treatment of recurrences after LIHR. Similarly, Ertem et al. (17) reported that a re-laparoscopic approach represents a safe and feasible strategy in recurrent cases following LIHR. Moreover, the safety and applicability of re-laparoscopic repair have also been demonstrated in pediatric populations (18).

In the literature, most recurrences following LHIR occur within the early stage (19). In early-stage recurrences, reasons such as surgical insufficiency, mesh migration, and selection of inappropriate mesh size are typically attributed (17). In their series of 12 cases involving same-sided recurrences following Ferzli and Khoury (20) TEP, they reimplemented TEP and asserted that it was an effective technique. The TAPP treatment has been reported to be effectively executed by skilled surgeons in cases of recurrence following LIHR (21). Global agreement suggests that a relaparoscopic intervention for recurrences following LIHR should be conducted by skilled specialists (22).

Previous literature suggests that greater experience in LIHR is associated with improved perioperative outcomes, including lower complication and recurrence rates and reduced operative time (23,24). In line with this, our findings indicate that increasing laparoscopic case volume is associated with a higher tendency to adopt relaparoscopic strategies in recurrent cases. In multivariable analysis, LIHR experience emerged as the strongest independent predictor of relaparoscopic preference.

The literature indicates that recurrence rates following LIHR in women are minimal (25). Revealing the round ligament in the inguinal area is beneficial for managing other intra-abdominal conditions and facilitates the treatment of bilateral hernias (26,27). After recurrent inguinal hernias, a laparoscopic approach can be safe again with the current advantages.

Although re-laparoscopic approaches were generally preferred by high-volume surgeons, the adoption of advanced techniques such as e-TEP remained very limited. This finding likely reflects multiple factors. First, e-TEP requires a steeper learning curve and advanced laparoscopic expertise compared with conventional TEP or TAPP techniques. Second, the availability of appropriate equipment and institutional support may vary between centers. Finally, recurrent hernia surgery presents altered anatomy and dense adhesions, which may lead surgeons to favor more familiar or standardized techniques. Therefore, the low utilization of e-TEP in our survey probably represents a combination of training exposure, technical complexity, and case-related considerations rather than a single underlying cause.

Despite the existence of recommendations pertaining to LIHR, published in 2011 and revised in 2015 (22,28) a consensus on recurrent instances arising post-LIHR remains elusive, particularly with the advent of novel approaches. A renewed consensus and extensive studies are required to achieve a common approach.

Study Limitations

This study has several limitations. First, the sample frame was restricted to 300 surgeons invited from 25 centers, and participation was voluntary with a response rate of 59.7%; therefore, respondents may not fully represent the overall general surgical population in Türkiye. In addition, distribution of the survey through WhatsApp communication groups may have preferentially reached younger, digitally active, and more laparoscopically oriented surgeons, introducing potential selection bias and limiting generalizability.

Second, as this was a questionnaire-based survey, recurrence was evaluated as a standardized clinical scenario rather than a confirmed patient diagnosis, and no uniform diagnostic modality (clinical examination, imaging, or symptoms) was imposed. Accordingly, the findings reflect surgeons' decision-making preferences rather than actual clinical outcomes.

Finally, recurrence was categorized as early (≤2 years) and late (>2 years) to standardize responses; however, this represents a pragmatic classification rather than a strict biological distinction. Recurrent inguinal hernia is a heterogeneous condition, and technical and patient-related factors may overlap in individual cases. Therefore, this categorization should be interpreted cautiously.

CONCLUSION

This research is the inaugural investigation on surgeons' strategies for managing recurrence patients after LIHR in Türkiye. It illustrates that with increased surgical experience, the utilization of relaparoscopic techniques for LIHR recurrences rises. The utilization of minimally invasive techniques by proficient surgeons is expected to rise following the establishment of national and worldwide consensus guidelines.

Ethics

Ethics Committee Approval: This study was designed as a cross-sectional, questionnaire-based descriptive research. Ethical approval was obtained from the Local Ethics Committee of Kahramanmaraş Sütçü İmam University on September 22, 2025 (approval no: 24 following approval, the survey was conducted between October 1 and October 15, 2025).

Informed Consent: Informed consent was obtained from patients.

Footnotes

Author Contributions

Concept - Ö.Ç.; Design - Ö.Ç., R.C.Ç.; Data Collection or Processing - Ö.Ç., R.C.Ç.; Analysis or Interpretation - Ö.Ç., R.C.Ç.; Literature Search - Ö.Ç., R.C.Ç.; Writing - Ö.Ç., R.C.Ç.

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The effects of preoperative anaemia on postoperative complications in patients undergoing thoracic surgery: A prospective descriptive study

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ABSTRACT

Objective: Preoperative anaemia is a risk factor for an increased requirement for blood and blood-product transfusions in patients undergoing thoracic surgery. Our aim was to study the association between preoperative anaemia and adverse outcomes in patients undergoing thoracic surgery.

Material and Methods: This was a prospective descriptive study of adult patients undergoing thoracic surgery. Patients were classified into preoperative anaemia (Group A: Hb <13 g/dL in males, <12 g/dL in females) and non-anaemia (Group B). Collected data included demographics, intraoperative parameters, laboratory values, and postoperative outcomes, including complications, transfusion requirements, intensive care unit stay, and length of hospital stay. Statistical analyses were conducted to assess differences between the groups.

Results: A total of 104 patients were included: 29 with preoperative anaemia (Group A) and 75 with normal haemoglobin levels (Group B). Both groups were predominantly male. Patients with preoperative anaemia experienced significantly higher rates of intraoperative bleeding and perioperative crystalloid use, greater chest tube drainage volumes and longer durations, and increased postoperative pRBC transfusion requirements. Complications were more frequent in Group A than in Group B (31% vs. 8%, p=0.005) and hospital stays were longer (9.6±5.5 days vs. 7.7±4.7 days, p=0.014).

Conclusion: This study highlights the significant impact of preoperative anaemia on patients undergoing thoracic surgery. Preoperative anaemia was associated with increased intraoperative bleeding, higher complication rates, and longer hospital stays. These findings emphasise the need for thorough preoperative evaluation and optimisation of anaemia to improve surgical outcomes.

Keywords: Preoperative anaemia, thoracic surgery, postoperative complications

INTRODUCTION

Preoperative anaemia is a common and significant condition associated with various complications (1). The estimated prevalence of preoperative anaemia ranges from 16% to 54% (2). Retrospective studies involving large patient cohorts have demonstrated that preoperative anaemia is linked to an increased risk of 30-day postoperative mortality, highlighting its role as a critical risk factor for poor perioperative outcomes (3).

The World Health Organization (WHO) defines anaemia as haemoglobin (Hb) levels below 13.0 g/dL in males and below 12.0 g/dL in females (4). However, it remains unclear whether the adverse impact of anaemia on postoperative outcomes is directly attributable to low Hb levels, underlying risk factors, or blood transfusion-related effects.

A meta-analysis of cardiac surgery patients found that preoperative anaemia was associated with a significant 2.7-fold increased risk of mortality (2). Furthermore, anaemia is frequently linked to comorbidities such as coronary heart disease, diabetes mellitus, or cirrhosis (3). Research has also indicated that preoperative

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anaemia is associated with a a 3.13-fold increased risk of acute kidney injury and a 2.65-fold increased risk of infections (2).

Experimental studies have confirmed that anaemia reduces oxygen delivery, leading to hypoxia in multiple organs, including the brain and kidneys, and ultimately causing organ dysfunction (5). Hypoxia caused by anaemia has been directly associated with acute kidney injury and heightened risks of postoperative infections. Additionally, preoperative anaemia is associated with an increased likelihood of allogeneic blood transfusion, which can suppress cellular immunity and thereby increase the risk of surgical-site infection (6-8).

Secondary analyses of the European Surgical Outcomes Study have further evaluated the impact of abnormal preoperative Hb levels (3). Patients with anaemia experienced longer hospital stays, more frequent intensive care unit (ICU) admissions, greater reliance on mechanical ventilation within the first 24 postoperative hours, and increased use of inotropes or vasopressors (3).

The aim of this study was to determine whether preoperative anaemia, which has been established as a risk factor for postoperative morbidity and mortality in major surgery, is similarly associated with adverse outcomes in patients undergoing thoracic surgery.

MATERIAL and METHODS

Study Design, Setting and Eligibility Criteria

This was a prospective descriptive study of adult patients undergoing thoracic surgery. Patients aged 18 years or older who underwent open thoracic or thoracoscopic surgery under general anaesthesia at our university hospital between 2018 and 2019 were included. Excluded patients were paediatric patients younger than 18 years; patients with a known bleeding disorder, chronic kidney disease, hepatic failure, or congestive heart failure; and patients undergoing emergency surgery who were not assessed preoperatively in the anaesthesia assessment clinic.

This study received approval from the Marmara University Clinical Research Ethics Committee (decision number 09.2018.137, dated 2 February 2018). Written informed consent was obtained from all included participants. The study was registered in the ANZCTR Clinical Trials Registry (ACTRN12619000043134).

Anaesthesia Management

Preoperative preparation was conducted in the anaesthesia assessment clinic. Comorbid conditions were identified, and relevant laboratory tests and imaging evaluations were reviewed. Blood preparation was completed for all patients, and the need for postoperative intensive care was assessed based on comorbidities and the complexity of the surgery. Patients with Hb levels below 12 g/dL for females and below 13 g/dL for males, as defined by the WHO (4), were categorised as the anaemia group (Group A), whereas those with levels above these thresholds were categorised as the non-anaemic group (Group B).

The same thoracic anaesthetist attended all surgeries. Routine monitoring included electrocardiogram, peripheral oxygen saturation (SpO_2), and non-invasive blood pressure, with baseline values recorded. Radial artery cannulation with a 20-G cannula and central jugular cannulation were performed after induction of anaesthesia. Induction was achieved with propofol (2 mg/kg), rocuronium bromide (0.6 mg/kg), and fentanyl (2 µg/kg), using a gas mixture of 80% oxygen and 20% air. Anaesthesia was maintained with 2% sevoflurane, and remifentanil was initiated at 0.5 µg/kg/min after intubation and continued at 0.25 µg/kg/min.

Mechanical ventilation settings were adjusted to maintain an end-tidal carbon dioxide ($EtCO_2$) value of 35-40 mmHg. To prevent hypothermia, patients were warmed intraoperatively using air-warming systems (Bair Hugger Warming System, Augustine Medical, Eden Prairie, MN, USA), with body temperature monitored via an oral temperature probe. Balanced electrolyte solutions were administered for intravenous fluid maintenance, with additional boluses of colloids [Gelofusine 4%, Braun, Sheffield, UK; Hydroxyethyl Starch (Voluven) 6%, 130/0.4, Fresenius, Bad Hamburg, Germany] given as needed. In cases of persistent hypotension despite adequate fluid replacement, intravenous vasopressors or inotropes, such as norepinephrine (0.02-0.2 µg/kg/min) or dopamine (5-10 µg/kg/min), were administered.

Data Collection and Variables

Demographic data, including age, sex, body weight, and the American Society of Anesthesiologists physical status classification, were documented for all patients. Vital parameters such as mean arterial pressure, heart rate, SpO_2, body temperature, $EtCO_2$, and central venous pressure were monitored and recorded. Blood gas analyses included measurements of lactate, pH, base excess, bicarbonate (HCO_3), sodium, potassium, and glucose. Arterial blood gas samples were analysed hourly using the Radiometer ABL800 Flex (Radiometer, Copenhagen, Denmark).

Intraoperative data collected included blood loss, blood transfusions, crystalloid and colloid administration, surgical and anaesthetic durations, and urine output. Preoperative and postoperative Hb, platelet count, creatinine, and international normalized ratio (INR) levels were documented for both groups. Postoperative parameters included 24-hour chest tube drainage volume, total drainage amount, drain removal time, ICU length of stay, and total hospital stay. Blood transfusions in the ward were also recorded.

Transfusion management aimed to maintain Hb levels >9 g/dL, guided by blood gas analyses and the European Society of Anaesthesiology recommendations for intraoperative bleeding management.

Outcomes

The outcomes of this study include 1) postoperative complications; 2) need for perioperative or postoperative blood or blood product transfusions; 3) ICU length of stay; and 4) hospital length of stay.

Statistical Analysis

Numerical data were summarised as mean ± standard deviation for normally distributed variables or as median and interquartile range for non-normally distributed variables. Group comparisons for normally distributed numerical data were conducted using the Student's t-test, while the Mann-Whitney U test was used for skewed data. Categorical data were presented as frequencies and percentages, with hypotheses tested using Pearson's chi-squared test or Fisher's exact test as appropriate. We reported exact p-values, with p-values <0.05 considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 22.

RESULTS

Table 1 outlines the demographic characteristics of the study participants. A total of 104 patients were included, with 29 patients having preoperative anaemia (Group A) and 75 patients presenting with normal Hb levels (Group B). Both groups predominantly comprised male patients. The mean age of participants was higher in Group A than in Group B (60.5±11.7 years vs. 52.7±16.6 years). The durations of surgery and anaesthesia were comparable between the two groups. Most patients underwent lobectomy (n=50); other procedures included wedge resection (n=32), pleurectomy for mesothelioma (n=12), thymectomy (n=3), pneumonectomy (n=2), tracheal resection (n=2), thymic cystectomy (n=1), chest wall tumour resection (n=1), and oesophageal resection (n=1).

Table 1. Demographic characteristics of the participants

Variable	Level	Group A (n=29)	Group B (n=75)	p-value
Sex, n (%)	Female	9 (31%)	21 (28%)	0.948
	Male	20 (69%)	54 (72%)	
Age (years)		60.5±11.7 (64)	52.7±16.6 (58)	0.031
BMI (kg/m^2)		27.7±5.5 (26.4)	27.8±5.2 (26.7)	0.786
ASA physical status, n (%)	ASA 1	1 (3%)	6 (8%)	0.269
	ASA 2	24 (83%)	65 (87%)	
	ASA 3	4 (14%)	4 (5%)	
Anaesthesia duration (min)		258.1±89.2 (240)	249.3±95.8 (225)	0.506
Surgery duration (min)		210±81.1 (185)	201.7±88.6 (180)	0.450

Values are given as mean ± standard deviation (median), BMI: Body mass index, ASA: American Society of Anesthesiologists.

Table 2 highlights the preoperative and postoperative laboratory values. Preoperative and postoperative creatinine and INR levels were comparable between the two groups. Platelet counts were consistently higher in Group A than in Group B. A postoperative drop in Hb levels was observed in both groups, with Group A experiencing a mean reduction of 1.9 g/dL compared to 2.3 g/dL in Group B.

Table 3 summarises the observed study outcomes. Complications were significantly more frequent in Group A (31%) than in Group B (8%) (p=0.005). Among these, seven patients developed pneumonia, three required re-exploration, two experienced subcutaneous emphysema, and one patient each experienced prolonged chest tube drainage, a prolonged air leak, or death after discharge. The only death observed in this study occurred in Group A. Among the pneumonia cases, one patient also developed a pulmonary embolism and another developed critical myopathy, both of whom were in Group A.

Mean intraoperative blood loss was higher in Group A than in Group B (435.2±331.6 mL vs. 343.2±513 mL; p=0.008). Patients in Group A exhibited higher chest tube drainage volumes both at 24 hours and in total, as well as longer chest tube durations (Table 3). Although the ICU length of stay was similar between the groups, Group A patients had significantly longer hospital stays than Group B patients (9.6±5.5 days vs. 7.7±4.7 days, respectively; p=0.014).

Table 2. Preoperative and postoperative laboratory values

Variable	Group A (n=29)	Group B (n=75)	p-value
Preoperative Hb (g/dL)	11.4±0.9	14.4±1.2	0.001
Preoperative platelet (x10^3)	318±101 (325)	246±78 (236)	0.001
Preoperative creatinine (mg/dL)	0.96±0.44 (0.99)	0.87±0.18 (0.88)	0.398
Preoperative INR	1.09±0.51 (1.04)	0.97±0.19 (1)	0.251
Postoperative Hb (g/dL)	9.5±1.3	12.1±1.8	0.001
Postoperative platelet (x10^3)	349±166 (329)	252±108 (222)	0.002
Postoperative creatinine (mg/dL)	0.85±0.44 (0.72)	0.75±0.25 (0.72)	0.619
Postoperative INR	1.13±0.2 (1.12)	1.09±0.1 (1.09)	0.030

Values are presented as mean ± standard deviation (median), Hb: Haemoglobin, INR: International normalised ratio.

Table 4 provides data on perioperative and postoperative blood and blood product transfusions. A significantly higher proportion of patients in Group A received perioperative crystalloids than in Group B. While perioperative packed red blood cell (pRBC) and fresh frozen plasma use was similar in both groups, postoperative pRBC transfusion requirements on the ward were higher in Group A (0.86±1.46 mL) than in Group B (0.13±0.48 mL). Table 5 summarises the distribution of postoperative complications by group.

DISCUSSION

This study examined the association between preoperative anaemia and adverse outcomes in patients undergoing thoracic surgery. Patients with preoperative anaemia (Group A) demonstrated significantly higher volumes and longer durations of chest tube drainage, increased intraoperative bleeding, greater perioperative crystalloid fluid administration, and higher postoperative pRBC transfusion requirements in the ward compared to those without anaemia (Group B). Furthermore, the hospital length of stay was notably longer in Group A.

The complication rate was notably higher in Group A (31%) than in Group B (8%) (p=0.005). This aligns with existing literature, in which preoperative anaemia has been associated with increased postoperative complications, particularly in cardiac surgery patients (2,9,10). Alan et al. (1) observed that severe anaemia increased 30-day complication rates, such as acute kidney injury and surgical-site infections, among cranial surgery patients. Similarly, Janssen et al. (6) reported that blood transfusion significantly increased the risk of surgical site infections, urinary tract infections, and pneumonia in patients undergoing lumbar spine surgery.

Our study also observed that the mean age of patients in Group A was higher than that in Group B, suggesting that age-related comorbidities may contribute to the higher incidence of anaemia. This is consistent with findings of Ranucci et al. (11), who noted an association between advanced age and postoperative complications among anaemic patients undergoing cardiac surgery. In contrast, Musallam et al. (9) reported that age and sex did not influence postoperative complications among anaemic patients. The EuroSCORE (12), the European System for Cardiac Operative Risk Evaluation, is a universal risk-scoring system that does not currently include preoperative anaemia as a risk factor. However, based on our findings, we propose that preoperative anaemia should be considered a significant risk factor in such scoring systems to improve patient preparation and risk assessment.

According to the cell-based coagulation model, platelets play a crucial role in the formation of the clot core during the initial phase of haemostasis. An increased platelet count is generally considered protective, reducing the risk of uncontrolled bleeding from vascular injury during surgery. In our study, despite a higher platelet count in the preoperative anaemia group (Group A), both intraoperative bleeding and postoperative drainage were

Table 3. Summary of study outcomes between groups

Variable	Group A (n=29)	Group B (n=75)	p-value
Postoperative complications, n (%)	9 (31%)	6 (8%)	0.005
Intraoperative bleeding (mL)	435.2±331.6 (350)	343.2±513 (200)	0.008
Perioperative urine output (mL)	393.1±249.9 (320)	347.1±277.1 (250)	0.241
24-hour chest tube drainage (mL)	361±163.3 (350)	322±207.5 (300)	0.113
Total chest tube drainage (mL)	1276±522 (1300)	979±520 (900)	0.001
Chest tube duration (days)	7±3.2 (6)	5.5±3.6 (5)	0.006
ICU stay (days)	0.21±0.41 (0)	0.31±1.15 (0)	0.546
Hospital stay (days)	9.6±5.5 (8)	7.7±4.7 (7)	0.014

Values are given as mean ± standard deviation (median), ICU: Intensive care unit.

Table 4. Perioperative and postoperative blood and blood product transfusions

Variable	Group A (n=29)	Group B (n=75)	p-value
Perioperative crystalloid use (mL)	1538±506 (1500)	1357±648 (1200)	0.018
Perioperative colloid use (mL)	378±383 (500)	337±399 (100)	0.485
Perioperative FFP use (mL)	0.1±0.56 (0)	0.07±0.38 (0)	0.904
Perioperative pRBC use (mL)	0.1±0.41 (0)	0.12±0.84 (0)	0.341
Postoperative FFP use (mL)	0.03±0.19 (0)	0.07±0.38 (0)	0.674
Postoperative pRBC use (mL)	0.86±1.46 (0)	0.13±0.48 (0)	0.001

Values are given as mean ± standard deviation (median), FFP: Fresh frozen plasma, pRBC: Packed red blood cell.

Table 5. Distribution of postoperative complications by group		
Complication	**Group A (anaemia, n=29)**	**Group B (non-anaemia, n=75)**
Pneumonia, n	4	3
Re-exploration for bleeding, n	1	2
Subcutaneous emphysema, n	1	1
Prolonged chest tube drainage, n	1	0
Prolonged air leak, n	1	0
Pulmonary embolism, n	1	0
Critical myopathy, n	1	0
Mortality, n	1	0

significantly greater in this group. This finding may be explained by the lateral migration theory (13). According to this theory, during bleeding, erythrocytes migrate to the centre of blood vessels, pushing other cells such as leucocytes and platelets towards the blood vessel walls. In patients with anaemia, the reduced number of erythrocytes may impair this hydrodynamic interaction, preventing platelets from effectively reaching the vessel wall and forming clots. This mechanism may explain the increased bleeding observed in Group A, despite higher platelet counts. In the anaemia group, a higher proportion of complex surgical procedures was observed; this may have contributed to increased intraoperative bleeding. Furthermore, most thoracic surgical interventions in our cohort were performed for malignant disease. Malignancy-related inflammatory changes, including elevated platelet counts, are well known to predispose to both thromboembolic events and bleeding complications. These factors should therefore be considered when interpreting the association between preoperative anaemia and perioperative bleeding observed in our study.

Preoperative anaemia was also linked to prolonged hospital stays, consistent with Muñoz et al. (14), who found that preoperative anaemia in colectomy patients increased length of stay and worsened postoperative outcomes. Wu et al. (10) reported higher mortality rates and cardiac complications in patients with low preoperative haematocrit levels undergoing non-cardiac surgery. Similarly, Kılıç et al. (15) reported that preoperative anaemia was a prognostic marker in patients undergoing pneumonectomy for non-small-cell lung cancer and associated with adverse postoperative outcomes. Based on these findings, we hypothesise that preoperative anaemia contributes to prolonged chest tube duration and hospitalisation.

Our data reveal a smaller drop in Hb levels in the anaemia group (Group A). A possible explanation for this finding is that patients in the anaemia group had lower baseline Hb values; therefore, the absolute perioperative decline in Hb was numerically smaller, despite similar transfusion rates and greater intraoperative blood loss. Moreover, perioperative fluid administration and haemodilution might have contributed to different extents across groups, potentially masking the true extent of blood loss as measured by decreases in Hb concentration. Although intraoperative blood loss was higher in the anaemia group, similar transfusion rates between groups may have partially compensated for the decline in haemoglobin. Additionally, low baseline Hb levels in Group A could have led to a smaller relative reduction compared with Group B, where patients started from higher baseline levels.

Study Limitations

Our study has several important limitations that merit acknowledgement. First, the anaemia group had a significantly higher mean age than that of the non-anaemia group (60.5±11.7 vs. 52.7±16.6 years). Advanced age is independently associated with both the comorbidity burden and postoperative complications, and may therefore confound the observed relationship between preoperative anaemia and adverse outcomes. Future larger multicentre studies with prospectively collected comorbidity and frailty indices are warranted to confirm the independent effect of preoperative anaemia on postoperative complications and to determine whether targeted preoperative anaemia management modifies this risk.

Chest tube duration is influenced by multiple factors, particularly the underlying lung parenchymal status and the type of surgical procedure. In our study, the limited number of events did not allow for a robust multivariate analysis to adjust for these variables; therefore, our observation regarding the association between preoperative anaemia and longer chest tube duration should be interpreted as exploratory rather than definitive.

CONCLUSION

This study highlights the significant impact of preoperative anaemia on patients undergoing thoracic surgery. Preoperative anaemia was associated with increased intraoperative bleeding, greater volume and longer duration of chest tube drainage, increased postoperative pRBC transfusion requirements, and longer hospital stays. Moreover, the complication rate was markedly higher among anaemic patients. These findings emphasise the need for thorough preoperative evaluation and optimisation of anaemia to improve surgical outcomes. Additionally, integrating preoperative anaemia as a risk factor in scoring systems may enhance patient risk stratification and perioperative planning. Future research should address the limitations of this study to validate and expand upon our results.

Ethics

Ethics Committee Approval: This study received approval from the Marmara University Clinical Research Ethics Committee (decision number 09.2018.137, dated 2 February 2018). The study was registered in the ANZCTR Clinical Trials Registry (ACTRN12619000043134).

Informed Consent: Written informed consent was obtained from all included participants.

Footnotes

Author Contributions

Concept A.S., G.Ç., E.Y., K.Ç.Y., B.Y., M.Y., Z.A.; Design - A.S., G.Ç., E.Y., K.Ç.Y., B.Y., M.Y., Z.A.; Data Collection or Processing - A.S., G.Ç., B.Y., M.Y., Z.A; Analysis or Interpretation - A.S., G.Ç., B.M.A.; Literature Search - B.M.A., E.Y., K.Ç.Y.; Writing - A.S., G.Ç., B.M.A., E.Y., K.Ç.Y., B.Y., M.Y., Z.A.

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ORIGINAL ARTICLE
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Effectiveness of prophylactic single-dose IV antibiotic versus postoperative multi-dose oral antibiotic regimen for preventing surgical site infections: A prospective comparative study

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ABSTRACT

Objective: Surgical site infections (SSIs) are among the most common postoperative complications, contributing to morbidity, prolonged hospital stays, and healthcare costs. Prophylactic antibiotics are widely used, but the optimal regimen for clean elective surgeries remains debated.

Material and Methods: A hospital-based analytical cross-sectional study was conducted over a six-month period (March-August 2025) in the department of general surgery of a tertiary-care teaching hospital. Ninety-four consecutive patients undergoing clean elective surgeries were enrolled and allocated to two groups: Group A (n=52) received a single intravenous (IV) dose of cefotaxime 30 minutes prior to incision, and Group B (n=42) received postoperative multidose oral antibiotics according to institutional protocol. Baseline demographic and clinical data were recorded, and patients were monitored for signs of SSI, including fever, tachycardia, redness, and wound discharge.

Results: The mean age of Group A participants was 28.3±5.9 years compared to 36.4±7.3 years in Group B (p=0.042), though other socio-demographic variables were comparable. The overall incidence of SSI signs was low in both groups. Fever occurred in 13.4% of Group A and 14.2% of Group B; tachycardia occurred in 9.6% and 7.1%; redness in 1.9% and 7.1%; and wound discharge in 3.8% and 2.3% in Groups A and B, respectively; none of these differences were statistically significant (p>0.05 for all).

Conclusion: Single-dose IV prophylaxis was as effective as postoperative multi-dose oral antibiotics in preventing SSIs in clean elective surgeries. Short-course prophylaxis is sufficient in this setting and supports rational antibiotic stewardship.

Keywords: Surgical site infection, prophylaxis, intravenous antibiotics, oral antibiotics, elective surgery, antimicrobial stewardship

INTRODUCTION

Surgical site infections (SSIs) represent the third most frequently reported hospital-acquired infection and considerably affect patient outcomes by causing complications that hinder recovery and diminish quality of life. They also impose a substantial clinical and financial strain on healthcare systems (1,2). SSIs are described as infections involving the surgical wound or deeper tissues occurring within 30 days of the procedure, or up to one year if an implant is used (3). According to the World Health Organization, they are characterized by purulent discharge, local cellulitis, or infection at a drain insertion site (4). Globally, around 160,000-300,000 SSIs are documented annually, many of which require re-operations, prolong hospital stay, delay wound healing, and negatively influence cosmetic outcomes (5-7).

While most SSIs remain limited to superficial tissues, some can progress to severe necrotizing infections. Common clinical features include pain, redness, swelling, local warmth, and discharge of pus (8). These infections substantially increase healthcare costs and length of hospitalization (9-11). Patients who develop SSIs have over a 60% higher likelihood of requiring intensive care unit admission, are 15 times more likely to be readmitted within 30 days, and typically have an additional hospital stay of 6.5 days, with an average direct cost of about $3000 per episode (12). Methicillin-resistant *Staphylococcus aureus*-related SSIs are associated with higher morbidity and mortality compared to methicillin-sensitive strains (13).

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The use of prophylactic antibiotics has significantly reduced SSI rates in the last two decades. Ensuring adequate drug concentrations in tissues above the minimum inhibitory level during surgery is crucial to reinforce host defences (12,13). Consequently, perioperative prophylaxis, in conjunction with strict aseptic measures, has become a standard preventive practice in major surgeries (13).

The effectiveness of antibiotic prophylaxis largely depends on its timing. Classen et al. reported that infection risk was minimal when prophylaxis was administered within two hours before incision, whereas the TRAPE trial suggested the most effective window was within 30 minutes for cephalosporins and one hour for vancomycin or fluoroquinolones (14,15). Administration after incision is linked to a significantly higher risk of infection. Given that perioperative prophylaxis accounts for a substantial proportion of hospital antibiotic usage (16), this study focuses on evaluating the effectiveness of single-dose antibiotic prophylaxis in elective surgeries, specifically when administered 30 minutes before incision, in clean and clean-contaminated cases.

Aim & Objectives

Aim: The study aims to evaluate the role of prophylactic antibiotics to prevent SSIs in clean and elective surgeries

Objectives: 1. To study the effectiveness of intravenous (IV) single dose pre-operative prophylactic antibiotic vs. multiple postoperative oral doses of antibiotics in preventing SSI. 2. To compare the SSIs in both groups of patients.

MATERIAL and METHODS

Study Design

This investigation was a hospital-based prospective comparative study.

Study Population

The participants comprised patients admitted through the outpatient and inpatient departments and scheduled for minor surgical procedures. The study population included all individuals undergoing elective clean and clean-contaminated surgeries in the department of general surgery during the specified period.

Study setting: The research was conducted in the department of surgery of a tertiary care teaching hospital.

Study period: The study was conducted from March 2025 to August 2025 (six months).

Inclusion Criteria

i) Patients undergoing clean or clean-contaminated surgeries at the study site during the study period.
ii) Patients who provided written informed consent for participation.

Exclusion Criteria

i) Patients unwilling or unable to provide informed consent.
ii) Patients undergoing contaminated procedures where wound exposure to blood, body fluids, or bowel contents occurred.
iii) Patients with comorbidities that could independently influence SSI occurrence, such as uncontrolled diabetes, malnutrition, or anemia.
iv) Patients undergoing emergency surgical interventions.

Sample Size

The sample size was estimated using OpenEpi software (version 3). A prior study by Srivastav et al. (17) reported a 5.2% SSI rate. With approximately 1000 surgeries performed annually at the study hospital and considering an absolute precision of 5%, the required sample size was calculated to be 76. However, during the six-month study period, 94 eligible cases were available and included (17).

Ethical

Approval for the study was obtained from the Institutional Ethics Committee of NKP Salve Institute of Medical Sciences & Research Center, and Lata Mangeshkar Hospital (date: 27.03.2025, registration number: ECR/88/Inst/MH/2013/RR-24). Written informed consent was obtained from all participants.

Data

Collection: Eligible patients undergoing clean and clean-contaminated surgeries were enrolled. Socio-demographic variables such as age, sex, place of residence, educational level, and socio-economic background were collected using a pretested questionnaire. Patients were allocated into two groups:

- **Group A** (study group) received 1 g IV cefotaxime 30 minutes prior to skin incision.
- **Group B** (control group) did not receive prophylactic preoperative antibiotics but received postoperative antibiotics according to institutional guidelines. They were given oral cefixime 200 mg BD for five days.

All surgical procedures were performed under uniform aseptic precautions to reduce bias. Cases from both groups were followed up in the outpatient department after 30 days; those who did not attend (6 cases from group A and 2 cases from group B) were contacted by telephone to inquire about any signs or symptoms of SSI.

Clinical

Assessment: Data regarding type and duration of surgery, wound classification, presence of drains, comorbidities, and duration of hospital stay were recorded. Patients were monitored for manifestations of postoperative SSI, including fever, erythema, induration, stitch abscess, wound discharge, granuloma, and

wound dehiscence. In suspected cases, complete blood counts and pus cultures with antimicrobial sensitivity testing were performed. Wound swabs from infected cases were processed using standard microbiological techniques, as per institutional protocols, for both study groups (18).

The SSIs were defined in accordance with the CDC criteria for superficial SSIs, that included infection occurring within 30 days after the operation involving only skin or subcutaneous tissue of the incision and at least one of the following: i) purulent drainage, with or without laboratory confirmation, from the superficial incision ii) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision. iii) at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is deliberately opened by surgeon, unless incision is culture-negative and iv) diagnosis of superficial incisional SSI by the surgeon (19).

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using SPSS version 25. Descriptive statistics such as mean, standard deviation, frequencies, and percentages were calculated for baseline variables. The incidence of SSI in the two groups was compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were analyzed using Student's t-test or Mann-Whitney U test, depending on the data distribution. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 94 consecutive patients undergoing clean elective surgeries were included in the study. Of these patients, two groups were formed based on the antibiotic regimen received: One received a single prophylactic IV dose preoperatively, while the other received multiple postoperative oral doses. The baseline demographic and clinical characteristics, such as age, sex, and type of surgery, were comparable between the two groups, ensuring homogeneity for analysis.

The incidence of SSIs was systematically recorded and compared between the two groups. The outcomes were evaluated in terms of the proportion of patients who developed SSI, the time to onset of infection, and the severity of infection, if any.

A total of 94 patients undergoing clean-contaminated elective surgeries were included in the study: 52 in Group A (single-dose IV antibiotic) and 42 in Group B (postoperative multi-dose oral antibiotic). The baseline characteristics of the participants are summarized in Table 1.

The mean age of participants in Group A was 28.3±5.9 years, while in Group B it was 36.4±7.3 years, and this difference was statistically significant (p=0.042). However, when participants were stratified into age groups, no significant difference was observed between the two age groups (p=0.9297). The gender distribution was comparable, with males constituting 57.6% in Group A and 52.0% in Group B (p=0.5154). Similarly, residence (urban vs. rural) and socio-economic status, assessed using the Modified B.G. Prasad scale, did not differ significantly between groups ($p>0.05$). These findings indicate that the groups were generally comparable at baseline, except that Group B had a marginally higher mean age.

The clinical diagnoses of participants are shown in Figure 1. In group A, breast lump accounted for 40.0% of cases, whereas in group B, lipoma predominated, accounting for 36.2% of cases. Both groups were comparable in terms of surgical indications and operative procedures, thereby minimizing the likelihood of confounding due to the type of surgery performed. The occurrence of SSI signs in both groups is presented in Table 2. Fever was observed in 13.4% of patients in Group A and 14.2% in Group B (p=0.908). Tachycardia was present in 9.6% of participants in Group A and in 7.1% of participants in Group B (p=0.669). Redness at the suture line was noted in 1.9% of Group A patients and 7.1% of Group B patients, though this difference was not statistically significant (p=0.213). Wound discharge was observed in 3.8% of Group A, compared with 2.3% of Group B (p=0.687).

Overall, no statistically significant difference was found in the incidence of SSI-related signs between the single-dose IV antibiotic group and the multi-dose oral antibiotic group. The rates of fever, tachycardia, wound discharge, and local redness were low and comparable in both groups, suggesting that prophylactic single-dose IV antibiotics were as effective as postoperative multi-dose oral regimens in preventing SSIs.

The findings of this study indicate that both regimens—single-dose IV prophylaxis and postoperative oral multi-dose antibiotics—were effective in preventing SSIs in clean, elective surgeries, with no significant difference in infection-related outcomes between the two groups. Importantly, the low overall incidence of SSI highlights the adequacy of short-course prophylaxis, supporting antibiotic stewardship by reducing unnecessary exposure to prolonged postoperative antibiotics.

DISCUSSION

In this prospective comparative study of 94 patients undergoing clean elective operations, we found no statistically significant difference in SSI indicators between patients who received a single prophylactic IV antibiotic dose and those who received a postoperative multi-dose oral antibiotic course. Comparable frequencies of fever, tachycardia, erythema, and wound discharge in both groups suggest no statistically significant difference between single-dose prophylaxis and multi-dose regimens for clean surgical procedures.

Table 1. Baseline characteristics of the study participants (n=94)				
Socio-demographic variables	**Group A (n=52) n (%)**	**Group B (n=42) n (%)**	**Statistic**	**p-value**
Age (in years)				
Mean age ± SD	28.3±5.9	36.4±7.3	t=-2.492	0.042
Range	21-56	24-73		
Age groups				
≤30	7 (13.6)	5 (12.0)	Fischer's Exact test	0.9297
31-40	16 (30.8)	11 (26.1)		
41-50	20 (38.5)	16 (38.0)		
51-60	3 (5.7)	5 (12.0)		
61-70	4 (7.6)	3 (7.1)		
>70	2 (3.8)	2 (4.8)		
Gender				
Male	30 (57.6)	27 (52.0)	Chi-square =0.432	0.5154
Female	22 (42.4)	15 (48.0)		
Place of residence				
Urban	39 (75.0)	33 (78.5)	Chi-square =0.165	0.6843
Rural	13 (25.0)	9 (21.5)		
Socio-economic status*				
Class I (upper)	3 (5.7)	1 (2.4)	Chi-square =5.415	0.2473
Class II (upper-middle)	7 (13.5)	12 (28.6)		
Class III (middle)	15 (28.8)	9 (21.5)		
Class IV (lower-middle)	17 (32.7)	16 (38.0)		
Class V (lower)	10 (19.3)	4 (9.5)		
*: Modified B.G. Prasad scale was used to assess the socio-economic status, SD: Standard deviation.				

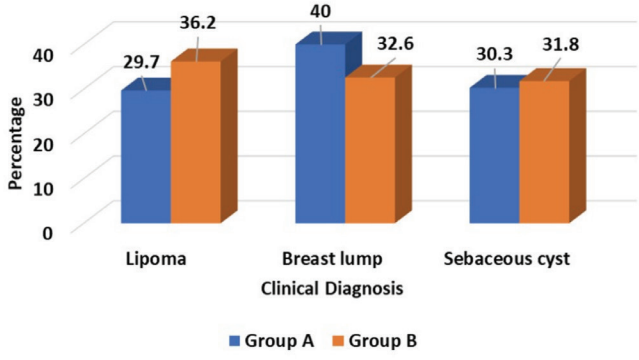

Figure 1. Distribution of the cases according to clinical diagnosis (n=94).

Table 2. Signs of SSI in both groups (n=94)			
Signs of SSI	**Group A**	**Group B**	**p-value**
Fever - Yes	7 (13.4)	6 (14.2)	0.908
Fever - No	45 (86.6)	36 (85.8)	
Tachycardia - Yes	5 (9.6)	3 (7.1)	0.669
Tachycardia - No	47 (90.4)	39 (92.9)	
Redness on the suture line - Yes	1 (1.9)	3 (7.1)	0.213
Redness on the suture line - No	51 (98.1)	39 (92.9)	
Wound discharge - Yes	2 (3.8)	1 (2.3)	0.687
Wound discharge - No	50 (96.2)	41 (97.7)	
SSI: Surgical site infection.			

The mean age difference between the two groups was statistically significant (p=0.042). Group A had a lower mean age (28.3±5.9 years) compared to Group B (36.4±7.3 years). Although the categorical distribution of age groups did not show a significant difference (p=0.9297), the difference in mean age could still be clinically relevant, as age is a potential confounding factor influencing wound healing and susceptibility to infection. Older patients generally have slower tissue repair and may be at higher risk of SSIs due to comorbidities or a reduced immune response. The age disparity between groups should be considered when interpreting the results; statistical adjustments or stratified analyses may be necessary to isolate the true effect of the antibiotic regimen on SSI rates.

Our results are consistent with several recent investigations and systematic reviews that have reported no added benefit of prolonged antibiotic courses over a single perioperative dose in lowering SSI risk (20). A comparative study in general and clean-contaminated surgeries also observed no significant advantage of multi-dose therapy, emphasizing that optimal aseptic techniques may suffice without extended dosing (21). Similarly, a randomized trial in implant-based breast reconstruction found that additional doses did not reduce infection rates but increased adverse reactions, underscoring an unfavorable risk-benefit profile (22). Reviews of gastrointestinal surgery outcomes likewise concluded that single-dose prophylaxis is as effective as longer regimens, discouraging routine extended use (23). These findings collectively indicate that with robust asepsis and perioperative practices, extended prophylaxis offers minimal additional value (23). The findings of this study align with the WHO (2018) and CDC (2017) Surgical Site Infection Prevention Guidelines, both of which emphasize that prophylactic antibiotics should be administered as a single pre-operative dose and not continued postoperatively in clean surgeries. Prolonged or unnecessary antibiotic use offers no additional protection against SSIs and instead contributes to antimicrobial resistance, adverse drug effects, and increased healthcare costs. Therefore, minimizing the duration of antibiotic prophylaxis, as demonstrated in this study, supports key antimicrobial stewardship principles aimed at optimizing patient outcomes while reducing the emergence of resistant organisms (19,24).

Nevertheless, evidence from certain surgical subspecialties cautions against universal application of single-dose protocols. Tamayo et al. (25). reported higher SSI rates with a single cefazolin dose compared to a 24-hour regimen in cardiac surgery. However, the infection risk in cardiac operations—owing to cardiopulmonary bypass, prosthetic grafts, and longer wound exposure—is not directly comparable to clean soft-tissue surgeries. In orthopedic trauma, Slobogean et al. (26) noted SSI rates of 2.5% with single-dose prophylaxis versus 2.0% with multiple doses, a non-significant difference, further supporting shorter regimens in that context. Thus, the antibiotic strategy should remain tailored to the procedure type and the associated risk conditions.

A notable strength of this study is the relatively uniform patient cohort, limited to clean elective surgeries, minimizing confounding factors such as emergency settings or risk of contamination. Baseline demographics, including sex, residence, and socio-economic status, were evenly distributed, and despite minor differences in mean age, stratified analysis confirmed no significant imbalance. Moreover, focusing on direct SSI-related signs (fever, tachycardia, redness, discharge) ensured clinically meaningful outcomes instead of relying on surrogate measures.

From practical and stewardship perspectives, our findings support the use of single-dose IV prophylaxis for clean elective surgeries performed under optimal sterile conditions. This approach reduces unnecessary antibiotic exposure adverse drug effects antimicrobial resistance pressure, and treatment costs. Nonetheless, clinical decisions should incorporate procedure complexity, comorbidity profiles (such as diabetes or immunosuppression), and institutional SSI trends.

Study Limitations

The study is limited by the absence of microbiological data, heterogeneity of surgical procedures that could influence SSI rates, and a small, non-randomized sample size, which may affect the generalizability and validity of the findings.

CONCLUSION

The present study adds to the growing body of evidence that single-dose antibiotic prophylaxis is both safe and effective in clean elective surgical procedures. Larger multicenter randomized trials with microbiological confirmation and longer follow-up are needed to identify situations where extended prophylaxis might still be warranted.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Institutional Ethics Committee of NKP Salve Institute of Medical Sciences & Research Center, and Lata Mangeshkar Hospital (date: 27.03.2025, registration number: ECR/88/Inst/MH/2013/RR-24).

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

Footnotes

Author Contributions

Surgical and Medical Practices - V.P.P.; Concept - V.P.P.; Design - V.P.P., G.D.; Data Collection or Processing - V.P.P., G.D., P.B., A.H., V.Y., N.V.; Analysis or Interpretation - V.P.P., G.D., P.B., A.H., V.Y.; Literature Search - V.P.P., G.D., P.B., A.H., V.Y., N.V.; Writing - V.P.P., G.D., P.B., A.H., V.Y., N.V.

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

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ORIGINAL ARTICLE
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Neuroblastoma treatment in children: Single-center case series and review of the literature

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ABSTRACT

Objective: Description of the clinical presentation and tumor behavior, its general and pathological characteristics, diagnostic and therapeutic approaches, as well as treatment outcomes in children with neuroblastoma (NB) at a single-center. Special focus was placed on the duration of the diagnostic process and the correlation between disease stage, presence of metastases, and treatment outcomes. Given the small cohort, this report is presented as a descriptive case series complemented by a focused review of the literature NB.

Material and Methods: A retrospective study was conducted for the time period from January 1st, 2010, to December 31st, 2024. The study included 13 patients (7 males, 6 females; median age: 44 months; range, 0-114) diagnosed with NB who underwent surgery and were hospitalized at the Department of Pediatric Surgery, Clinical Center of the University of Sarajevo. Demographic, clinical, biochemical, radiological, and treatment data were extracted from medical records. A narrative review of major published NB cohorts was conducted to compare our observations with existing evidence.

Results: The median age at diagnosis was 44 months. The largest number of patients were in the age group of 2-4 years, and most presented with stage four disease (according to International Neuroblastoma Staging System classification). The tumor was located in the adrenal gland in 92.3% of cases. The median survival time was 36 months. Patients had elevated serum neuron-specific enolase, urinary vanillylmandelic acid, as well as blood ferritin and lactate dehydrogenase levels. The most common symptoms were loss of appetite, presence of a palpable mass, and abdominal pain. Metastases were present in 76.9% of patients, and stage four was associated with aggressive metastatic dissemination. A multimodal approach was used in treatment. The median time from symptom onset to primary care physician consultation was 12 days, and the median time from physician consultation to diagnosis was 14 days. Relapse occurred in 46.2% of cases, most frequently in patients with stage four disease. A total of 7 patients (46.2%) survived.

Conclusion: Advanced-stage disease at diagnosis, metastatic burden, and unfavorable outcomes, are dominating factors in our single-center experience. When compared with larger published cohorts, our findings align with global patterns. Due to inherent sample size limitations, these observations are hypothesis-generating and the need for larger, multicenter studies remains.

Keywords: Neuroblastoma, child, neoplasm staging, neoplasm metastasis, combined modality therapy

INTRODUCTION

Neuroblastoma (NB) is the most common malignant extracranial tumor in children, whose embryogenic origin rises from progenitor neural crest cells (1,2). That implies that it can develop anywhere in the sympathetic nervous system, but most commonly it is located in the adrenal gland. On this ground, and its high rate of spontaneous regression, the tumor exhibits specific behaviour, clinical characteristics, and prognostic parameters (1).

NB accounts for around 7% of all childhood cancers and about 15% of childhood cancer mortality worldwide. The median age at diagnosis is 17-18 months, and around 90% of cases occur in children younger than 5 years (3). NB can develop sporadically or be inhibited, where cases of inhibited NB are much rarer (1-4). Dysregulation of key oncogenes, important for tumor growth initiation and progression, is noted in its development (5). Sporadical cases of NB are connected to mutations in important regulatory genes, such as *ALK* or *PHOX2B* (4,6). The most important molecular anomaly found is MYCN oncogene amplification (1,6,7).

The histological classification, distinguishes the following types: NB (Schwannian stroma-poor), ganglioneuroblastoma, intermixed (Schwannian stroma-rich), ganglioneuroblastoma, nodular (with both stroma-rich and stroma-poor areas), and ganglioneuroma (Schwannian stroma-dominant) (8,9).

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Clinical presentation is diverse, due to differences in localisation and stage at the diagnosis (10). NB is most often found in the area of the adrenal gland, but may also appear in retroperitoneal space, mediastinum, spine, or pelvis (1). Metastases are present in up to 70% of patients at diagnosis, and most commonly include bone, bone marrow, liver, and skin (11,12).

Because of the origin of NB, several significant biochemical parameters can be identified. Characteristically, elevated levels of catecholamines and their metabolites -vanillylmandelic acid (VMA) and homovanillic acid- are found in serum and urine, along with increased levels of lactate dehydrogenase (LDH), ferritin, and serum neuron-specific enolase (NSE) (13). Most valuable diagnostic modalities include computed tomography and magnetic resonance (1). The diagnostic criteria for NB include either a positive histopathological finding, or the demonstration of bone marrow metastases in the presence of elevated catecholamine or metabolite levels in urine or serum (14). Advanced disease at presentation is the main factor leading to unfavorable outcomes (15). Prognosis depends on several factors, including age, stage, pathohistology, molecular features such as presence of MYCN amplification, but also genetic anomalies and biological markers (10,16,17). Most used classification system is the International Neuroblastoma Staging System (INSS), where NB is divided into Stages 1-4, with special stage marked as 4s, reserved for infants younger than 1 year (14,18).

Various therapeutic modalities are available for NB, due to the heterogeneity of this disease in terms of its forms and stages. The treatment approach may include different combinations of the following options: Surgical resection, chemotherapy, radiotherapy, and immunotherapy. Prior to initiating any therapeutic intervention, prognostic factors are carefully evaluated (14,19-21).

Despite extensive global research, data from single centers in low and middle income regions still remain limited. Institutional experience often reflects unique diagnostic pathways, resource availability, and patient characteristics, that are not adequately represented in literature. This study is explicitly framed as a descriptive single-center case series, accompanied by a focused narrative review of the literature, due to the small cohort size. The findings should be interpreted within the broader context of major international NB studies. Because inferential statistics are not feasible with a cohort of this size, the results from our center should be considered hypothesis-generating and exploratory.

The aim of this study was to analyze the clinical presentation, pathological and biological features, diagnostic and therapeutic approaches, and treatment outcomes of children with NB treated at the Clinical Center of the University of Sarajevo. Special attention was given to diagnostic delay, disease stage, presence of metastases, and their association with survival. Main focus lies on defining patterns and objectives relevant for future multicenter work.

MATERIAL and METHODS

Study Design and Setting

This study is framed as a descriptive single-center case series with a focused narrative review of the literature. This clinical, retrospective study was conducted at the Clinic of Pediatric Surgery of the Clinical Center of the University of Sarajevo, covering the period from January 1, 2010 to December 31, 2024. The study included 13 patients (7 males, 6 females; median age: 44 months; range, 0-114) who were diagnosed with NB, who underwent surgery and were hospitalized at the Department of Pediatric Surgery, Clinical Center of the University of Sarajevo).

The data for the research were collected by reviewing the available medical documentation through the electronic database of the Clinical Center of the University of Sarajevo and the archives of the Clinic of Pediatric Surgery and Pediatric Clinic of the Clinical Center of the University of Sarajevo.

The study complied with the ethical principles of the Declaration of Helsinki and with all International Council for Harmonization and Good Clinical Practice Guidelines. The study was approved by the Local Institutional Review Board (Ethical Committee of the Clinical Center University of Sarajevo, protocol code: 51-45-1-6872/25, date: 24 February 2025).

The following features were reviewed: Gender, age at the time of diagnosis, history, clinical presentation, additional diagnoses, tumor localization and characteristics, diagnostic workup, time interval from symptoms appearance to physician checkup and from physician checkup to definite diagnosis, disease stage, presence and localization of metastases, immunohistopathological findings, treatment and surgical intervention performed, disease outcome, complications, and recurrence. The study was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, informed consent was waived.

Institutional Pathway for NB Management – Diagnostic, Staging, and Treatment Pathway

Patients diagnosed with NB were evaluated and treated according to an institutional protocol designed and alligned according to the International Neuroblastoma Risk Group (INRG) guidelines.

Diagnosis and staging: The diagnostic criteria for NB included either histopathological confirmation of the primary tumor with or without elevated catecholamine levels or metabolites in urine or serum, or evidence of bone marrow metastases in the presence of elevated urinary or serum catecholamines or their

metabolites. Initial assessment included clinical examination, routine laboratories, and measurement of tumor biomarkers (urinary VMA, serum neuron-specific enolase, LDH, and ferritin) where feasible. Local disease was assessed with ultrasonography followed by cross-sectional imaging (computed tomography or magnetic resonance imaging of chest/abdomen/pelvis). Metastatic staging was evaluated with I123-meta-iodobenylguanidine (MIBG) scintigraphy, with involvement of bone marrow assessed by flow cytometry. Obtained tumor tissue was analyzed for MYCN status (FISH) and ploidy (DNA index). Pretreatment staging used the INRG Staging System (INRGSS). The post-surgical staging using INSS was also recorded.

Risk stratification: The treatment-assigning risk groups were determined using the INRG classification, integrating age, histology, and tumor biology (MYCN, ploidy, genomic profile).

Therapeutic modalities: Surgery, chemotheraphy, MIBG Therapy, myeloablative therapy with ASCT, and immunotherapy were noted as treatment options. Timing for surgical treatment was risk-adapted. Primary resection was the ultimate goal for low-risk patients, however, for intermediate and high-risk groups, surgery followed neoadjuvant chemotherapy. Indications and regimens for all forms (both neoadjuvant and adjuvant) of chemotherapy were strictly protocol-defined regarding the INRG risk group. For MIBG therapy, patients were referred to other reference centers. Myeloablative therapy with ASCT was part of our high-risk protocol until approximately 2018-2019. Its reinstatement is planned for 2026. Immunotherapy (anti-GD2) was not administered in our center, and patients were referred externally.

Follow-up and relapse: Follow-up included clinical assessment, imaging studies, and laboratory monitoring according to institutional practice. Time-intervals varied individually, according to the patients risk-group. In reference to the International Neuroblastoma Response Criteria (INRC), relapse was defined as appearance of new site(s) of disease or progression of existing disease - defined as tumor size growth of >25% relative to the best documented response - after initial response (including partial ones) to the treatment. It was ascertained during scheduled follow-up assesments.

Study Endpoints

The primary endpoint was to characterize treatment outcomes-overall survival (OS), as well as treatment efficacy within our cohort. OS was defined as the time from diagnosis to death from any cause, and was analyzed as median OS. Secondary endpoints included: 1) clinical and pathological characterization-clinical presentation, diagnostic work-up, therapeutic approach, and general and pathological characteristics of patients with NB in our institution; 2) quantification of time intervals from symptom onset to first physician consultation and from that consultation to definitive diagnosis; 3) association between key variables, specifically between disease outcome (OS, relapse) and both disease stage at presentation and the presence of metastases at diagnosis, as well as baseline biomarker profiles (MYCN status, ploidy); 4) report of the incidence and nature of postoperative complications; 5) report of incidence of relapse- defined per the INRC.

Statistical Analysis

The data were processed using Microsoft Excel software (version 16.0, Microsoft 365 Apps; Microsoft Corporation, Redmond, WA, USA) and IBM SPSS Statistics software (version 30.0; IBM Corp., Armonk, NY, USA). Given the small sample size (n=13), the analysis was restricted to descriptive statistics. Categorical variables are presented as counts and proportions (n, %). Continuous variables are summarized as medians with ranges. OS was visualized using the Kaplan-Meier method; however, no comparative hypothesis testing was performed.

The follow-up duration for the cohort was calculated from the date of diagnosis to the date of last known contact or death. For the patients that survived, follow-up times were right-censored at their last documented clinical assessment. The median follow-up time for the entire cohort was 25 months (range: 10-120 months).

Regarding missing data, the available-case approach was used. Analyses were performed based on number of patients with available data and no imputation was performed due to the retrospective design and small sample size. Naturally, denominators are reported explicitly where applicable. The results are presented in textual, numerical and tabular form.

RESULTS

Patient Characteristics

The median age was 44 months (range, 0-114), meaning most patients (53.8%, 7/13) were in the age group of 2-4 years old. Among 13 patients, all (100%, 13/13) had negative family history for NB. Twelve patients (92.3%, 12/13) had no family history of malignancy, while in one patient a positive family history of malignancy was noted, specifically Hodgkin lymphoma. In 5 patients, the tumor was of Stage 2 according to INSS classification (38.5%, 5/13), one patient had Stage 3 (7.7%, 1/13) and 7 patients had Stage 4 (53.9%, 7/13). No patients were identified with Stage 1 or 4s. Primary tumor sites were the adrenal gland in 12 cases (92.3%, 12/13; 4 right and 8 left) and the head and neck region in 1 case (7.7%, 1/13). First symptoms were recognized by the doctor in 3 patients (23.1%) and by the parents in 10 patients (76.9%, 3/13). The median time from the initial appearance of symptoms to the first visit with a primary care physician was 12 days (range: 1-45 days). The median time from that first doctor's visit to the confirmation of a diagnosis was 14 days (range: 6-20

days). Total of 5 patients (38.5%, 5/13) had other diagnoses upon initial presentation, where 3 (23.1%, 3/13) presented with anemia, and 2 (15.4%, 2/13) had amblyopia. One patient (7.7%, 1/13) had opsoclonus-myoclonus syndrome with ataxia and one patient (7.7%, 1/13) was initally presented with the diagnosis of polyarthralgia. Six patients had lethal outcome (46.2%, 6/13) (Table 1).

Stage and the Disease Outcome

A total of 2 patients (15.4%, 2/13) were in the 0-2 years age group (both with Stage 2 disease), 7 patients (53.8%, 7/13) were in the 2-4 years age group (2 with Stage 2, 1 with Stage 3, and 4 with Stage 4), and 4 patients (30.8%, 4/13) were in the 6-15 years age group (1 with Stage 2 and 3 with Stage 4).

All of the 5 patients (100%, 5/5) with Stage 2 disease survived. In contrast, 6 out of 7 patients (85.7%, 6/7) with Stage 4 disease had a lethal outcome, with one survivor who had a follow-up period of 10 months. The single patient with Stage 3 disease also survived.

Kaplan-Meier analysis was used to describe OS (Figure 1). Median OS was 36 months. Around 91.7% survived at 12 months and 45.8% at 36 months. Several patients were censored during follow-up. Survival curve showed a plateau in later months.

MYCN Amplification and the Disease Outcome

Data on MYCN amplification analysis were available for 8 patients (61.6%, 8/13), among whom MYCN amplification was present in 4 (30.8% of the total cohort, 4/13) and absent in 4 patients (30.8%, 4/13). Overall, among the patients with a lethal outcome (n=6), 4 had confirmed MYCN amplification, 1 had a negative MYCN status, and 1 had missing data. Among the survivors (n=7), 3 patients had a negative MYCN status, and 4 had missing data. The descriptive analysis indicated a mortality rate of 100% (4/4) in the patients with confirmed MYCN amplification, compared to 25% (1/4) in those with a confirmed non-amplified status. MYCN amplification was documented in 3 out of 7 patients (42.9%) with Stage 4 disease, and in 1 out of 5 patients (20%) with Stage 2 disease, suggesting a trend of more frequent amplification in advanced stages. This is clinically relevant for prognosis, as MYCN is a marker of aggressiveness in NB. However, further studies with a larger sample size are necessary to confirm these findings with greater reliability.

Biological Markers

Baseline biomarker levels, collected at diagnosis prior to any treatment, were analyzed. Data on the initial serum NSE levels were available for 7 patients. All 7 had elevated NSE levels, with a median value of 101.0 µg/L [interquartile range (IQR): 370-20.9; range: 18.10-939 µg/L; normal range: 0-13 µg/L]. Initial urinary VMA level results were available for 9 patients. Of these, 7 patients had elevated VMA levels, with a median value of 15.1 mg/g (IQR: 66.9-9.25; range: 3.2-535.9 mg/g of creatinine). The other two (2/9) had results within the normal reference range (1-10 mg/g). Blood ferritin data was available for 10 patients, showing a median value of 238.0 ng/mL (IQR: 895.06-195.44; range: 62.0-1090.0 ng/mL). Five of them (5/10) had elevated ferritin levels (the median for this group was 818 ng/mL), while the other five had values within the normal range (10-225 ng/mL). Blood LDH levels were available for 9 patients. The median value was 1826 U/L (IQR: 2277-618; range: 445-5566 U/L). Eight patients (8/9) showed LDH levels above the normal range (195-470 U/L), and one patient (1/9) had a value within the normal limits (Table 2).

Applied Therapeutic Modalities

In our cohort included pre- and postoperative chemotherapy, surgery, myeloablative therapy, MIBG therapy, and immunotherapy, either as single interventions or in various combinations, with surgical procedures (adrenalectomy and complete tumor resection with or without lymphadenectomy) performed at the clinic for pediatric surgery (Table 3).

Symptoms

The most frequently reported symptoms among our patients were loss of appetite, the presence of a palpable mass, and abdominal pain, each occurring in 53.8% of cases (n=7, 7/13). Fatigue was present in 30.8% of cases (n=4, 4/13), while paleness and joint pain each appeared in 23.1% of cases (n=3, 3/13). Symptoms such as fever, hip pain, dyspnea, vomiting, dysuria,

Table 1. Overview of the association between clinical variables and relapse

Variable	Without relapse (n=7)	With relapse (n=6)	Total (n=13)
Outcome			
Lethal Survived	1 (7.7%) 6 (46.2%)	5 (38.5%) 1 (7.7%)	6 (46.2%) 7 (53.8%)
INSS stage			
2 3 4	4 (30.8%) 1 (7.7%) 2 (15.4%)	1 (7.7%) 0 5 (38.5%)	5 (38.5%) 1 (7.7%) 7 (53.8%)

INSS: International Neuroblastoma Staging System.

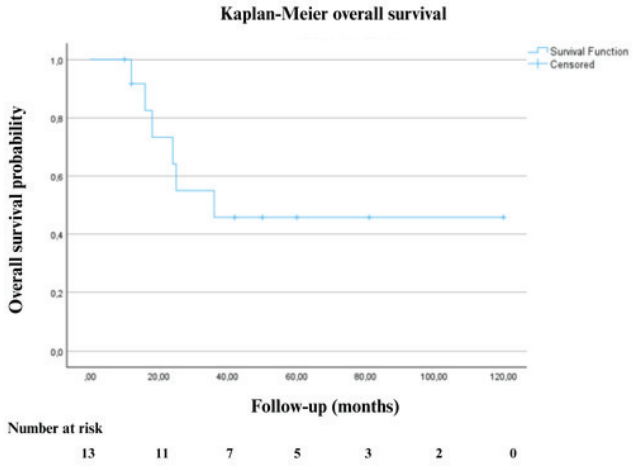

Figure 1. Kaplan-Meier curve describing overall survival of the study cohort. Median survival was 36 months. Estimated survival was 91.7% at 12 months and 45.8% at 36 months. Tick marks represent censored observations.

walking difficulties, constipation, prolonged crying, and groin pain were less common, each appearing in 15.4% of cases (n=2, 2/13). On the rare end, symptoms like the inability to bear weight on the legs, hand tremors, eyelid hematoma, and protrusion of the eyeball were each seen in only 7.7% of cases (n=1, 1/13). A large number of symptoms occurred only rarely (in just 1 or 2 patients), which may imply that the clinical presentation is significantly heterogeneous (Table 4).

Symptoms and the Disease Stage

In the Stage 2 (n=5), it is shown that the most common symptoms were a palpable mass (60%, 3/5), loss of appetite (60%, 3/5), abdominal pain (40%, 2/5), fatigue (40%, 2/5), and shortness of breath (20%, 1/5). The presentation was characterized by local symptoms with moderate systemic complaints. In Stage 4 (n=7), the most frequent symptoms were abdominal pain (71.4%, 5/7), a palpable mass (57.1%, 4/7), loss of appetite (42.9%, 3/7), joint pain (42.9%, 3/7), and paleness (42.9%, 3/7). Fever, difficulty walking, constipation, and hip pain were each present in 28.6% of cases (2/7). This stage also included specific, rarer symptoms like bulging eyeball, eyelid hematoma, prolonged crying, hand tremors, and the inability to bear weight (each at 7.7%, 1/13). A higher frequency of pain and systemic symptoms was observed in this advanced stage. In Stage 3 (n=1), only one patient was classified, providing insufficient data for a meaningful analysis. Certain clinical trends were observed, such as abdominal pain, joint pain, a palpable mass, and paleness being more common in Stage 4, potentially indicating disease progression. Loss of appetite was a symptom recorded across all Stages.

Metastases

Metastatic disease-including involvement of regional lymph nodes-was present in 10 patients (76.9%, 10/13). Only three patients (23.1%, 3/13) showed no evidence of metastasis. A detailed overview of the metastatic sites identified for each patient is provided in Table 3.

Analysis of metastatic locations in the affected group (n=10) showed lymph nodes to be the most commonly involved site, present in all patients (100%, 10/10) with metastatic disease. Review of records showed that abdominal (50%, 5/10) and retroperitoneal lymph nodes (20%, 2/10) were most involved. Metastases were found in para-aortic/paracaval lymph nodes in 20% of cases, while parailiac, retrosternal, and cervical lymph nodes were less frequently involved (12.5% each, 1/8). Bone metastases were also frequent, occurring in 50% of patients with metastatic disease (5/10). Within this group, the vertebrae were the most commonly affected site (80%, 4/5), with pelvic and cranial bones each involved in a single case (10% of metastatic patients, 1/10 each). Other metastatic sites included the liver, pleura, and intracranial region (20% each, 2/10), as well as paravertebral muscles and bone marrow (30% each, 3/10). Subcutaneous tissue and the lungs were each affected in one case (10%, 1/10).

Metastases and Stages of the Disease

As expected, the prevalence of metastases varied significantly based on disease stage. In Stage 2, metastases were present in 2 out of 5 patients (40%, 2/5), implying that disease dissemination can occur even in earlier stages. In contrast, all patients in Stage 3 and Stage 4 had confirmed metastases, representing a 100% metastasis rate in these groups (8/8). Analysis of metastases in Stage 4 patients revealed aggressive dissemination: 100% (7/7) had lymph node involvement, and 71.4% (5/7) had bone metastases. Metastases in paravertebral muscles and bone marrow were present in 42.9% of these patients. In Stage 2,

Table 2. Range of baseline biological marker values in patients at diagnosis

Biological marker (unit)	Median (IQR)	Range in patients	Patients with data (n/total)	Reference values*
NSE (µg/L)	101.0 (20.9-370.0)	18.10-939	7/13	0-13
VMA (mg/g of creatinine)	15.1 (9.25-66.9)	3.2-535.9	9/13	1-10
Ferritin (ng/mL)	238.0 (195.44-895.06)	62.0-1090.0	10/13	10-225
LDH (U/L)	1826 (618-2277)	445-5566	9/13	195-470

*: Reference ranges and units adapted from Bolkar ST, et al. Indian J Clin Biochem 2008;23(3):293-295.
IQR: Interquartile range, NSE: Neuron-specific enolase, VMA: Vanillylmandelic acid, LDH: Lactate dehydrogenase.

Table 3. Demographics and other characteristics of patients with neuroblastoma		
Criteria	**n**	**%**
Sex		
Male	7	53.8
Female	6	46.2
Family history		
Negative	13	100
Positive	0	0
Disease stage (INSS classification)		
1	0	0
2	5	38.5
3	1	7.7
4	7	53.9
4s	0	0
Tumor localization		
Adrenal gland	12	92.3
Left	8	66.7*
Right	4	33.3*
Head and neck area	1	7.7
MYCN amplification		
Yes	4	30.8
No	4	30.8
No data available	5	38.5
Therapeutic approach		
Chemotherapy only	3	23.1
Surgery + chemotherapy	4	30.8
Surgery only	2	15.4
Multimodal therapy[§]	4	30.8
Metastases at diagnosis		
Yes	10	76.9
Lymph nodes	10	100[#]
Bone	5	50[#]
Bone marrow	3	30[#]
Other sites[±]		
No	3	23.1
Histopathology		
Neuroblastoma	12	92.3
Ganglioneuroblastoma	1	7.7
Postoperative complications		
Yes	1	7.7
No	12	92.3
Relapse		
Yes	6	46.2
No	7	53.8
Survival status		
Lethal	6	46.2
Survived	7	53.8

*: Percentage of adrenal gland tumors (n=12), [§]: Includes therapies with combination of MIBG, myeloablation, surgery, chemotherapy, or immunotherapy (n=4), [±]: Other sites include pleura, liver, intracranial region, paravertebral muscles, subcutaneous tissue, and lungs, [#]: Percentage of patients with metastases (n=10), INSS: International Neuroblastoma Staging System.

metastases were exclusively localized to regional lymph nodes (n=2), consistent with INSS Stage 2B classification.

Histopathology and Immunohistochemistry

The type of NB was determined by histopathological examination. A total of 12 patients (92.3%, 12/13) received a histopathological diagnosis of NB. For the majority of patients (69.2%, 9/13), the diagnosis was designated simply as "NB" without further specification. In three patients (30.8%, 3/13), the diagnosis included additional specifications: Nodular NB (7.7%, 1/13), poorly differentiated NB (7.7%, 1/13), and undifferentiated NB (7.7%, 1/13). Each of these specifications was reported in one patient. One case (7.7%, 1/13) was diagnosed as ganglioneuroblastoma.

Postoperative Complications

Of the 13 cases examined, postoperative complications occurred in only one patient (7.7%, 1/13). These complications involved intestinal obstruction and hypokalemia, which required the patient to be readmitted to the clinic for pediatric surgery. The remaining 92.3% (12/13) of patients experienced no postoperative complications.

Relapse, Outcome and the Disease Stage

Relapse was documented in 6 patients (46.2%, 6/13), while the remaining 7 patients (53.8%, 7/13) experienced no relapse. Among patients with a fatal outcome (n=6), 5 had experienced a relapse (83.3%, 5/6), and 1 had not (16.7%, 1/6). Descriptively, patients with a fatal outcome had a higher proportion of relapse (83.3%, 5/6) compared to those with a positive outcome (14.3%, 1/7).

No patients with Stage 2 disease experienced a relapse (0/5). Among the 7 patients with Stage 4 disease, 5 (71.4%, 5/7) had a documented relapse, while 2 (28.6%, 2/7) did not. The single patient with Stage 3 disease (1/1) did not experience a relapse. For descriptive analysis, stages were grouped into two categories: Lower stages (Stages 1 and 2, n=5) and higher stages (Stages 3 and 4, n=8). Patients with higher-stage disease experienced relapse more frequently (62.5%, 5/8) compared to those with lower-stage disease (20%, 1/5). The associations between outcome, relapse, and disease stage are shown in Table 1.

DISCUSSION

In our single-center case series, the vast majority of patients presented with advanced-stage NB, with already developed metastatic disease and elevated tumor biomarkers-thus, survival outcomes were unfavorable. As it is expected, delayed diagnosis appears to be connected to the poorer clinical and overall outcomes. Consistency with the patterns reported in larger published papers is present. However, due to study limitations, these findings are strictly descriptive and hypothesis-generating.

The management of unpredictable diseases such as NB, demands clear and guided assessment. Current international risk stratification systems depend primarily on patients age, disease stage and specific molecular markers. Contemporary analyses from large cohorts work on reinforcement of critical epidemiological and biological patterns. For context, findings in contemporary NB studies are summarized in Table 5.

Gender and Prognosis: Unlike earlier views that the gender was not relevant for prognosis, there is an evidence today that indicate a slight predominance of NB in males (22-24). Studies from the past (22) reported that gender has neither prognostic significance nor relevance for the incidence of NB. However, more recently, studies have focused on differences related to gender, showing a higher incidence in boys (23,24). According to research by Tas et al. (24), the incidence of NB is slightly higher in boys than in girls (51.7% versus 48.3%, respectively). Several contemporary studies (25,26) analyzing the correlation between gender and NB have concentrated on differences in outcomes and therapeutic success, noting that boys tend to have somewhat worse outcomes. A comprehensive study of global NB incidence and mortality from 2025 (3) reported the greatest gender difference in the 2-4 year age group, with a male-to-female ratio of 1.96:1. In our study, we have also observed a slightly higher incidence in boys (54%).

Table 4. Presentation of symptoms by disease stage

Symptom	Stage 2 (n=5)	Stage 3 (n=1)	Stage 4 (n=7)
Localized symptoms			
Palpable mass	3 (60%)	0 (0%)	4 (57.1%)
Dysuria	0 (0%)	1 (100%)	1 (14.3%)
Pain in abdomen	2 (40%)	0 (0%)	5 (71.4%)
Systemic symptoms			
Loss of appetite	3 (60%)	1 (100%)	3 (42.9%)
Fatigue	2 (40%)	1 (100%)	1 (14.3%)
Elevated body temperature	0 (0%)	0 (0%)	2 (28.6%)
Metastatic symptoms			
Paleness	0 (0%)	0 (0%)	3 (42.9%)
Joint pain	0 (0%)	0 (0%)	3 (42.9%)
Dyspnea	1 (20%)	0 (0%)	1 (14.3%)

Table 5. Summary of key large cohort studies in neuroblastoma

Study/cohort (year)	Sample size (n)	Key stage distribution	MYCN status rates	Primary treatment strategy	Reported OS/EFS	Relapse rate
Tas et al. (Netherlands, 2020)	593	52% Stage 4	NA	High dose chemotherapy followed by autologous stem cell transplant and anti GD2 based immunotherapy	5-yr OS: all patients – increase of OS from 44 +/- 5% to 61 +/- 4%; Stage 4: from 19 +/- 6% to 44 +/- 6% (1990-2014); EFS - NA	NA (implied high in Stage 4)
Liu et al. (China, 2023)	1 224	48.9% with distant mets	20-25%	Multimodal standard	Without bone metastases 5-yr OS: 87.2%; bone metastasis 5-yr OS: 66.9%; EFS NA	Implied high with metastases
Lucena et al. (Brazil, 2018)	258	46% Stage 4	Test was performed in 17%; 25% of tested had *MYCN* amp	Risk-adapted, per INRG	5-yr OS: 62% (all); 5-yr EFS: 52%	72%
Al-Tonbary et al. (Egypt, 2015)	142	76.7% Stage 4;	Test available in 17%; NA	Risk-based chemotherpy	2-yr OS: males- 47.6 +/-14.0%, females – 10.4% +/- 9.8%	NR
Current study (Sarajevo, 2025)	**13**	**53.9% Stage 4**	**30.8% (of tested)**	**Multimodal, per INRG**	**Median OS: 36 mo; Stage 4 survival: 14.3%**	**46.2% (all); 62.5% (Stage 3 and 4)**

OS: Overall survival, EFS: Event-free survival, NR: Not reported, NA: Not applicable, INRG: International Neuroblastoma Risk Group.

Age Distribution: Approximately 90% of NB occurs in children <5 years, with a median age at diagnosis of 17-18 months (4,14). Older age (>18 months) at diagnosis is a poor prognostic factor, especially when combined with advanced disease (24). In the study conducted by Williams and Williams Spector (25), there were approximately 50% of patients within the 1-4 year age group. According to a study by Ting et al. (23), the median age at diagnosis of malignant tumors in children was 4 years. Considering that 18 months represents an important prognostic cut-off (according to the - INRGSS), some studies have shown that about 45% of patients are diagnosed before this age (24). We have noted that most patients (53.8%) belonged to the 2-4 year age group, with a median age of 44 months.

Family History and Predisposition: Family predisposition for NB development is very rare–with only 1-2% of patients reported to have positive family history for NB (27). Moreover, no exogenous factors have been associated with NB development (28). In our study, none of the patients had a family history of NB. In 12 patients (92.3%), the family history was negative for malignancies, while in one patient a positive family history of malignancy was noted, specifically Hodgkin lymphoma.

Patterns of Time Intervals Relevant for Diagnostics: It is very commonly reported that a majority of NB patients had experienced a diagnostic delay (29,30). A paper from Beijing (29) reported a median diagnostic interval of 1 month (range, 0.2-24 months). In that cohort, 52 out of 62 patients experienced a diagnostic delay, with time interval between symptom onset to diagnosis longer than 2 weeks. In another study of patients with NB presenting with intracranial metastases (30), the median time from the first symptoms to diagnosis was 4.2 months. In our cohort, the distribution of the interval from symptom/sign onset to the first physician visit was asymetrical–which implies that some parents sought medical attention later than others. The time from the first physician visit to the diagnosis was also asymetrically distributed, with 75% of cases diagnosed within 15 days, and only a few outliers extending up to 20 days.

Primary Tumor Location: Primary NB tumors mostly originate in the adrenal gland and abdominal cavity (24). They are far less common in the neck, chest, or pelvis (11). In our cohort, twelve (92.3%) patients had NB localized in the adrenal gland, while one patient (7.7%) presented with NB in the head and neck region, thus our findings support the notion of the predominant primary site of NB in children.

Stage at Presentation: Advanced-stage (INSS Stage 4) disease accounts for 50-70% of presentations in unselected cohorts and is the primary factor contributing to mortality (24,30). Based on definitive histopathological diagnosis, most of the patients from our cohort (53.9%) were classified as Stage 4. Liu et al. (30) reported that 74.4% of NB cases are diagnosed at an advanced age, while Tas et al. (24) stated that the most patients had Stage 4 upon diagnosis (52%). Our research is consistent with these observations, confirming that a substantial proportio of patients present when the stage of NB is advanced.

Presenting Symptoms: The presenting symptoms at the moment of diagnosis of NB in the vast majority of cases are abdominal pain, a palpable mass, as well as systemic signs such as fever and weight loss (23,31). In our cohort of thirteen patients, the most frequently observed presenting symptoms were loss of appetite, a palpable abdominal mass, and abdominal pain, each occurring in 58.8% of cases. These findings are in line with previous reports. A recent study from China (23) analyzed common symptoms of pediatric solid tumors, and it has reported that the most frequent ones are palpable masses in 34.9% of cases, abdominal pain in 21.1%, and fever in 6.3%. Nonetheless, literature emphasizes the great clinical significance of systemic symptoms such as fever, appetite loss, and weight loss (31). Other reported symptoms in our patients included fatigue, pallor, joint pain, fever, dyspnea, vomiting, dysuria, difficulty walking, constipation, prolonged crying, and groin pain, whereas less common findings included inability to bear weight, hand tremors, eyelid hematomas, and proptosis. In our study, the "raccoon eyes" phenomenon was observed in 7.7% of cases. Paper from Ghosh et al. (32) reports this phenomenon in up to 20% of cases, hence, its presence is consistent with the one in our cohort. Specific symptom patterns often correlate with metastatic spread: bone metastases typically manifest as musculoskeletal pain or impaired mobility, and bone marrow involvement is usually associated with anemia or thrombocytopenia (31). Similarly, studies from Brazil (29) noted fever, abdominal pain, abdominal mass, and bone pain as the most common presenting features, confirming that our findings align with established patterns in NB. Overall, the variability in symptom presentation is important for maintaining a high index of suspicion for NB across a broad spectrum of clinical signs.

Metastatic Patterns: Metastatic disease at diagnosis is very common in NB, and it involves regional lymph nodes, bone, bone marrow, and liver most frequently (11,12,33). Previous studies have shown that up to 70% of patients with NB present with metastases at diagnosis (11). A large Chinese cohort which included 1224 patients reported distant metastases in 48.9% of cases, results that are consistent with other similar studies (12,33). Most common secondary tumor sites for NB are regional lymph nodes, bones, bone marrow and liver (11). Our results are in line with these observations, as metastases were identified in 76.9% of patients, with lymph node involvement present in all cases. Bone metastases were observed in 50% of patients, compared to 33% reported in a study from Sao Paulo (34). As expected, we have also observed an association between advanced stages (3 and 4) and the presence of metastases. That confirmed current

knowledge that high-risk patients exhibit greater mortality and more aggressive NB behavior (4,16).

Due to the activity of immune system, 2-3% of children with NB develop opsoclonus-myoclonus syndrome (35). In our cohort, this diagnosis was identified in 7.7% of patients. Anemia is also a common manifestation of NB, which explains why 23.1% of our patients had been diagnosed with anemia prior to the confirmation of NB (31). In total of 38.5% of our patients, additional diagnoses were recorded prior to NB, including, apart from those previously mentioned, amblyopia and polyarthralgia.

Diagnostic Biomarkers: Serum NSE, LDH, ferritin, and urinary catecholamine metabolites (VMA) are well established diagnostic and prognostic markers. In a paper published by Bolkar et al. (13) which analyzed biochemical parameters in children with NB, it was reported that urinary VMA, serum NSE, ferritin, and LDH were significantly elevated in histologically confirmed cases compared to healthy controls. The relevance of these parameters has long been recognized in the literature (36), with several studies making an emphasize on their importance in prognosis of the disease, particularly NSE and LDH, but also LDH and ferritin (19,29). In our study, all patients had elevated serum NSE levels, while 88.9% had high LDH values. Additionally, 77.8% of patients had increased VMA in urine, and ferritin was elevated in 50% of cases. Our results confirm importance of these paramters, named in previous studies. These markers have great clinical value-they are good diagnostic indicators but also useful for monitoring progression of the disease. Considering that more than 90% of children with NB present with high levels of catecholamines and their metabolites (19), biochemical testing is crucial component of monitoring of patients with NB.

Treatment Modalities: Therapy modality is dependent on risk-group (18). Low-risk disease often requires surgery alone, while high-risk disease demands a multimodal approach: Intensive induction chemotherapy, surgical resection of the primary tumor, myeloablative therapy with autologous stem cell transplant, chemotherapy, radiotherapy, and immunotherapy (anti-GD2 antibodies). This paradigm has improved survival for high-risk patients (3). All of our patients underwent multimodal therapy, adjusted to the stage of their disease.

Histopathological Classification: Literature most frequently identifies NB as the most common histopathological type of this disease, but it is not the only one. Other variants, such as ganglioneuroblastoma and ganglioneuroma are also described, as well as their own subtypes (9). A study from the United States (37) that included 145 children reported histopathological diagnosis NB in 130 cases (80.7%), which is consistent with our findings, where it was defined in 92.3% of patients.

Relapse Patterns and Outcomes: Many studies have examined the relationship between the characteristics of NB and outcomes of treatments following disease relapse. The INRC defines relapse as the occurrence of a new disease site or a tumor increase of at least 25% after initial response to treatment (38). According to the research based on the INRG data base, which included 8 800 patients younger than 21 years of age diagnosed between 1990 and 2002, 2 266 experienced a first relapse, progression of the disease or development of a secondary tumor. More than half of patients with high-risk NB either fail to respond to treatment or eventually relapse (39). Although relapse can occur in intermediate-risk groups, it is reported in only 20% of cases. Survival after relapse in high-risk NB remains less than 10% (40). Our results further underscore the connection between relapse and lethal outcomes -46.2% of our patients had relapse, and it was more common in those with advanced stages (3 and 4). Based on these results, questions can be raised on developing new therapeutic strategies aimed at reducing relapse rates and improving OS in patients with advanced stages or high-risk NB.

Postoperative complications after NB treatment were reported in 44.7% of cases in one study from China (41). In our study, only one experienced a postoperative complication, which was intestinal obstruction. Minimally invasive surgery is generally recommended for reducing the risk of postoperative ileus and adhesion formation (42).

Survival Outcomes and Mortality: Long-term survival in NB in localized stages (1-3) still remains excellent (>90%), but in advanced Stage 4 disease, it is persistently poor (3,16,24,43,44). In our study, 46.2% of patients had a lethal outcome. NB is a tumor characterized by high mortality rates, with 10-year survival reaching 91% for Stages 1-3, and only 38% for Stage 4 (16). A more recent study from 2025 (3) reported that high-risk NB has mortality rates of 50%, whereas low-risk and intermediate-risk NB has mortality rate lower than 10%. Our results are limited by the fact that mortality was not analyzed separately according to disease stage and risk-group, the aggressive nature of the tumor was once again evident.

A paper published by Berthold et al. (43) reported that 10-year survival in children with Stages 1-3 has consistently been high, whereas for Stage 4 it has remained lower, increasing from 2% to 38% between 1979 and 2015. Our findings are consistent with these observations -85.7% of children with Stage 4 had lethal outcomes, while all children with Stage 2 survived.

The median survival time in our study is 36 months, with the Kaplan-Meier curve showing a steep decline in the early phases: 1-year survival was 91.7%, and 3-year survival is 45.8%. Similarly, a study from Egypt (44) reported a 2-year survival of 19.0±16.8% in children with NB and poor prognosis, in contrast to 71.4±17.1% in those with favorable prognosis. Another study from the Netherlands (24) found a 5-year survival rate 35±3% for Stage 4, and 93±2% for Stages 1-2. Although our analysis was not

stratified by stage, the observed survival trends are consistent with global data. Once again, the aggressive nature of advanced NB is a central concern.

Molecular Landscape: MYCN amplification, present in around 20% of cases, is a well-established marker of tumor aggressiveness and poor prognosis, particularly in advanced-stage disease (45). Its presence is the most relevant piece of data, regarding genetic material, that influence prognosis of disease. The association between *MYCN* gene amplification and disease stage was observed and described descriptively in our cohort. The MYCN amplification was more frequently present in patients with advanced-stage NB.

Our study aimed to examine the impact of early diagnosis of NB at the initial stage of the disease on treatment outcomes. We followed thirteen patients treated at the clinic for pediatric surgery KCUS. The predominance of advanced-stage disease at diagnosis, commonly present metastatic involvement, adrenal localization, elevated tumor biomarkers and poor survival outcomes in advanced stages are similar to observations from international registries and population-based studies. In contrast, some differences were present–the proportion of patients presenting with Stage 4 disease, the high relapse rate, and the elevated mortality in our cohort appear higher than those present in other studies. That can be the result of several limitations of the study. For comparing mentioned findings with our institutional experience, refer to the Table 6.

Study Limitations

This study has several limitations. The small size of this cohort (n=13), due to single-center, retrospective nature of this analysis, remains biggest limitation. It limits external validity, and contributes to the possibility of selection and information bias. Furthermore, statistical power is restricted, due to the limited sample size. Limited availability of MYCN status should also be noted, as well as limited and heterogeneous follow-up time interval. Therefore, the findings should be considered hypothesis-generating and exploratory.

Mentioned study limitations show why the need for larger, prospective, multicenter studies persists, which-within current research setting in Bosnia and Herzegovina, remain difficult to conduct. Nonetheless, this report is initial step toward structured data collection and further research, in the field of pediatric oncology.

Table 6. Comparison of current study findings with major series

Outcome parameter	Current Sarajevo cohort (n=13)	Findings from large series	Interpretation & divergence
Stage distribution	53.9% Stage 4 (INSS)	46-80% Stage 4/metastatic	**Aligned.** High proportion of advanced-stage disease at presentation is consistent globally.
Age at diagnosis	Median: 44 months	Median: 17-18 months	**Divergent.** Our cohort is significantly older. This likely has contribution to the observed poor prognosis, as age >18 months is one of the prognostic factors in metastatic NB.
MYCN amplification	30.8% of tested (4/13); 100% mortality in amplified	Around 25-40% overall; strong poor prognostic factor	**Trend aligned, rate higher.** Proportion with *MYCN* amp is descriptively higher. The 100% mortality in amplified cases (though n=4) brings out the importance of developing bigger studies regrading this trend.
Metastasis at Dx	76.9% (10/13)	Between 50-70%	**Aligned.** Our rate is at the upper end of reported ranges, consistent with the high stage distribution. Lymph node (100%) and bone (50%) involvement patterns are typical.
Biomarker elevation	NSE: 100% (7/7); LDH: 88.9% (8/9); VMA: 77.8% (7/9)	>90% elevation in catecholamines and its metabolites;	**Aligned.** High rates of biomarker elevation confirm diagnostic utility.
Treatment approach	Multimodal (Surgery, Chemo, MIBG, Immuno)	Risk-stratified multimodal standard (per INRG)	**Aligned.** Multimodal approach was applied.
Relapse rate	46.2% overall; 62.5% in Stage 3 and 4	40-60% in high-risk	**Aligned for Stage 4.** Our overall rate is product of the high proportion of advanced-stage patients. The pattern (relapse concentrated in Stage 4) is expected.
Survival (Stage 4)	14.3% (1/7) survived	5-yr OS: 35-60% in modern series	**Divergent/lower.** Our Stage 4 survival appears lower. Potential contributors: older age at diagnosis and small sample size.
Diagnostic intervals	Symptom to MD: median 12 days; MD to Dx: median 14 days	Often weeks to months; delay of around 2 weeks is common	**Aligned.** Our diagnostic timelines appear relatively efficient and are not excessively prolonged compared to literature reports.

INSS: International Neuroblastoma Staging System, LDH: Lactate dehydrogenase, VMA: Vanillylmandelic acid, NSE: Neuron-specific enolase, OS: Overall survival, INRG: International Neuroblastoma Risk Group, MIBG: Meta-iodobenylguanidine, MD: Medical doctor, Dx: Diagnosis.

CONCLUSION

In our single-center series of 13 patients with NB, the most common clinical signs and symptoms were loss of appetite, a palpable abdominal mass, and abdominal pain. The majority of patients had a primary tumor localized in the adrenal gland. Disease relapse was confirmed in 46.2% of patients, with relapse occurring more frequently in those diagnosed at advanced stages. The OS rate in our cohort was 53.8%. All patients with stage 2 disease survived, while 85.7% of patients with stage 4 disease had a fatal outcome. Elevated tumor biomarkers, including NSE, LDH, ferritin, and VMA, were noted in patients with advanced-stage disease, which is consistent with international observations. Disease stage at diagnosis was observed relating to the outcomes: Patients who presented with low stages have survived, while the ones with high stages were connected with high mortality and frequent relapses.

Upon these findings, we can state that the early recognition is one of the most important factors defining the outcomes of children with NB. Early recognition is associated with lower disease stages at diagnosis, hence, patients have more favorable outcomes. There is a need for multimodal, risk-adapted therapy and more structured follow-up protocols for high-risk patients, to address their higher likelihood of relapse.

For improving OS in children with NB-especially in low and middle income countries-future studies should focus on multicenter designs including patients with comprehensive molecular profiling, standardized staging, and uniform follow-up. That could better refine prognostic assessment and therefore contribute to the better outcomes in patients with NB.

Ethics

Ethics Committee Approval: The study was approved by the Local Institutional Review Board (Ethical Committee of the Clinical Center University of Sarajevo, protocol code: 51-45-1-6872/25, date: 24 February 2025).

Informed Consent: Due to the retrospective nature of the study, informed consent was waived.

Footnotes

Author Contributions

Surgical and Medical Practices - A.J., I.T., B.K., Z.Z.; Concept - A.J., I.T., B.K., P.I., Z.Z.; Design - A.J., I.T.; Data Collection or Processing - A.J., I.T., B.K., P.I., Z.Z.; Analysis or Interpretation - A.J., I.T., B.K., P.I., Z.Z.; Literature Search - A.J., I.T.; Writing - A.J., I.T.

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CASE SERIES
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Kidney transplantation in Alport syndrome: A genotype-guided case series and literature review

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ABSTRACT

Alport syndrome (AS) is a hereditary nephropathy caused by pathogenic variants in COL4A3, COL4A4, or COL4A5, leading to type IV collagen defects and progressive glomerular basement membrane dysfunction. Kidney transplantation provides excellent long-term outcomes; however, donor eligibility, genotype-specific prognosis, and post-transplant complications continue to raise important clinical considerations in the era of precision medicine. We present a comparative case series of three genetically confirmed patients with AS who underwent kidney transplantation: Two with X-linked disease and one with autosomal-dominant inheritance. Genetic, clinical, and immunologic findings were analyzed and contextualized within current literature and recommendations. All patients initially achieved functioning grafts. The autosomal-dominant case demonstrated stable long-term function under cyclosporine-based immunosuppression. Among the X-linked cases, one experienced coronavirus diease-2019–associated arterial thrombosis requiring graft nephrectomy and subsequently underwent successful deceased-donor transplantation one year later; the other developed late antibody-mediated rejection six years post-transplant, with partial recovery following corticosteroid therapy. Kidney transplantation is an effective treatment for AS when guided by molecular confirmation and careful donor evaluation. In this national case series of three patients, outcomes were generally favorable across inheritance types; however, vascular events and late humoral immune complications affected the long-term course of the graft and underscored the need for individualized surveillance.

Keywords: Alport syndrome, antibody-mediated rejection, COL4A3, COL4A4, COL4A5 mutations, donor selection, kidney transplantation

INTRODUCTION

Alport syndrome (AS) is an inherited nephropathy caused by pathogenic variants in COL4A3, COL4A4, or COL4A5, which encode the α3-α5 chains of type IV collagen, a key structural component of the glomerular basement membrane (GBM) (1-3). Clinically, AS manifests with progressive renal dysfunction, sensorineural hearing loss, and ocular abnormalities (4). Approximately 80% of affected individuals have X-linked disease due to COL4A5 variants, while autosomal dominant and autosomal recessive forms result from COL4A3 or COL4A4 mutations (5,6). Disease severity often correlates with the specific genotype and its impact on collagen stability (7,8).

Contemporary recommendations from the ERKNet-ERA-ESPN working group emphasize the importance of molecular diagnostics, standardized donor evaluation, and genotype-based clinical management (9,10). Most affected individuals ultimately progress to end-stage renal disease (ESRD), for which kidney transplantation remains the preferred treatment, with survival outcomes comparable to those seen in other causes of ESRD (11,12).

Although post-transplant prognosis is generally favorable, certain considerations remain essential. A subset of males with X-linked AS may develop *de novo* anti-GBM nephritis following exposure to donor-derived α5 (IV) collagen, a historically severe but rare complication (13). In addition, evaluating potential living donors, particularly heterozygous female carriers, requires careful clinical and molecular assessment due to their increased lifetime risk of renal decline (14,15).

This report aims to distill practical, case-based lessons relevant to contemporary Alport transplant care: (i) how molecular diagnosis shapes donor eligibility and

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counseling, (ii) how late immune-mediated graft dysfunction may emerge despite long-term stability, and (iii) how major systemic infections such as coronavirus disease-2019 (COVID-19) may precipitate catastrophic vascular complications in selected recipients.

MATERIAL and METHODS

Patient selection – the three cases represent the complete national experience of genetically confirmed AS recipients who have undergone kidney transplantation in North Macedonia to date, reflecting the rarity of the condition and the centralized transplant referral pathway. Each patient reached ESRD and received a kidney transplant. For every recipient, we recorded age, sex, mode of inheritance (X-linked, autosomal dominant, or autosomal recessive) and baseline renal function (serum creatinine, estimated glomerular filtration rate). For each recipient, available baseline phenotypic data were extracted from records and included age at ESRD, dialysis history (when applicable), and documented extrarenal manifestations (hearing impairment and ocular findings) when present.

DNA extraction and quality control–genomic DNA was isolated from peripheral blood leukocytes using a silica column–based extraction kit. Purity was assessed by spectrophotometry (A260/280≈1.8-2.0) and concentration by Qubit fluorometry, requiring > 30 ng/μL for downstream analysis. Samples failing these thresholds were reextracted.

Targeted gene panel sequencing-a custom capture panel covering the full coding regions and exon intron boundaries of COL4A3, COL4A4, and COL4A5 was employed. Library preparation followed the Illumina TruSeq protocol, and pairedend sequencing (2 × 150 bp) was performed on a MiSeq instrument, achieving a minimum mean coverage of 100×.

Bioinformatic pipeline-reads were aligned to the human reference genome (hg38) with BWAMEM. Variant calling was performed using GATK HaplotypeCaller and variants were annotated using ClinVar, gnomAD, and ACMG guidelines. Variants were classified as pathogenic/likely pathogenic, variants of uncertain significance or benign.

Donor evaluation-all potential living donors underwent the same targeted panel. Individuals harboring pathogenic COL4A3/A4/A5 variants or exhibiting abnormal urinalysis (hematuria, proteinuria) were excluded. Standard immunologic workup (HLAcrossmatch andABO compatibility) was documented for each donor-recipient pair.

CASE SERIES

Three patients with genetically confirmed AS underwent kidney transplantation. Two procedures were performed using living-related donors, while one patient first underwent living donation and, due to complications and graft nephrectomy, later received a deceased-donor graft. All living donors underwent standard immunological evaluation, including cross-match and HLA typing, with negative results in all cases. Preoperative imaging confirmed suitable iliac vasculature and single-vessel donor anatomy. All donor nephrectomies were performed laparoscopically, with uneventful postoperative recoveries. The evaluation was conducted in accordance with institutional ethical standards; Institutional Review Board approval was obtained, and all patients provided written informed consent. The clinical courses and corresponding genetic findings are summarized below.

Case 1

A 26-year-old male with ESRD secondary to X-linked AS underwent an elective living-related kidney transplantation from his father. His mother confirmed by genetic testing to be heterozygous for COL4A5 and was therefore not considered for donation based on the donor eligibility criteria recommended at that time. Molecular testing identified a hemizygous COL4A5 non-sense variant (c.1117C>T; p.Arg373Ter) and an additional heterozygous CDC5L variant of uncertain significance (Table 1). The CDC5L finding was interpreted as an incidental variant of uncertain significance without an established link to type IV collagen nephropathy and was not considered contributory to the renal phenotype.

Initial recovery was satisfactory, although the decline in serum creatinine was slower than anticipated. Standard

Table 1. Genetic findings in three renal transplant recipients with Alport syndrome

Case	Gene	Variant (cDNA/protein)	Zygosity	Inheritance	Testing summary
1	*COL4A5*	c.1117C>T (p.Arg373Ter)	Hemizygous	X-linked (maternal carrier)	Pathogenic variant inherited from heterozygous mother.
	CDC5L	c.2014C>T (p.Pro672Ser)	Heterozygous	Autosomal (paternal)	Variant of uncertain significance, likely benign.
2	*COL4A4*	c.755G>A (p.Gly252Asp)	Heterozygous	Autosomal-dominant (likely familial)	Likely pathogenic variant; family testing ongoing.
3	*COL4A5*	c.81G>T	Hemizygous	X-linked (maternal testing pending)	Genetic confirmation of COL4A5 mutation; family testing recommended.

immunosuppression consisted of cyclosporine, mycophenolate mofetil, and prednisone. Four weeks post-transplant, shortly after a confirmed severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection, the patient developed abdominal pain and graft-site tenderness. Imaging demonstrated a large peritransplant hematoma and thrombosis of the renal and external iliac arteries. Due to the extent of vascular compromise, urgent surgical revision was performed, resulting in graft nephrectomy.

Baseline extrarenal manifestations were assessed based on available specialist documentation. An ophthalmologic evaluation performed in 2021 demonstrated myopic astigmatism with preserved visual acuity and no Alport-specific ocular abnormalities, such as anterior lenticonus or retinal flecks. No documented sensorineural hearing loss was identified in the available medical records, and no audiometric abnormalities were reported. He subsequently resumed hemodialysis and maintained clinical stability. One year later, he successfully underwent deceased-donor kidney transplantation, with a functioning graft at the most recent follow-up.

Case 2

A 15-year-old boy with autosomal-dominant AS caused by a heterozygous COL4A4 missense variant (c.755G>A; p.Gly252Asp) underwent a pre-emptive living-related kidney transplantation from his paternal aunt (Table 1). At the time of surgery, he was the youngest transplant recipient at our center to undergo the procedure after transitioning from pediatric nephrology care.

Postoperative recovery was uncomplicated, and graft function stabilized early under maintenance immunosuppression with cyclosporine, mycophenolate, and prednisone. At the two-year follow-up, graft function remained stable based on routine biochemical parameters, including renal function tests and immunosuppressive drug-level monitoring; there were no biopsy-proven rejections or clinically significant infectious events.

Baseline extrarenal symptoms were comprehensively recorded in Case 2. The otolaryngologic assessment indicated bilateral hearing impairment, with audiometric testing showing a mixed sensorineural hearing loss of 50-60 dB, which was corroborated by subsequent evaluations. Ophthalmologic evaluations conducted during childhood and adolescence revealed preserved visual acuity and normal retinal and anterior segment findings, without Alport-specific ocular anomalies.

Case 3

A 22-year-old male with X-linked AS due to a hemizygous COL4A5 variant, c.81G>T (Table 1), underwent living-donor kidney transplantation from his father after a period of hemodialysis. The graft was implanted into the left iliac fossa. Early postoperative recovery was complicated by a small peritransplant hematoma requiring surgical evacuation, after which renal function stabilized (Table 2). He was maintained on tacrolimus, mycophenolate mofetil, and prednisone. Six years post-transplant, he developed a progressive increase in serum creatinine accompanied by newly detected class II HLA antibodies, consistent with antibody-mediated rejection. Treatment with pulse methylprednisolone and anticoagulation resulted in improved graft function. He remains clinically stable, with preserved graft function and no further rejection events reported during follow-up.

Table 2. Comparative laboratory parameters across three renal transplant cases

System	Parameter	Reference range	Day 1 (C1/C2/C3)	Day 7 (C1/C2/C3)	Month 1 (C1/C2/C3)	Month 12 (C1/C2/C3)
Renal function	Creatinine (µmol/L)	45-109	725/308/166	490/63/130	381/60/188	629/55/152
	Urea (mmol/L)	2.7-7.8	25.6/9.3/8.3	21.8/6.7/7.1	18.2/6.6/6.9	16.4/5.5/7.5
Inflammatory markers	CRP (mg/L)	≤6	180/39.6/<1.0	97/3.0/2.5	55/2.9/1.8	35/<1.0/<1.0
	LDH (U/L)	≤250	950/178/198	700/241/220	486/316/304	320/300/245
Protein status	Albumin (g/L)	35-50	28/27/43	34/31/41	36/36/44	40/43/45
Immunosuppression monitoring	Calcineurin inhibitor level (ng/mL)	100-400	CSA 380/CSA 405/TAC 7.8	CSA 310/CSA 753/ TAC 8.5	CSA 250/CSA 405/ TAC 7.1	CSA 185/CSA 320/TAC 6.9
Hematologic	Hemoglobin (g/L)	120–180	70/104/130	98/75/122	92/97/128	110/118/135
Electrolytes	Sodium (mmol/L)	135-145	130/140/138	138/143/140	140/142/139	142/141/140
	Potassium (mmol/L)	3.5-5.1	5.2/3.5/3.5	4.8/4.8/4.1	4.5/4.3/4.0	4.4/4.2/4.1
	Calcium (mmol/L)	2.1-2.6	2.34/2.0/2.2	2.27/2.3/2.3	2.30/2.34/2.35	2.38/2.41/2.36

Values represent serial laboratory measurements obtained at standardized postoperative intervals (Day 1, Day 7, Month 1, and Month 12). Data are presented in the format Case 1 (C1), Case 2 (C2), and Case 3 (C3).
For Case 1, Month 12 laboratory values (serum creatinine and urea) reflect the interval following graft loss and return to dialysis prior to re-transplantation, rather than post-second transplantation graft function.
CSA: Cyclosporine, TAC: Tacrolimus, CRP: C-reactive protein, LDH: Lactate dehydrogenase.

The relative timing and sequence of key clinical events for each recipient are summarized in Table 3 to facilitate comparison across cases.

In Case 3, extrarenal involvement was prominent and evolved over time. Audiologic follow-up revealed an early-onset bilateral sensorineural hearing impairment, documented since adolescence, with progressive deterioration during serial otolaryngologic assessments. The severity of hearing loss necessitated bilateral hearing amplification and ongoing auditory rehabilitation. Initial ophthalmologic evaluations demonstrated myopic astigmatism, preserved visual acuity, and unremarkable anterior segment findings. During later follow-up, additional ocular abnormalities were identified, including incipient posterior subcapsular cataract and recurrent episodes of herpetic keratitis, both occurring in the setting of long-term immunosuppressive therapy after kidney transplantation. Retinal imaging showed peripapillary and pigmentary alterations, with no evidence of anterior lenticonus. Genetic testing confirmed the molecular basis and inheritance pattern of AS in all three recipients. The main variants identified and their clinical relevance are summarized in Table 1.

Patient Perspective

Due to the retrospective nature of this case series, formal patient-reported outcome measures were not systematically collected. Nevertheless, all patients were informed about their diagnosis, treatment options, and genetic implications and provided written informed consent for transplantation and the publication of anonymized clinical data. At the last follow-up, patients with functioning grafts reported satisfactory overall clinical status and improved quality of life compared with the pre-transplant period, which is consistent with routine post-transplant clinical assessments.

DISCUSSION

The three presented cases illustrate the genetic and clinical heterogeneity of AS and demonstrate how inheritance patterns may shape post-transplant outcomes. Cases 1 and 3, both with X-linked disease, and Case 2, with autosomal-dominant inheritance, align with current evidence showing that genotype correlates with clinical severity and renal progression (1-4).

Kidney transplantation remains the treatment of choice for patients with AS, with long-term graft survival frequently exceeding 80% (3,7-9). Gillion et al. (3) reported no significant differences in graft outcomes between X-linked and autosomal forms, supporting the view that transplantation is safe and effective across genotypes when donor selection and immunologic risk are appropriately addressed (7). In our series, all three recipients achieved functioning grafts following transplantation, further reinforcing the favorable overall prognosis in AS.

Donor and Recipient Evaluation in Genotype-guided Alport Transplantation

Molecular confirmation of COL4A3-COL4A5–related disease is central to transplant planning in AS and informs both recipient assessment and living-donor eligibility. In clinical practice, first-line molecular testing for transplant candidates should employ targeted next-generation sequencing panels covering the full coding regions and exon-intron boundaries of COL4A3, COL4A4, and COL4A5, which collectively account for the majority of AS cases. Broader approaches such as whole-exome or whole-genome sequencing should be reserved for unresolved cases or atypical phenotypes, in accordance with contemporary ERKNet-ERA-ESPN recommendations (10,16).

Living-donor selection must account for the inheritance pattern. In X-linked AS, affected males are not suitable donors, and heterozygous COL4A5 females should be considered as donors only after careful evaluation and counseling because of their increased renal risk. In autosomal recessive AS, both parents are obligate heterozygotes; therefore, related donors require careful molecular testing and clinical evaluation; donation should be considered only for asymptomatic carriers with preserved

Table 3. Chronological timeline of diagnosis, transplantation, complications, and outcomes

Case	Diagnosis/ ESRD	Transplant (donor type)	Early course (0-3 months)	Major complication(s)	Key interventions	Latest follow-up status
1	XLAS → ESRD (age 26)	Living-related (father)	Slow creatinine decline	Post–COVID vascular thrombosis, graft loss	Surgical revision + graft nephrectomy; dialysis; re-transplant at 12 months	Functioning deceased-donor graft at last follow-up
2	ADAS → ESRD (age 15)	Pre-emptive living-related (aunt)	Uncomplicated recovery	None reported	Standard maintenance immunosuppression	Stable graft function at 2 years
3	XLAS → ESRD (age 22)	Living-related (father)	Hematoma → evacuation	Late ABMR (year 6)	Pulse methylprednisolone (+ supportive therapy)	Stable graft function at last follow-up

COVID: Coronavirus, ESRD: End-stage renal disease.

renal function and normal urinalysis. In autosomal dominant diseases, related donors may carry pathogenic variants with age-dependent penetrance, making cascade genetic testing, combined with renal assessment, essential before donation.

In the present series, molecular testing directly guided donor selection: A COL4A5-carrier mother was excluded in Case 1, while donors in Cases 2 and 3 were genetically unaffected relatives, consistent with contemporary guideline-based practice. Extrarenal manifestations were inconsistently observed across the three cases, illustrating the recognized phenotypic variability of AS. In the autosomal-dominant case, extrarenal involvement was minimal, whereas both X-linked cases exhibited more pronounced and progressive features, particularly sensorineural hearing loss. This pattern aligns with published data demonstrating earlier onset and greater severity of extrarenal manifestations in X-linked forms than in autosomal-dominant forms. Ocular findings were absent or non-specific during early evaluations but evolved over time in one X-linked recipient, with subsequent changes occurring in the context of prolonged immunosuppression after transplantation. These observations suggest that extrarenal features may be incomplete at baseline and emerge longitudinally, underscoring the importance of careful documentation during long-term follow-up rather than relying on a single time-point assessment.

Post-transplant Anti-GBM Nephritis in AS

De novo anti-GBM nephritis is a rare but potentially severe complication after kidney transplantation in AS, and it is reported mainly in males with X-linked disease and, less frequently, in autosomal forms, affecting fewer than 3-5% of recipients. It is thought to result from alloimmune responses against donor-derived type IV collagen epitopes—particularly the α5 (IV) chain—leading to anti-GBM antibody formation in recipients previously unexposed to these antigens. Clinically, the condition typically presents early after transplantation with rapidly progressive graft dysfunction and carries a substantial risk of graft loss.

Prevention relies on appropriate candidate selection, optimized immunosuppression, and close post-transplant surveillance. When suspected, establishing the diagnosis requires prompt serologic testing and graft biopsy, and treatment strategies include intensified immunosuppression and antibody-removal therapies, although outcomes remain variable. In the present series, no recipient developed clinical or serologic evidence of *de novo* anti-GBM nephritis during follow-up. Across the three cases, immunosuppressive regimens were selected according to institutional protocols at the time of transplantation and were subsequently adjusted in response to clinical course and complications, rather than according to predefined genotype-based strategies. Donor evaluation remains a cornerstone of clinical decision-making, particularly when considering living-related donation. Traditional recommendations discouraged the use of heterozygous COL4A5 female carriers as donors due to their lifelong risk of proteinuria and progressive renal impairment (7,11,12). Updated ERKNet-ERA-ESPN guidelines now advise that such carriers be considered only as a last resort, and that individuals carrying COL4A3 or COL4A4 variants should generally be excluded unless comprehensive evaluation demonstrates minimal future risk (15,16). Several mother-to-son transplant reports demonstrate acceptable short- and medium-term outcomes yet also emphasize the potential for long-term renal decline in carriers (8,14). These data highlight the need for individualized donor assessment, multidisciplinary review, and sustained long-term monitoring of living donors.

In our series, all living donors were genetically unaffected relatives, consistent with contemporary recommendations. In Case 1, the patient's mother, a COL4A5 carrier, was appropriately excluded from donation. Donors for Cases 2 and 3 exhibited no pathogenic variants and experienced uneventful postoperative recovery.

Immunologic complications in AS remain relatively uncommon. *De novo* anti-GBM nephritis affects fewer than 5% of males with X-linked disease (13). None of our patients developed this condition, in agreement with recent observations suggesting that optimized immunosuppression and close monitoring reduce occurrence (7,13,15). Case 3 developed late antibody-mediated rejection six years post-transplant, an increasingly recognized contributor to late graft dysfunction (9,15). His favorable response to corticosteroid therapy highlights the importance of long-term immunologic surveillance even in otherwise stable recipients.

The vascular complications observed in Case 1 following SARS-CoV-2 infection reflect the growing body of evidence linking COVID-19 with endothelial injury and heightened thrombotic risk in transplant recipients. Reports describe graft infarction, intrarenal arterial thrombosis, and rapid allograft loss associated with COVID-19-mediated hypercoagulability (17-20). The clear temporal association in this case underscores the need for heightened vigilance regarding post-infectious vascular complications in this population. Although causality cannot be definitively established in a single case, the close temporal association, the vascular distribution of thrombosis, and published transplant reports are consistent with the contribution of COVID-19–associated endothelial injury and hypercoagulability to allograft-threatening events.

Our findings correspond with previously published experiences, including cases summarized in Table 4, which integrate both hereditary nephropathies and COVID-19-associated vascular events (8,14,19,20-23). These parallels reinforce the importance

Table 4. Published cases and series of kidney transplantation in Alport syndrome and related conditions

Study (year)	Inheritance/gene	Age/sex	Donor type	Main issue/ complication	Outcome/ follow-up	Relevance to present series
Katayama et al. (8)	X-linked (COL4A5)	39 M, 36 M	Living-related (mothers)	Calcineurin inhibitor toxicity (1 case); no rejection	Stable grafts at 5 and 10 years	Highlights importance of genetic testing before maternal donation
Girimaji et al. (14)	Autosomal recessive (COL4A3)	22 M	Living-related (mother)	None reported	Excellent graft function	Demonstrates acceptable outcomes with maternal donation when heterozygous and asymptomatic
Webb et al. (17)	Not specified (post-transplant complication)	49 M	Deceased donor	COVID-19–related renal infarction	Graft loss with return to dialysis	Supports COVID-19–associated vascular injury as a mechanism of graft loss
Oto et al. (19)	Alport syndrome spectrum	31 donors (mean age 40 years)	Living-related	Hypertension (56%); cardiac events (20%)	Preserved renal function at 10 years	Highlights long-term cardiovascular risk in related living donors
Present series (2025)	Mixed inheritance (two X-linked, one autosomal-dominant)	15-26 years (3 male recipients)	Two living-related; one deceased donor	Late antibody-mediated rejection; COVID-related vascular thrombosis	Two functioning grafts; one graft loss	Case-based illustration of genotype-guided donor selection, late immune complications, and post-COVID vascular risk

of precise molecular diagnosis, thorough donor evaluation, and comprehensive long-term follow-up in AS transplant recipients.

Although emerging disease-modifying therapies may delay progression to ESRD in selected patients, kidney transplantation remains the definitive treatment once ESRD is reached, as illustrated by the present cases (10,21). Nonetheless, post-transplant management remains grounded in established immunosuppressive protocols and coordinated multidisciplinary care, as demonstrated by the variable clinical courses, immunologic complications, and long-term outcomes observed across the three recipients in this series.

This case series highlights key principles in the management of AS transplant recipients. Genetic confirmation remains essential for safe donor selection and accurate risk stratification. Sustained immunologic monitoring enables the early detection of late rejection episodes. Finally, awareness of COVID-19-related vascular risks is crucial for long-term graft preservation. As precision medicine evolves, genotype-guided decision-making and improved surveillance strategies are expected to enhance post-transplant outcomes in this rare hereditary nephropathy.

CONCLUSION

Kidney transplantation is an effective treatment option for patients with AS. In our series, favorable graft outcomes were achievable across different inheritance patterns when donor selection was guided by molecular testing and clinical risk assessment. Nevertheless, the heterogeneity of post-transplant trajectories observed—including late antibody-mediated dysfunction and severe vascular complications temporally associated with COVID-19—highlights the need for individualized long-term surveillance and cautious interpretation of generalizability.

Ethics

Informed Consent: Written informed consent was obtained from all participants and/or their legal guardians for participation and publication of anonymized clinical data.

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Footnotes

Author Contributions

Surgical and Medical Practices - A.G-B., N.G., A.T.; Concept - A.G-B., H.S., N.B.; Design - A.G-B., H.S., S.D., G.S., M.J.S., N.B.; Data Collection or Processing - A.G-B., H.S., S.D., G.S., N.G., A.T., D.T.; Analysis or Interpretation - A.G-B., H.S., S.D., G.S., M.J.S.; Literature Search - A.G-B., H.S., S.D., G.S., M.J.S., N.B.; Writing - A.G-B., H.S., G.S.

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REVIEW
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From science fiction to operating room: Representations of surgery and AI in film and their ethical implications

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ABSTRACT

This paper examines the intricate relationship between surgical practice, artificial intelligence (AI), and science fiction movies, focusing on how imaginative storytelling has foreshadowed and influenced the development of modern medical technologies. Tracing the timeline from the Industrial Revolution to the digital era, it discusses key advancements such as robotic-assisted operations, virtual reality-based surgical education, augmented reality applications, and telehealth services. The analysis draws on well-known films—including Prometheus, 2001: A Space Odyssey, Star Wars, and Fantastic Voyage—to examine how cinema has portrayed autonomous surgical tools, ethical challenges, and the evolving interaction between humans and machines. These fictional examples are compared with real-world innovations like the Da Vinci robotic system, mobile messaging for remote consultations, and AI-driven diagnostic methods. The article also addresses broader cultural shifts, including the rise of patient-focused care, greater inclusion of women in surgical roles, and the prioritization of empathy and ethical reasoning in clinical practice. Ultimately, the study asserts that while technology continues to transform surgery, the human touch remains essential. A harmonious integration of advanced tools and compassionate care is necessary to sustain the ethical and humane foundations of surgical medicine.

Keywords: Science, surgery, artificial intelligence, robotic surgery, augmented reality ethics

INTRODUCTION

The rate of social change and transformation is increasing. Futurist Toffler (1) envisioned human history as a series of three revolutionary ages—the information, the industrial, and the agricultural ages—in his 1980 book The Third Wave. He suggested that the information age would end in just one hundred years, whereas the agricultural and industrial revolutions lasted approximately one thousand and three hundred years, respectively (1).

The rapid technological development over the last forty years has raised the possibility that the information era will end even sooner than Toffler (1) predicted.

The healthcare industry is one of the fields most significantly impacted by these quick developments. In the past, the goal of medicine has been to improve the effectiveness, accessibility, and quality of its services.

This evolution has been supported by several important forces, such as;

• Changes in the demographics

• Modifications in illness futures and patient expectations,

• Constant developments in technology.

Scientific discoveries have made radical changes in medicine since the beginning of the industrial revolution.

Some of the noteworthy milestones are:

• The invention of the microscope, which made it possible to identify microorganisms as disease-causing agents,

• The introduction of anesthetics, which transformed the comfort and safety,

• The official founding of hospitals and specialties and subspecialties within the medical field.

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Even though progress has accelerated, not all innovations have been warmly received. The quote from the ancient philosopher Confucius that best captures humanity's persistent resistance to change is, "Life is simple, but we insist on making it complicated". Resistance to innovation has been a recurring phenomenon throughout history, as illustrated in Figure 1. However, a failure to understand and adjust to change may ultimately impede the progress of society.

A still from 1899's film, which is regarded as the first known cinematic representation of a surgical procedure, is seen in Figure 2. Alejandro Posadas (1870-1902), an Argentine surgeon, is shown operating with the assistance of medical students in this vintage video. Interestingly, Rodolfo Santiago Roccatagliata, an assistant, regularly drips anesthetic from a vial onto a mask. Although these scenes provide insight into the history of surgery, they also encourage contemplation of the limitations of the time and stimulate ideas about what surgery might be able to do in the future (2).

Science fiction has been a literary genre that pushes the boundaries of human imagination for over 200 years. In technologically advanced cultures, writers have always conjectured about what doctors and surgeons could be capable of. Surprisingly, science fiction has frequently been a prophetic medium, foreshadowing advancements in medicine. Robotic prosthetics and nanobots, two technologies that were previously only seen in science fiction books and movies, are increasingly finding real-world uses in contemporary healthcare.

Science fiction has been a literary genre that pushes the boundaries of human imagination for over 200 years. In technologically advanced cultures, writers have always conjectured about what doctors and surgeons could be capable of. Surprisingly, science fiction has frequently been a prophetic medium, foreshadowing advancements in medicine. Robotic

Figure 1. Throughout history, people have worked for change, yet they have also shown resistance to it. (https://www.google.com/url?sa=i&url=https%3A%2F%2 Ftr.pinterest.com%2Fouido%2F&psig=AOvVaw2eJXLV1zZ6ih7Z8dmM8Jhz&ust=1753787763837000&source=images&cd=vfe&opi =89978449&ved= 0CBEQj Rxq FwoTCIjK4Nq2 344DFQAAAAA dAAAAABAz)

prosthetics and nanobots, two technologies that were previously only seen in science fiction books and movies, are increasingly finding real-world uses in contemporary healthcare. Science fiction is a conceptual roadmap for future innovation as well as a mirror of human aspirations. Once merely theoretical ideas, robotic technologies have quickly developed into instruments in the field of surgery. These technologies, which were first sparked by the fantastical worlds of science fiction, have since been integrated into actual industrial and medical systems. In addition to being commercially available, robotic surgical platforms are now often used in clinical settings. We can now do several procedures that were previously done laparoscopically because of our institution's recent adoption of the Da Vinci robotic surgical equipment (3,4).

Hugo Gernsback, a pioneer in early radio broadcasting and print publishing, was one of the first to imagine remote medical engagement. This technology integration has improved surgical precision and expanded the range of minimally invasive interventions (Figure 3). Long before the telemedicine era, he proposed the "teledactyl" (Figure 4), a novel device with mechanical arms and a display that would allow doctors to physically interact and visually assess patients from a distance. The teledactyl was envisioned as a futuristic tool that would allow doctors to perform remote physical examinations with tactile feedback. Its prospective uses extended beyond remote real-time diagnostics to in-room patient monitoring. In order to make accurate and thorough diagnoses in the future, the device was designed to detect thermal and aural clues (5,6). These forward-thinking ideas foresaw a paradigm shift in the doctor-patient interaction, one that was becoming more and more mediated by technology.

This pattern has been confirmed by developments since the 1970s. Notably, telehealth became an essential tool for sustaining medical care during the coronavirus disease-2019 (COVID-19) epidemic, much like virtual education did in terms of maintaining continuity in the face of worldwide upheaval (7).

Figure 2. A scene from what is believed to be the oldest film depicting a surgical procedure, dated 1899 (2).

An important turning point in the delivery of digital healthcare was reached when our hospital was the first in Türkiye to employ WhatsApp for video-based medical consultations, reviewing their data through our hospital's electronic records and software systems, and offering diagnoses and recommendations accordingly (Figure 5). Physicians could remotely access patient data and provide diagnostic assessments and suggestions by integrating with our institution's clinical software and electronic health records (EHRs). Despite being new at first, these methods are now widely used, especially in disciplines like psychiatry. In Türkiye, one such professional application now implemented by many private and public health institutions is called "E-vital" (8). The practice of prescribing drugs remotely has grown in popularity, and advances in telepresence applications have also been made in the surgical field. Notably, the first-time robotic assistance was used for a brain biopsy was in 1985 (9). The first robot-assisted laparoscopic cholecystectomy was carried out two years later (10). The potential for cross-continental surgical treatment was shown in 2001 when a surgical team in New York used cutting-edge robotic technology to successfully perform a tele-surgical procedure on a patient in Strasbourg (11). The strategic significance of tele-surgical capabilities in military and remote contexts is highlighted by the potential of such breakthroughs, especially for situations where urgent surgical competence is absent, such as emergency surgeries onboard naval vessels stationed at sea. But can people truly entrust their bodies to a machine, allowing it to alter their physical integrity? As a surgeon, I may be speaking emotionally, but I am among those who doubt this will become widely acceptable.

The use of self-operating robotic equipment, the "MEDPOD", by Elizabeth Shaw to execute an open abdominal treatment and remove an alien organism is a noteworthy cinematic example of autonomous surgical intervention in the film Prometheus

Figure 3. Robotic surgery in our operating room.

H. Gernsback, Editor od RADIO NEWS, receiving the television broadcast from WRNY at his home in New York City, with the simple apparatus described in this article. For purposes of the test, the neon tube and lond speaker were connected in series temporarily, with successful operation simultaneously.

Figure 4. Hugo Gernsback and the "teledactyl" (https://tr.m.wikipedia.org/wiki/Dosya:Gernsback_Television_1928.png).

Figure 5. A first in Türkiye: video consultations with patients via WhatsApp in our hospital.

(12). Speculative narratives about the possible autonomy of surgical systems—concepts that were originally purely fictional but are now being discussed more and more in real-world technical discourse—are reflected in this dramatization. In the United States, a fully autonomous robot completed a whole surgical procedure, marking a significant advancement in surgical robotics (13). Even though these incidents are still unusual, they represent a significant change in the ethical issues and technological capabilities related to machine-led medical interventions. Today, advancing technology allows doctors and patients to remain connected even when in-person visits are impossible. In our era, both doctors and patients can access and download their medical records; doctors can consult with one another without institutional limitations. Soon, even lab tests may be conducted from home. Türkiye's "E-Nabız" platform is a notable illustration of digital health innovation, offering consumers immediate, secure access to a variety of healthcare services, including their medical information. This approach is a prime example of how technology can empower patients by promoting openness, independence, and involvement in their treatment (14). Virtual consultations have attracted a lot of attention in the face of a global physician shortage and restricted access to healthcare in underprivileged areas.

Telemedicine does not mean that the doctor-patient connection is ending, even while it encourages patient self-management and convenience. Instead, it reinterprets this relationship in a digital context, utilizing technology efficiency while maintaining interpersonal engagement. As mentioned earlier, Hollywood often envisions the future of technology before it materializes. Table 1 lists the top 10 best-known fictional surgeons from classic science fiction works (15). This study is based on a qualitative analysis of selected Hollywood films produced between 1950 and 2023, focusing on surgery, robotics, artificial intelligence (AI), or medical technology, and influencing public perception. Each film was examined for its representation of surgical practices, the presentation of AI and robotic technologies, and ethical and educational implications. The study is limited to the selected films and does not encompass all popular culture products. The findings from the films were compared and evaluated with existing literature (including systematic reviews and meta-analyses obtained through PubMed searches).

Table 1. The ten iconic characters in the role of surgeons from science fiction classics

Victor Frankestein
Miles Bennell
Doctor Blair
Helena Russel
White uniform men
Three doctors who slept criyogen sleep
Leonard McCoy
Robotic surgeon
Dr. Ash
Peter Duval

The protagonist in the film adaptation of Mary Shelley's novel, "Frankenstein", personifies the stereotypical figure of the overreaching surgeon motivated by a warped pursuit of perfection. He creates a monster out of cadaveric remains and eventually succumbs to the life he made. The historical background of surgical practice in the 20th century, where patients were routinely subjected to medical judgments without sufficient explanation or participation, is paralleled in this fictitious story. Physicians frequently made unilateral decisions about treatment plans, which reflected a paternalistic paradigm with little patient autonomy. Patient empowerment is becoming more and more accepted in modern surgical practice. Patients today want open communication about their medical options, actively seek out information, and engage in support groups. As a result, surgeons are now more dedicated than ever to obtaining informed consent and offering thorough explanations. This change is indicative of a more morally based doctor-patient relationship and a larger trend toward shared decision-making (15,16).

In the last 5 decades: Significant improvements in communication between surgeons and patients have significantly made. Yet, we still struggle with mutual trust. Modern patients increasingly seek second opinions, which leads to more medical procedures and diagnostic tests, requiring shared responsibility between doctors, patients, and their families. Dr. Miles Bennell is a prophetic character in "Invasion of the Body Snatchers" who sees an increasing danger but is disregarded by his community. He is the only one who ignores his warnings as extraterrestrial replicas gradually replace his patients (17).

This fictional representation reflects contemporary obligations on the part of doctors, who are required by law and ethics to notify public health authorities about unusual cases, outbreaks, or systemic failures.

Even unlikely or infrequent presentations are taken seriously and dealt with effectively thanks to today's emphasis on responsibility, openness, and documentation. Although patient complaints may sometimes be exaggerated, doctors now must provide clearer explanations and maintain more thorough documentation to avoid malpractice claims. No matter how strange complaints may seem, doctors and patients are obligated to take one another seriously today (15). An extraterrestrial being infiltrates a scientific research station in Antarctica, taking over and mimicking the researchers in John

Carpenter's 1982 novel The Thing. When Dr. Blair disregards fundamental safety procedures during an autopsy, he becomes a vector of infection and eventually falls victim to the alien entity.

This story emphasizes how crucial infection control procedures are in contemporary surgical settings (18). To reduce occupational risks, surgeons now follow stringent safety procedures, such as wearing gloves, masks, and goggles, and getting regular vaccinations against communicable infections. Risks like needlestick injuries and virus exposure still exist despite these safeguards, highlighting the ongoing importance of surgical safety regulations and informed patient consent, particularly concerning bloodborne infections like human immunodeficiency virus (HIV) and hepatitis C (15). During the COVID-19 pandemic, many healthcare workers, including surgeons, contracted the virus. In surgeries, infection with HIV and other viruses remains an occupational hazard. Over the past 50 years, protective equipment and screening tests have greatly improved surgeons' ability to avoid infections.

During a time when women were mainly underrepresented in the medical sector, Dr. Helena Russell, who was portrayed in the BBC series Space: 1999, became a trailblazing example of female surgical ability. Her persona defied accepted gender stereotypes by exhibiting emotional intelligence, leadership, and clinical knowledge. Less than 8% of surgeons were women by the end of the 20th century (19). But things have changed much since then, and women are now highly skilled in all areas of surgery. International luminaries like Prof. Dr. Monica Morrow and Prof. Dr. Giuseppe Galimberti, as well as notable individuals like Prof. Dr. Güldeniz K. Çakmak, Prof. Dr. Yeşim Erbil and Prof. Dr. Seher Demirer in Türkiye, demonstrate the crucial role that women today play in improving surgical knowledge and practice. Government officials, disguised as anonymous medical professionals, break into a little boy's house in Steven Spielberg's E.T. and brutally and dehumanizingly experiment on the extraterrestrial creature. Their disregard for the emotional root of E.T.'s disease (homesickness) is indicative of a larger criticism of impersonal, cold medicine (20).

On the other hand, contemporary medical and surgical ethics place equal emphasis on patient-centered care and clinical efficacy. Today's treatment choices necessitate a careful balancing act between quality of life, procedural risks, and survival outcomes. This development highlights a crucial change away from intrusive paternalism and toward compassionate, cooperative doctor-patient decision-making. The cryogenic preservation of doctors on board the spaceship Discovery One in Stanley Kubrick's 2001: A Space Odyssey represents both reliance on AI and faith in future medical needs. Concerns about an over-reliance on autonomous technologies are reflected when the onboard AI system HAL-9000 takes over human command and kills the frozen crew (21). Clinical practice in modern medicine has been significantly impacted by the digitization of healthcare, especially EHRs. These systems enhance legal protection, accessibility, and data preservation, but they have also introduced additional paperwork constraints that impact medical workflow and medico-legal defense strategies (15,22).

As the chief medical officer of the USS Enterprise in Star Trek, Dr. Leonard McCoy is a figure of paradox—a doctor in a technologically advanced future yet with a strong foundation in orthodox medical beliefs. Despite having state-of-the-art diagnostic tools that enabled non-invasive, real-time assessments, his postoperative care strategy was still outdated. This comparison highlights the difficulty of adjusting established clinical practices to contemporary, evidence-based norms. For example, surgical care used to lack early postoperative mobilization, which is now a standard practice. Thus, McCoy's character serves as an example of how paradigm shifts in clinical thought and behavior must coexist with technical innovation (23).

During the battle between the Light Side and the Dark Side, a young hero loses his arm. In the movie Star Wars: The Empire Strikes Back. A robotic surgeon—the autonomous humanoid 2-1B surgical robot—replaces it with a bionic arm effortlessly (24).

Over the past 30-40 years, surgery has made incredible strides: Complex operations can now be performed through small incisions. Laparoscopic or minimally invasive procedures, Robotic surgery (e.g., Da Vinci systems), navigation tools, and virtual reality (VR) technologies are available. Still, such interventions must be led by human surgeons. Although robotic systems offer great possibilities, these surgeries can still be performed manually today. Interestingly, films like The Matrix (1999) and Total Recall (1990) present more realistic scenarios than Star Wars when it comes to future medicine (25,26). In Alien, the doctor on board the Nostromo, Dr. Ash, is eventually shown to be an android whose primary purpose is to protect alien life ahead of human life. His disdain for crew safety and disengagement from ethical standards serve as an example of the dangers associated with removing morality and human empathy from medical decision-making (27).

On the other hand, modern healthcare places a strong emphasis on patients and surgeons working together to make decisions. Work together to decide on the treatment plan. In order to maintain ethically sound and patient-centered care, doctors—especially surgeons—must continue to play a key role in clinical decision-making processes, even while healthcare administrators may push for cost-cutting or protocol adherence (15).

Dr. Peter Duval is portrayed in Fantastic Voyage (1966) as a

metaphorical forerunner of contemporary minimally invasive surgery. On board the miniature submarine Proteus, he uses a laser instrument to remove a cerebral clot from an ill scientist's vascular system. This creative depiction figuratively foreshadows current surgical objectives, which include maximizing therapeutic impact with the least amount of invasiveness. The aspirations first envisioned in such speculative narratives are reflected in the rising number of technologies used in operating rooms today that are intended to minimize incision size, maximize precision, and speed recovery (15,28,29). Science fiction books and films have proliferated during the last 20 years, challenging and stimulating medical imagination (Figure 6) (30).

These artistic endeavors frequently function as conceptual labs where new technologies and moral conundrums are explored through story testing. As mentioned, intellectual curiosity is still necessary for innovation, especially in the medical field. A doctor who stops being curious runs the risk of losing interest in the direction of advancement and losing the chance to influence how healthcare is developed in the future. There are significant technological developments in healthcare from the early 2000s to the present, with AI being highlighted as a key development (31).

These advancements highlight how digital tools and clinical practice are increasingly overlapping. In light of this change, it is critical to proactively assess both established and new technologies to make sure that their application continues to be morally righteous and therapeutically advantageous.

VR in Surgery and Medical Education

In surgical practice and teaching, VR has become a game-changing instrument. Using immersive 360-degree camera systems, surgeon Shafi Ahmed carried out the first VR-assisted treatment in history at Royal London Hospital in April 2016 (32,33). Students, reporters, and family members could see the treatment in real time using the Medical Realities platform because it was streamed worldwide. This milestone marked the start of a new age in surgical training, where students can watch, practice, and hone their abilities in simulated operating rooms thanks to immersive technologies (34,35).

For surgical education, VR technology provides immersive, scalable, and internationally accessible platforms. Trainees can now experience operations from the surgeon's point of view instead of just watching them passively from behind the operating table. With the use of VR-based technologies, surgeries can be streamed in real time across international borders, allowing students wearing headsets to virtually experience the operating room. In order to improve radiological interpretation, procedural planning, and the educational experience of surgical

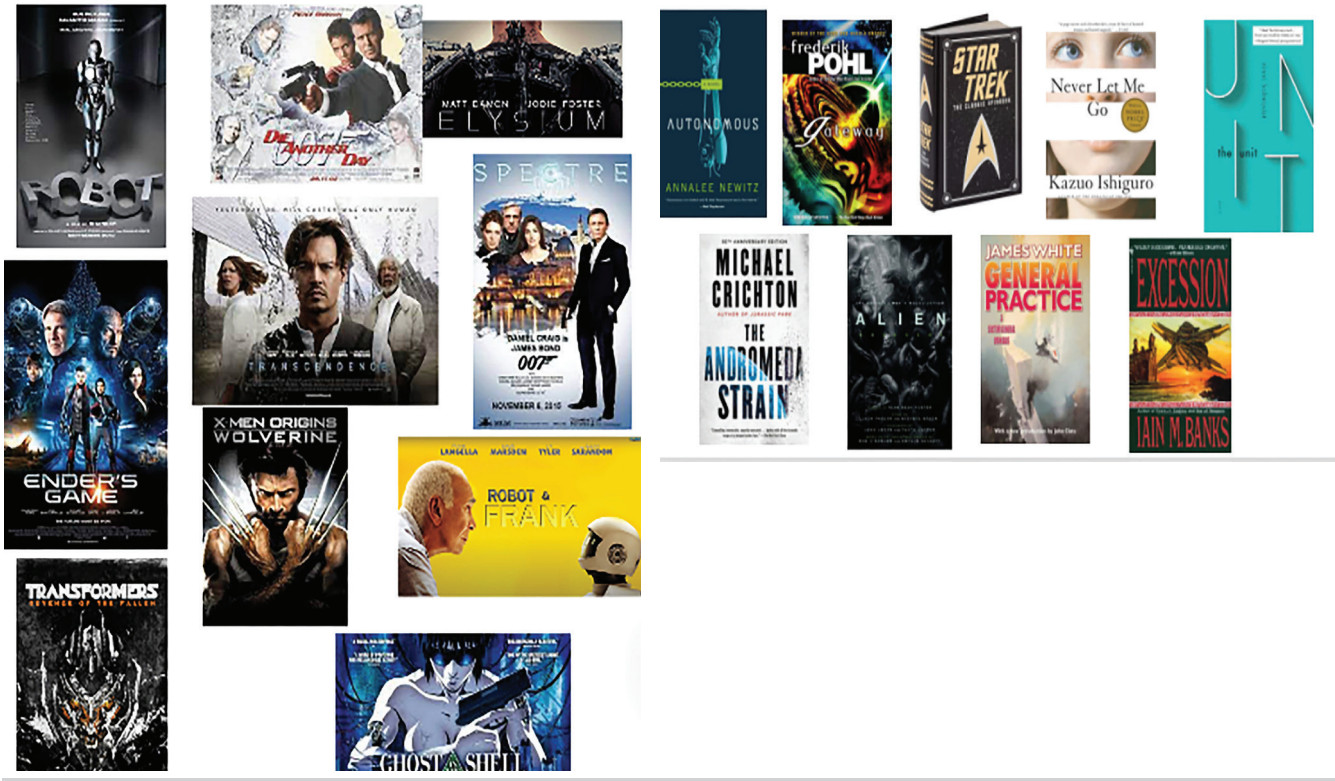

Figure 6. Some notable science fiction books and films from the last 10-20 years.

trainees, teams like The body VR are actively creating simulation tools and interactive material (Figure 7) (36,37).

Augmented Reality (AR) in Surgical Precision

By directly superimposing important anatomical and procedural information into the surgeon's field of vision, AR enhances the surgical environment. In contrast to VR, AR enhances perception rather than replaces it by preserving the user's link to the real world (38). This capacity is particularly helpful for intricate processes like tumor localization or minimally invasive surgery (MIS) navigation. AR is being used to maximize intraoperative precision and enhance patient outcomes, as demonstrated by cutting-edge systems like Medsights Tech's tumor modeling software and Atheer's wearable interface (39,40).

An example of the cutting edge of interactive medical visualization is the "True 3D" system from EchoPixel (41). With the help of this platform, physicians may work in real time with three-dimensional (3D) models of a patient's anatomy, generating an open virtual environment that allows organs and tissues to be examined from various perspectives. Such technology could improve surgical planning, boost the safety and effectiveness of complex treatments, and improve the accuracy of diagnostics.

Surgical Robots: Engineering Marvels in Modern Surgery

The extensive use and confidence in these cutting-edge devices are demonstrated by the fact that the global surgical robotics market had grown to over $6.4 billion by 2020. For more than 15 years, the da Vinci Surgical System in particular has been the industry standard. With the use of high-definition, 3D imagery and articulated tools that are more accurate than human hands, the technology allows for small incisions and precision surgeries. Surgeons retain complete control over these sophisticated instruments, guaranteeing patient safety and clinical responsibility (42).

Figure 7. An example of a surgical application using a VR headset.
VR: Virtual reality

The development of next-generation robotic systems has been hastened by recent partnerships with major pharmaceutical and technology companies. The area of robotic application in microsurgery is expanded by these more recent systems, which have precision-driven components and small, flexible arms designed to execute complex procedures involving delicate tissues (43,44).

MIS

Reducing patient trauma while maintaining or regaining physiological function has continuously been at the forefront of surgical innovation. The post-Edison era saw the emergence of early endoscopic instruments, which developed in the late 20th century with the introduction of fiber optics and microcameras. These innovations made it possible to visualize and manipulate internal processes with never-before-seen clarity. More recently, innovations like FlexDex's mechanical wrist-extension tools and Levita's magnetic surgical system have increased the potential of MIS and provided affordable, ergonomic substitutes for fully robotic systems (45,46).

3D Printing and Simulation for Preoperative Planning and Training

Preoperative planning and surgical education have both benefited greatly from the use of 3D printing. A congenital abnormality was successfully corrected in 2016 by Chinese surgeons using a full-scale 3D printed model of a newborn's heart (47). Similar technology was used later that year by a team in the United Arab Emirates to precisely direct the excision of a kidney tumor. These instances demonstrate how useful patient-specific anatomical models are for increasing surgical accuracy. Additionally, 3D printing is becoming more and more popular in classrooms, providing students with tactile organ models for simulation and procedural practice (48). The simulation platform Touch Surgery has developed systems for practicing various procedures, from cardiac surgery to carpal tunnel release (49).

Live Diagnostic: The Smart Scalpel

Zoltan Takats of Imperial College London created the intelligent surgical knife (iKnife), which combines real-time mass spectrometry and electrosurgical dissection. The chemical makeup of the tissue that is vaporized during incision is instantly examined, enabling the surgeon to make an immediate distinction between benign and cancerous tissue. By converting

surgery into a dynamic, intraoperative detection process, this breakthrough offers a fresh diagnostic paradigm that holds promise for earlier, more precise cancer therapies (50).

AI and Surgical Robotics

Many people believe that the future of operative medicine lies in the fusion of surgical robotics and AI. AI programs like Google's DeepMind and IBM's Watson are already showcasing their powers in clinical decision assistance (51).

Deep learning algorithms based on clinical and radiologic datasets are used by platforms such as Enlitic to accurately identify pathological anomalies (52). It is anticipated that surgical treatments will become more individualized, safer, and faster as AI technologies are incorporated into robotic and minimally invasive devices (53,54).

Despite the experimental demonstration of fully autonomous surgical systems, it seems doubtful that human surgeons will become obsolete (Figure 8) (13). Patient care still requires empathy, clinical insight, and ethical judgment—elements that no machine or algorithm can replace. Even in the age of AI and robotics, there will always be a need for a skilled human—man or woman—holding the scalpel, making critical decisions, and connecting with the patient. So, the human aspect must be maintained as automation and AI become more and more integrated into surgical practice. In order to ensure that patient welfare always comes first, the future of medicine will need a symbiotic interaction between clinical competence and technological innovation. Despite rapid technological progress, robots and machines cannot replace the human element of care. Surgeons must retain their presence and voice in the decision-making processes of healthcare. Empathy, ethical reasoning, and human intuition are qualities no algorithm can replicate.

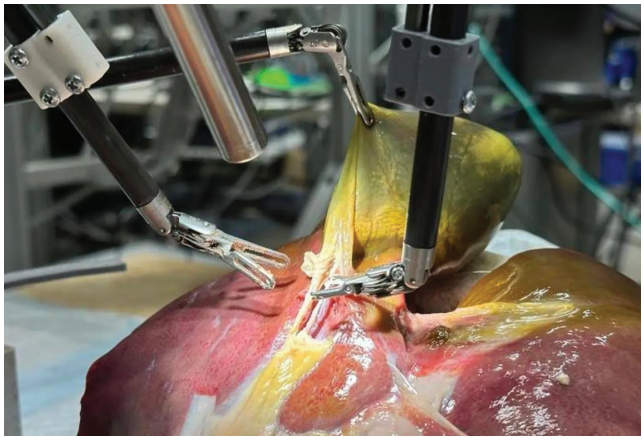

Figure 8. A historic image of the world's first fully autonomous robot-performed surgery.

Footnotes

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REVIEW
Turk J Surg 2026;42(2):267-278

Re-arming checkpoint blockade in MSS colorectal cancer: A precision-microbiome playbook from mechanisms to clinic

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ABSTRACT

Immune checkpoint blockade transforms outcomes for the 15% of colorectal cancers (CRCs) with mismatch-repair deficiency; yet most tumours remain refractory. Beneficial gut microbes can change this. *Akkermansia muciniphila*, *Bacteroides fragilis,* and short-chain fatty acid producers prime dendritic cells to produce interleukin (IL)-12, polarise Th1 cells, and reinvigorate $CD8^+$ T-cells. Antibiotics, Western-style diets, and *Fusobacterium nucleatum* foster myeloid suppression and β-catenin- or IL-17-mediated signalling, which blunt checkpoint activity. Multi-omics analyses link biosynthetic genes for inosine, riboflavin, and folate to durable clinical benefit. Faecal microbiota transplantation from responders has produced objective regressions in otherwise refractory microsatellite-stable disease. This narrative review maps CRC–microbiota–immune crosstalk, evaluates biomarkers and interventions, and proposes a CRC-specific, three-tiered clinical algorithm. We outline standards for trial design and manufacturing processes to facilitate the translation of microbiota-guided therapy into routine practice.

Keywords: MSS CRC, fecal microbiota transplantation, live biotherapeutic products, short-chain fatty acids, microbiome biomarkers, qPCR panel, antibiotic stewardship, inosine, riboflavin pathway

INTRODUCTION

Colorectal cancer (CRC) remains the second leading cause of cancer-related mortality worldwide despite incremental advances in screening and systemic therapy (1). The advent of immune-checkpoint blockade (ICB) targeting programmed death-1 (PD-1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) has delivered durable responses in mismatch-repair-deficient (dMMR) tumours; however, fewer than 15% of CRCs exhibit dMMR, and response rates in the microsatellite-stable (MSS) majority remain below 10% (2). Understanding and overcoming this resistance constitute a pressing clinical need.

Over the past decade, the gut microbiota has emerged as a pivotal modulator of anticancer immunity. Landmark murine experiments showed that broad-spectrum antibiotics abrogate, while specific commensals restore, the efficacy of anti-PD-1 therapy (3). Subsequent work delineated mechanistic pathways: Short-chain fatty acids enhancing dendritic cell interleukin (IL)-12 production (4), microbial inosine acting on A_2A receptors to potentiate Th1 polarisation (5), and bacterial outer membrane vesicles amplifying STING signalling in tumour-infiltrating myeloid cells (6). Crucially, these effects are not generic across tumour types; colorectal models display unique dependencies on intraluminal taxa that modulate the Wnt-β-catenin and IL-17 networks (7).

Clinical investigations corroborate these findings. In prospective cohorts, higher alpha diversity and enrichment of *Bacteroides* spp. are associated with objective response and prolonged progression-free (PFS) survival with anti-PD-1 therapy (8). Multi-omics profiling links microbial gene clusters for tryptophan metabolism and vitamin B biosynthesis to heightened $CD8^+$ T-cell infiltration (9), while antibiotic exposure within 60 days of ICB initiation independently predicts poorer outcomes (10). Importantly, early-phase trials of faecal-microbiota transplantation (FMT) from

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ICB responders into refractory metastatic CRC patients have reported partial responses and disease stabilisation without grade ≥3 toxicity (11).

Nevertheless, the field is rife with contradictions. Some studies fail to reproduce predictive taxa across geographic cohorts (12), and dietary fibre interventions that enhance ICB efficacy in melanoma yield neutral effects in CRC models (13). Disparities likely arise from tumour-intrinsic immunogenicity, host genetics, cancer stage, and methodological heterogeneity in microbial sampling and bioinformatics pipelines. These discrepancies underscore the necessity for CRC-specific standardised research approaches.

Against this backdrop, we undertake a comprehensive narrative synthesis of the literature published from January 2019 to July 2025, restricted to PubMed-indexed sources to ensure rigorous curation. Our objectives are fourfold:

1. Map mechanistic crosstalk between gut microbes, epithelial/immune compartments and tumour genomics that influences ICB outcomes (5,7,14),

2. Critically appraise biomarker studies delineating microbial signatures of response and resistance (8,10,15),

3. Evaluate interventional strategies—dietary modulation, pre-, pro-, and post-biotics, FMT, defined bacterial consortia, and targeted antibiotics—that aim to "re-arm" checkpoint blockade (11,16-18),

4. Identify controversies and future priorities, including causal inference challenges, regulatory hurdles for live biotherapeutics, and equitable access in low-resource settings.

Consistent with the Turkish Journal of Surgery's directive that review articles encompass "Clinical and Research Consequences" before concluding, the subsequent sections translate mechanistic insights into clinical algorithms and considerations for trial design. By weaving bench and bedside evidence into a coherent translational narrative, we aspire to furnish surgeons, oncologists, and microbiome scientists with actionable knowledge that can accelerate the integration of microbiota-guided strategies into routine CRC care.

Current Landscape of ICB in CRC

Immune checkpoint inhibitors (ICIs) have redefined management of the approximately 15% of metastatic colorectal cancers that harbour mismatch-repair deficiency (dMMR) or high microsatellite instability (MSI-H). Pembrolizumab monotherapy is a first-line standard of care, having demonstrated superior PFS survival compared with chemotherapy in KEYNOTE-177 (2). Nivolumab, alone or in combination with low-dose ipilimumab, provides durable responses in previously treated patients with dMMR/MSI-H mCRC, with 5-year overall survival exceeding 60% (1). These successes have prompted exploration of earlier-stage settings: For example, neoadjuvant short-course nivolumab plus ipilimumab achieved pathological complete response in 95% of dMMR rectal cancers, enabling organ preservation strategies (2).

By contrast, patients with MSS tumours—comprising 85% of CRC—derive minimal benefit, with objective response rates <10% despite combination regimens that add chemotherapy, radiotherapy, VEGF or EGFR blockade (2). Biomarker-driven efforts reveal that an "inflamed" tumour microenvironment (TME), characterised by high $CD8^+$ T-cell density and interferon-γ signatures, predicts ICI response regardless of MSI status; yet such phenotypes are rare in *de novo* MSS disease (8). Accordingly, current research pivots toward strategies that convert "cold" MSS lesions into "hot" lesions, including oncolytic viruses, personalised vaccines, KRAS G12C inhibitors, and—most prominently—gut-microbiota modulation (10).

Antibiotic exposure around the time of ICI initiation is independently associated with inferior outcomes across multiple solid tumours, including CRC (10), implicating commensal disruption as a clinically relevant resistance factor. Conversely, faecal microbiota transplantation (FMT) from ICI responders has achieved partial responses in refractory mCRC (11). These observations, coupled with mechanistic data reviewed below, position the intestinal ecosystem as a tractable patient-specific lever to re-arm checkpoint blockade for the MSS majority. The rapid progression of these discoveries is outlined chronologically in Figure 1, which maps key microbiota-immunotherapy milestones from 2019 to 2025.

Gut Microbiota-immune Crosstalk: Mechanistic Foundations

Microbiota-primed innate immunity

Pattern recognition of microbial-associated molecular patterns (educates intestinal innate cells long before malignant transformation. In murine CRC, colonisation with *Akkermansia muciniphila* or a defined *Bacteroides* consortium promotes maturation of dendritic cells and increases IL-12 production, thereby boosting type I interferon and downstream STAT1, which are required for anti-PD-1 efficacy (5). Outer membrane vesicles from *Bacteroides fragilis* amplify STING-dependent cyclic GMP-AMP signalling in tumour-resident myeloid cells, enhancing cross-presentation and $CD8^+$ T-cell priming (6). Conversely, enrichment of *Fusobacterium nucleatum* engages TLR4/MyD88, recruits myeloid-derived suppressor cells, and blunts anti-PD-1 activity.

Innate re-arming checklist (CRC): DC IL-12 priming (*Akkermansia/Bacteroides*) (5); STING amplification in tumour-myeloid cells (6); containment of TLR4/MyD88-driven suppressor recruitment (*Fusobacterium*) (19-21); preservation of CXCL9/10 trafficking

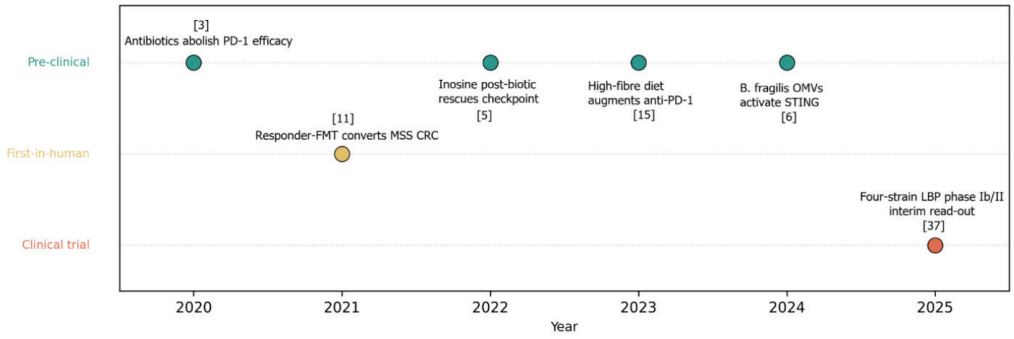

Figure 1. Chronology of seminal microbiota–ICI studies in CRC (2019-2025).

ICI: Immune-checkpoint inhibitor, CRC: Colorectal cancer, PD-1: Programmed death-1, LBP: Live biotherapeutic product, MSS: Microsatellite-stable, FMT: Faecal-microbiota transplantation

under anaerobe-sparing antibiotic stewardship (4). These levers converge on the restoration of intratumoral IFN-γ and $CD8^+$ during anti-PD-1 therapy.

Adaptive-immune sculpting by specific taxa

Adaptive effects arise through antigenic mimicry and metabolite-mediated signalling. T-cell receptor sequencing shows clonal convergence between bacterial and tumour neo-epitopes; *Enterococcus hirae* peptides resembling KRAS mutations expand cross-reactive $CD8^+$ cells that infiltrate MSS tumours after FMT (19). Microbial inosine from *Bifidobacterium pseudolongum* activates A_2A receptors on naïve T-cells, lowering the threshold for Th1 polarisation during anti-PD-1 therapy (5). Short-chain fatty acids, such as butyrate, enhance memory T-cell glycolysis and effector-gene acetylation, thereby sustaining cytotoxicity during chronic antigen exposure (20). In contrast, overrepresentation of *Fusobacterium nucleatum* drives TLR4–NF-κB–dependent myeloid-derived suppressor cell recruitment and reduces ICI responsiveness (21).

Metabolic and barrier-integrity axes

Tumour metabolism intersects with microbial products to shape the therapeutic outcome (Table 1).

Tryptophan catabolites from indoleamine-2,3-dioxygenase-expressing bacteria generate kynurenine, an aryl hydrocarbon receptor ligand that skews regulatory T-cell differentiation and impairs anti-PD-1 efficacy (22). Conversely, propionate and pentanoate restore dendritic-cell oxidative phosphorylation, rescuing ICI response in germ-free mice (23). Barrier dysfunction, common in CRC, promotes the translocation of lipopolysaccharide into the portal circulation, activating Kupffer-cell IL-6 release and systemic neutrophilia, which neutralises cytotoxic lymphocytes (7). Commensal-induced up-regulation of mucin-2 and tight-junction proteins mitigates this leakiness, partially explaining why high-fibre diets correlate with better ICI outcomes in some cohorts (24).

Tumour-intrinsic genomic interplay

Microbial metabolites interface with oncogenic pathways, creating vulnerabilities that microbiota manipulation can exploit to restore ICI sensitivity. Secondary bile acids produced by *Clostridium* spp. trigger Wnt-β-catenin signalling, reducing dendritic cell recruitment and fostering an "immune-excluded" phenotype characteristic of MSS CRC (25). Conversely, bacterial polyamines inhibit ERK phosphorylation, enhancing MHC-I expression and antigenicity under IFN-γ stimulation (14).

Table 1. Metabolic and barrier levers by which the gut microbiota modulates ICI efficacy in colorectal cancer

Lever	Microbial / metabolite driver	Expected effect on ICI	Evidence strength
SCFAs (butyrate, propionate)	*Eubacterium, Ruminococcaceae*	↑ Memory-T fitness, ↑ GZMB, more durable control	Strong (mouse); pilot human supportive
Inosine → A2A signalling	*Bifidobacterium/Akkermansia*	Lowers Th1 activation threshold; ↑ $CD8^+$ activity	Strong (mouse); emerging human correlative
Barrier integrity/mucin	*A. muciniphila*; high-fibre diet	↓ LPS leak → ↓ IL-6–driven neutrophilia	Moderate
Kynurenine/AhR axis	IDO-linked bacteria	↑ Treg skew; blunts PD-1 efficacy	Moderate

SCFA: Short-chain fatty acid, GZMB: Granzyme B, ICI: Immune-checkpoint inhibitor, A2A: Adenosine A2A receptor, Th1: T helper type 1, $CD8^+$: CD8-positive cytotoxic T lymphocyte, LPS: Lipopolysaccharide, IL-6: Interleukin-6, AhR: Aryl hydrocarbon receptor, IDO: Indoleamine 2,3-dioxygenase, CRC: Colorectal cancer, PD-1: Programmed death-1.

Genome-scale CRISPR screens reveal that loss of tumour STING renders anti-PD-1 therapy ineffective unless compensated for by microbial cyclic-di-AMP producers, such as *Lactococcus lactis* (26). These data suggest that selecting or engineering commensals to target tumour-specific vulnerabilities could personalise microbiota-guided immunotherapy.

Systems-level insights

Multi-omics integration underscores the complexity of CRC–microbiota–immune interactions. A prospective study combining metagenomics, metabolomics, and single-cell RNA-seq identified a responder-associated consortium enriched for genes encoding enzymes involved in riboflavin and folate synthesis pathways, which are linked to enhanced oxidative phosphorylation in intratumoral T-cells (27). Network analysis shows that microbial modules correlate more strongly with ICI outcome than does tumour mutational burden after adjusting for clinical covariates (28). Notably, machinelearning models trained on microbial gene signatures achieved external validation AUCs >0.85 in independent MSS cohorts (29), supporting clinical translation.

Interim synthesis

Collectively, these mechanistic findings establish the gut microbiota as both sentinel and sculptor of anti-tumour immunity (Figure 2). They also illuminate multiple intervention points—from enhancing beneficial taxa and metabolites to blocking deleterious microbial pathways—that may convert ICI-refractory MSS CRC into an ICI-responsive disease.

Microbiota-driven Resistance and Sensitisation in Pre-clinical Models

Pre-clinical CRC models show that dysbiosis blocks ICI efficacy, while specific taxa or metabolites can rescue the response to anti-PD-1.

Antibiotic-induced resistance

In the syngeneic MC38 CRC model, a five-day cocktail of ampicillin, vancomycin, and metronidazole abolished the tumour-regressive effect of anti-PD-1 despite preserved drug exposure (3). Depletion of Gram-positive *Clostridiales* eliminated butyrate-producing taxa essential for dendritic-cell (DC) IL-12 priming; faecal reconstitution with antibiotic-naïve microbiota restored the response (4). Similar resistance arises when germ-free mice receive stool from patients recently treated with broad-spectrum antibiotics compared with stool from responder donors (23), corroborating clinical observations that peri-therapeutic antibiotics worsen outcomes.

Dietary dysbiosis and loss of efficacy

Western-style, low-fibre/high-fat diets precipitate *Fusobacterium*-dominant dysbiosis in Apc^{Min}/+ mice, impairing anti-PD-1–mediated $CD8^+$ T-cell infiltration (30). By contrast, a high-prebiotic regimen enriches *Bifidobacterium pseudolongum* and increases luminal inosine, restoring Th1 polarisation and tumour control (13). These opposing results underscore diet as a modifiable variable that can either undermine or potentiate checkpoint therapy.

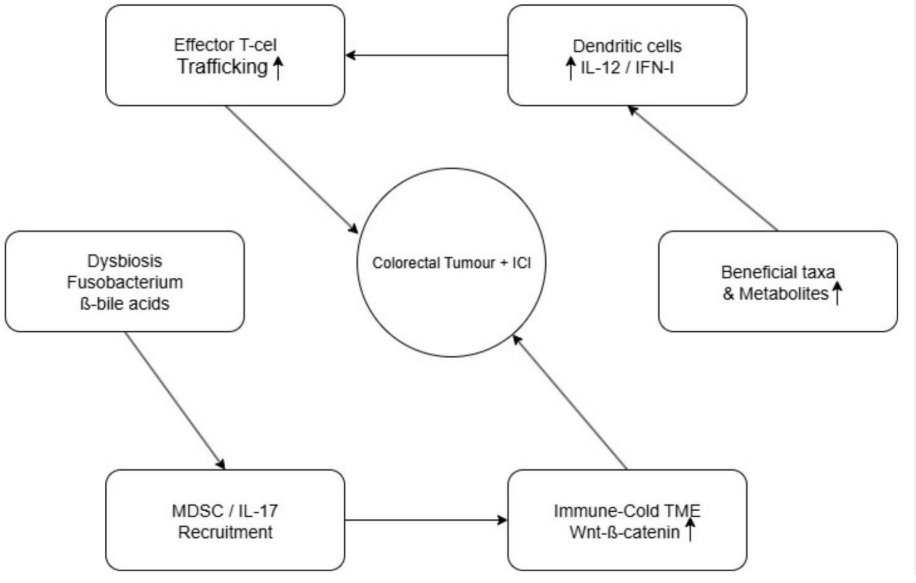

Figure 2. Bidirectional CRC–microbiota–immune loop.
ICI: Immune-checkpoint inhibitor, CRC: Colorectal cancer, TME: Tumour microenvironment, IL: Interleukin

Beneficial commensals that "re-arm" checkpoint blockade

Colonisation with *Akkermansia muciniphila* enhances DC maturation through TLR2 signalling, boosts intratumoral interferon-γ levels, and rescues anti-PD-1 efficacy in both MC38 and CT26 models (5). *Bacteroides fragilis* outer membrane vesicles activate STING in tumour-resident myeloid cells, increasing CXCL10 levels and effector cell recruitment (6). Butyrate produced by *Eubacterium rectale* promotes histone acetylation of Gzmb in memory T-cells, thereby prolonging cytotoxicity during chronic antigen exposure (20). Conversely, enrichment of *Fusobacterium nucleatum* activates TLR4/MyD88 signalling, which recruits myeloid-derived suppressor cells and negates the efficacy of anti-PD-1 therapy (21).

FMT experiments

FMT from melanoma or CRC patients who achieved durable clinical benefit reproducibly sensitises MSS tumour-bearing mice to anti-PD-1 or combined PD-1/CTLA-4 therapy, producing complete responses in 40-60% of recipients (11). Tumour rejection correlates with engraftment of *Ruminococcaceae* and increased faecal propionate, while non-responder FMT maintains dysbiosis and progressive disease.

Engineered consortia and post-biotics

A four-strain live biotherapeutic product (LBP) (31) comprising *A. muciniphila, B. fragilis, E. rectale*, and *Bifidobacterium longum* overcame primary PD-1 resistance in CT26 tumours, outperforming single-strain gavage and matching responder-FMT efficacy (31). In a complementary approach, delivery of purified inosine or butyrate postbiotics rescued checkpoint activity in the absence of viable bacteria, an important safety consideration for immunocompromised hosts (32). Narrow-spectrum bacteriocins that selectively deplete *F. nucleatum* restored the anti-PD-1 response while preserving commensal diversity (18).

Tumour-genomic interplay and synthetic lethality

CRISPR screens identified tumour STING loss as a driver of ICI resistance; colonisation with *Lactococcus lactis*— a cyclic-di-AMP producer— re-engaged STING-independent type I interferon signalling and reinstated PD-1 sensitivity (26). Secondary bile acids from *Clostridium* spp. activated Wnt-β-catenin, creating an "immune-excluded" phenotype that persisted despite anti-PD-1 (25); whereas bacterial polyamines inhibited ERK phosphorylation and augmented MHC-I expression and antigenicity (14). These findings highlight opportunities to pair microbiota manipulation with genomically matched, targeted therapies.

Translational lessons

Collectively, preclinical evidence demonstrates that (i) dysbiosis—whether antibiotic-, diet-, or bile-acid-driven—creates an immunosuppressive niche that nullifies ICIs, (ii) restoration or supplementation of specific commensals/metabolites can rearm therapy, and (iii) tumour-intrinsic pathways dictate which microbial cues are decisive. These principles underpin the rationale for biomarker-guided modulation strategies now moving into clinical trials (Table 2).

Clinical Biomarkers and Predictive Signatures

Human cohorts link microbial diversity, taxa, and functional pathways to ICI outcomes in CRC, with functional signatures outperforming taxonomic lists.

Taxonomic signatures

In a prospective multi-centre MSS mCRC cohort (n=63), higher baseline α-diversity and enrichment of *Ruminococcaceae_*UCG-013 and *Faecalibacterium prausnitzii* predicted objective response to PD-1 ± CTLA-4 blockade, yielding an area under the curve (AUC) of 0.82 after adjustment for MSI status (8). A Chinese single-institution study (n=58) corroborated the association between *Akkermansiaceae* abundance and PFS (15). Conversely, high relative abundance of *Fusobacterium nucleatum* or

Table 2. Pre-clinical models demonstrating microbiota-modulated ICI response in CRC

Ref	Year	Model	Manipulation	Checkpoint agent	Key outcome
(3)	2020	MC38 (mouse)	Broad antibiotics	Anti-PD-1	Abolished tumour regression
(5)	2022	MC38 & CT26	*A. muciniphila* gavage	Anti-PD-1	DC IL-12 ↑, IFN-γ $CD8^+$ ↑, complete responses 60%
(6)	2024	MC38	*B. fragilis* OMVs	Anti-PD-1	STING-CXCL10 axis ↑, T-cell trafficking ↑
(20)	2023	CT26	Butyrate supplement	Anti-PD-1	Memory-T histone acetylation ↑, durable control
(31)	2025	CT26	4-strain LBP	Anti-PD-1	Outperformed single-strain; 70% tumour rejection
(18)	2025	MC38	*F. nucleatum*-targeted endolysin	Anti-PD-1	MDSC ↓, response restored

ICI: Immune-checkpoint inhibitor, PD-1: Programmed death-1, LBP: Live biotherapeutic product, SCFA: Short-chain fatty acid, MSS: Microsatellite-stable, dMMR/MSI-H: Mismatch-repair-deficient/microsatellite-instability-high, ORR: Objective response rate, DCR: Disease control rate, PFS: Progression-free survival.

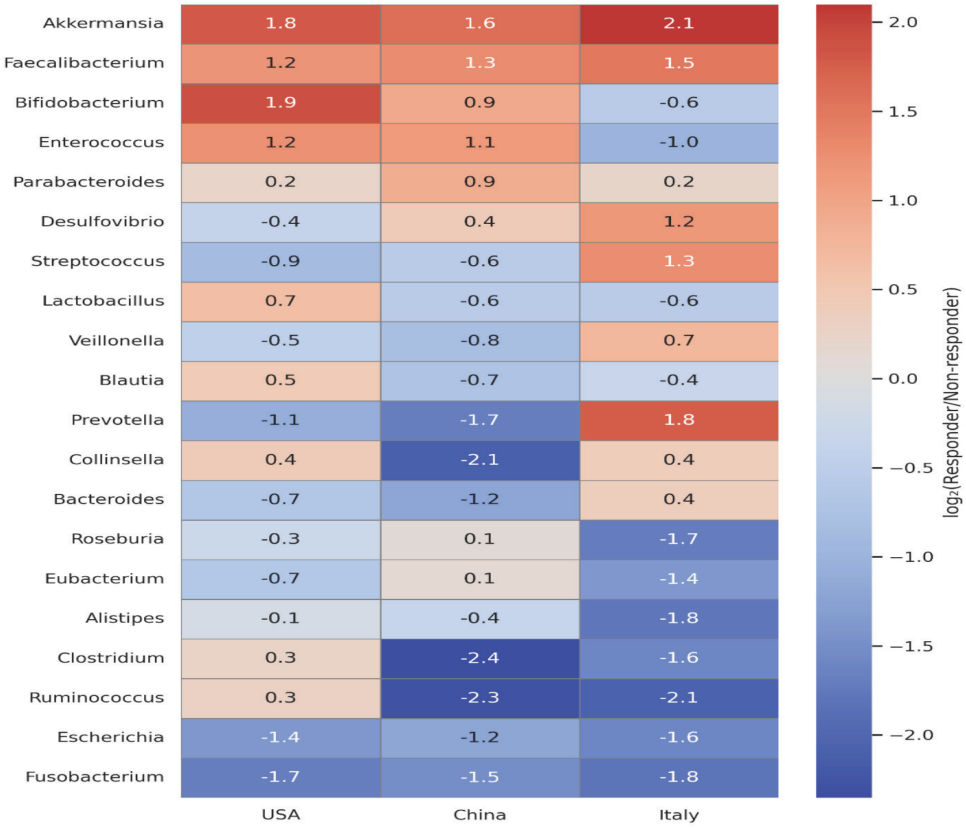

Figure 3. Responder-enriched vs. non-responder-enriched taxa across three independent cohorts.

Table 3. Human cohorts linking gut microbiota to ICI outcomes in CRC

Ref	Country	N (MSS/dMMR)	Sampling	Predictor(s) of benefit	ICI regimen	ORR or PFS gain
(8)	USA	63 (55/8)	Baseline stool 16S	High α-diversity; Ruminococcaceae_UCG-013 ↑	PD-1 ± CTLA-4	ORR 28% vs. 7%
(15)	China	58 (all MSS)	Shotgun stool	*Akkermansiaceae* >1%	PD-1 mono	Median PFS 6.1 vs. 2.9 mo
(12)	Italy	72 (all MSS)	Baseline + wk 6 stool	*F. nucleatum* >10% rel. abund. predicts resistance	PD-1 + regorafenib	HR progression 2.1
(9)	France	45 (33/12)	Multi-omics	Inosine/riboflavin gene clusters ↑	PD-1 or PD-1/CTLA-4	Durable benefit ≥18 mo

ICI: Immune-checkpoint inhibitor, PD-1: Programmed death-1, CTLA-4: Cytotoxic T-lymphocyte–associated antigen-4, FMT: Fecal microbiota transplantation, LBP: Live biotherapeutic product, SCFA: Short-chain fatty acid, MSS: Microsatellite-stable, dMMR/MSI-H: Mismatch-repair-deficient/microsatellite-instability-high, ORR: Objective response rate, DCR: Disease control rate, PFS: Progression-free survival.

Escherichia coli correlated with primary resistance and shorter overall survival (12). The genera most consistently enriched (or depleted) across the three largest MSS cohorts are visualised in Figure 3. Study designs and clinical read-outs for these and other prospective series are collated in Table 3.

Functional and multi-omic readouts

Shotgun metagenomics integrated with serum metabolomics identified responder-associated enrichment of inosine, riboflavin, and folate biosynthetic gene clusters; multivariate modelling achieved external-validation AUCs >0.85 (9). An Italian study combining single-cell RNA-seq of tumour biopsies with metagenome-assembled genomes linked microbial riboflavin synthesis to intratumoral $CD8^+$ oxidative phosphorylation signatures and durable benefit (27). Machine-learning algorithms trained on 176 metagenomic pathways outperformed taxonomic models (median AUC 0.87 vs. 0.71) and remained robust after controlling for diet and antibiotic use (29). These data support a shift from simple "bug lists" toward functional consortia.

Composite clinical scores

The microbial immunotherapy predictive index (MIPI) (10) combines alpha-diversity, responder taxa abundance, recent

antibiotic exposure, and neutrophil-to-lymphocyte ratio. In two validation cohorts totalling 212 mCRC patients, high MIPI independently predicted six-month disease control [hazard ratio (HR): 0.28, 95% confidence interval: 0.15-0.52]. Importantly, antibiotic exposure within 60 days of ICI initiation conferred a twofold risk of early progression, even in dMMR tumours, underscoring the clinical relevance of microbiota stewardship.

Stool-based qPCR panels

To facilitate real-world adoption, a five-gene qPCR panel quantifying *A. muciniphila, F. prausnitzii, F. nucleatum*, bacterial inosine-nucleoside hydrolase, and riboflavin kinase achieved 87% sensitivity and 79% specificity for predicting PD-1 response in an independent cohort of 80 patients (33). The assay requires ≤50 mg of stool, fits within standard pathology workflows, and is now incorporated into an adaptive FMT trial (NCT04988867).

Confounders and standardisation challenges

Diet, proton-pump inhibitors (PPIs), bowel-prep solutions, and tumour location (right versus left colon) all modulate microbial composition. Cross-study comparisons are hindered by variability in DNA-extraction kits, library-prep chemistries, and bioinformatic pipelines (34). The International Microbiome Quality Control Consortium now recommends (i) time-matched, diet-logged sampling, (ii) spike-in standards for absolute quantification, and (iii) dual analyses of taxonomic and functional profiles (35). Adoption of these guidelines is essential before microbiota biomarkers can inform regulatory decisions.

Clinical implications

Validated microbial signatures could stratify patients for (i) upfront FMT or LBP co-therapy, (ii) antibiotic avoidance or de-escalation protocols, and (iii) enrolment in trials combining diet, prebiotics or postbiotics with ICIs. Given that colonoscopy is routine in CRC care, synchronous mucosal and stool sampling may enable spatial mapping of microbiota-immune interactions, refining predictive accuracy beyond stool alone (36). Ultimately, composite indices integrating microbiota, tumour genomics, and host immunity promise the greatest precision.

Microbiota-targeted modulation strategies

Multiple interventions can re-arm ICI in MSS CRC, including FMT, defined consortia, diet, synbiotics, targeted antimicrobials, and postbiotics.

Checkpoint failure in MSS CRC is not immutable; multiple interventions can rearm immunity by reshaping the intestinal ecosystem. Here, we appraise each modality, emphasising mechanistic rationale, early clinical readouts, and implementation hurdles (Figure 4, Table 4).

FMT

First-in-human studies transferred stool from melanoma or CRC responders to heavily pretreated MSS mCRC patients; three of ten recipients achieved a partial response or durable stable disease, without grade ≥3 adverse events (11). Engraftment of *Ruminococcaceae* and *Bacteroidaceae* restored faecal short-chain fatty acids and increased intratumoral IFN-γ–expressing $CD8^+$ T-cells. An adaptive phase II trial (NCT04988867) combines donor-selected FMT with nivolumab; an interim analysis reports a 27% objective response rate and a median PFS of 4.8 months (23). Key hurdles are (i) donor-to-donor heterogeneity; (ii) risk of pathogen transmission—highlighted by sentinel *Escherichia coli* sepsis cases in immunocompromised hosts; and (iii) regulatory ambiguity as FMT straddles tissue, drug, and biologic definitions (35).

Live biotherapeutic products (LBPs)-defined consortia

Defined consortia seek to capture the benefits of FMT while meeting pharmaceutical quality standards. LBP (31), a four-strain cocktail (*Akkermansia muciniphila, Bacteroides fragilis, Eubacterium rectale, Bifidobacterium longum*), rescued anti-PD-1 efficacy in CT26 and MC38 tumor models and outperformed single-strain gavage (31). A Phase Ib dose-escalation trial in refractory MSS mCRC showed dose-dependent engraftment and a disease-control rate of 38% at 12 weeks; microbiome shifts mirrored responder FMT signatures with elevated inosine and propionate (37). Parallel efforts engineer commensals to secrete IL-12 or checkpoint nanobodies, enabling intratumoral payload delivery with minimal systemic exposure (38). A phase-

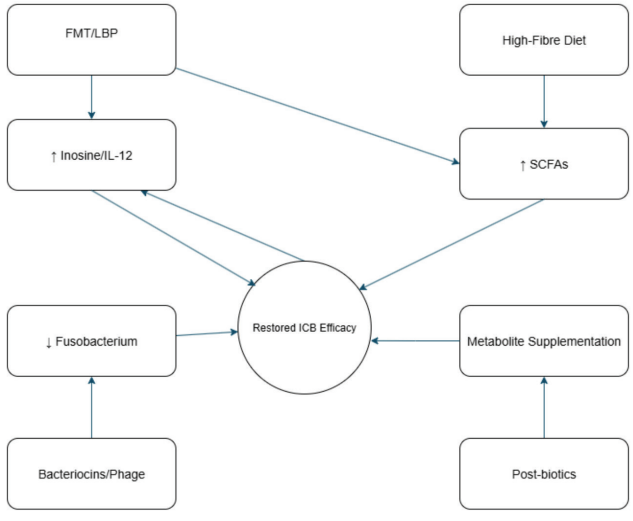

Figure 4. Therapeutic "re-arming" strategies and their mechanistic targets.

FMT: Fecal microbiota transplantation, SCFA: Short-chain fatty acid, ICB: Immune-checkpoint blockade, LBP: Live biotherapeutic product, IL: Interleukin

Table 4. Interventional trials of microbiota modulation plus ICI in CRC (registered 2021-2025)					
Trial ID/Ref	**Intervention**	**Phase**	**Population**	**Primary endpoint**	**Interim results/status**
NCT04988867	Responder-FMT + nivolumab	II	Refractory MSS mCRC	ORR	27% ORR (10/37); no Gr 3-4 toxicity
NCT05251389	Donor-screened FMT + pembrolizumab	I/II	MSS mCRC post-2L	Safety, ORR	Recruiting
— (9)	LBP-39755582 + PD-1	Ib/II	MSS mCRC (2L+)	DCR at 12 wk	38% DCR; engraftment dose-response
NCT05511270	High-fibre diet counselling + PD-1/CTLA-4	Pilot	MSS mCRC	Feasibility, SCFA levels	Diet adherence 85%; data pending

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Ib dose-escalation study in refractory MSS mCRC showed dose-dependent engraftment and a 12-week disease-control rate (DCR) of 38%.

Dietary, pre-biotic and probiotic interventions

High-fibre diets: In a prospective cohort of 164 mCRC patients initiating ICIs, the highest quintile of total fibre intake correlated with longer PFS (HR 0.46), independent of antibiotic use (16). Mechanistically, resistant-starch fermentation increases the abundance of butyrate-producing members of the family *Eubacteriaceae*, which enhance memory T-cell glycolysis (20). Nevertheless, a randomised 8-week soluble-fibre supplement failed to improve peripheral T-cell activation or early radiographic response (13), underscoring inter-individual variability.

Pre-biotics and synbiotics: Fructo-oligosaccharide/galacto-oligosaccharide blends increased *Bifidobacterium* spp., luminal inosine, and tumour IFN-γ expression in murine CRC, which translated into an additive benefit with anti-PD-1 (17). A pilot synbiotic capsule combining inulin with *Lactobacillus rhamnosus* resulted in a ≥10-fold expansion of *A. muciniphila* and a 22% partial-response rate among 18 MSS mCRC patients (39).

Probiotics: A single-strain, pasteurised *A. muciniphila* preparation (MucT™) was safe at doses up to 1×10^{10} CFU; early signals of an improved $CD8^+$/Treg ratio were noted, but objective responses were not yet assessable (40). Concerns remain regarding probiotic translocation during mucositis and competitive suppression of indigenous beneficial taxa.

Post-biotics and metabolite supplementation

Sterile filtrates circumvent risks associated with live bacteria. Intraperitoneal administration of inosine restored anti-PD-1 responsiveness in germ-free mice carrying PD-1-resistant stool, enhancing Th1 polarisation via A_2A signalling (5). Oral butyrate or tributyrin capsules replicated memory T-cell epigenetic reprogramming without altering the composition (32). Pilot human data show that a microencapsulated butyrate supplement increased intratumoral granzyme-B+ $CD8^+$ cells 1.9-fold after six weeks, although radiologic responses were modest (22).

Narrow-spectrum antibiotics, bacteriocins and phage therapy

Broad-spectrum antibiotics attenuate ICIs, whereas targeted depletion of pathogenic taxa may be advantageous. A synthetic endolysin cocktail selective for *Fusobacterium nucleatum* restored PD-1 efficacy and decreased myeloid-derived suppressor cell infiltration without compromising overall diversity (18). Similarly, an orally delivered bacteriocin peptide eliminated enterotoxigenic *Bacteroides fragilis*, reducing IL-17–driven resistance (21). Engineered lytic phages targeting *F. nucleatum* exhibit synergy with ICIs in humanised CRC xenografts, although human safety data are pending (7).

Safety, manufacturing and regulatory considerations

Safety profiles vary along the live-to-cell-free spectrum. FMT and LBPs carry theoretical risks of transmissible autoimmune flares, and mucosal barrier compromise; stringent donor screening, whole-genome sequencing, and lot-release potency assays are now mandated by several agencies (35). Postbiotics bypass the requirement for microbial viability but may induce metabolite toxicity at supraphysiological doses. From a regulatory standpoint, FMT is governed as human tissue in parts of Europe, as an investigational new drug in the USA, as a biologic in China—complicating multinational trials (41,42). Harmonisation efforts propose a classification based on manufacturing control and viability status rather than on source (34).

Clinical-trial landscape and evidence gradient

At least 14 interventional studies (registered 2021-2025) explore microbiota modulation plus ICIs in CRC. Designs cluster into three tiers:

1. Responder-derived FMT ± rigorous donor screening (NCT04988867, NCT05251389) – primary endpoints ORR and immune-related adverse events.

2. Defined LBPs, such as LBP or VE800 (multi-strain Veillonella-enriched), administered with pembrolizumab, have endpoints that include engraftment kinetics, PFS, and immune correlates (30).

3. Dietary/prebiotic optimisation incorporating dietitians, fibre-tracking apps, and metagenomic monitoring was applied; exploratory endpoints focused on metabolic and immune biomarker shifts (16).

Early efficacy signals are encouraging, but are still inferior to dMMR benchmarks. Randomised controlled trials with ICI-alone arms and mechanistic correlative studies are indispensable before changes in practice.

Update on CRC-specific interventional signals (2024-2025). Across CRC-focused studies initiated since 2021, emerging signals are consistent: donor-screened responder-FMT plus PD-1 show disease control with acceptable safety in refractory MSS cohorts; defined LBPs achieve dose-dependent engraftment with early DCR and biomarker shifts; and diet and synbiotic programs are feasible with high adherence when dietitians are embedded in oncology workflows. Several trials now incorporate stool qPCR or metagenomic pre-stratification, aligning with the tiered algorithm presented here and advancing selection based on functional features rather than taxonomy alone. Randomized ICI-alone comparator trials are the next step toward practice change.

Controversies and Knowledge Gaps

Key uncertainties persist around causality, donor selection, stage specificity, safety in compromised hosts, regulation, and equitable access.

Despite the momentum, several unresolved issues temper clinical enthusiasm.

1. Causality versus correlation: Many taxa linked to ICI success in melanoma or lung cancer show weaker or opposite trends in CRC; causal transfer experiments confirm only a subset (12). Multi-omic functional profiling, rather than taxonomy, may yield more generalisable predictors (28).

2. Donor-recipient matching: FMT efficacy appears donor-specific, yet predictive donor features remain ill defined. HLA-matched FMT improved engraftment and $CD8^+$ T-cell clonality in mice, but human validation is pending (19).

3. Tumour-stage and site specificity: Right-sided tumours harbour distinct microbiota and immune microenvironments compared with left-sided lesions, which may modify the effects of interventions (36). Neoadjuvant settings introduce variables related to chemoradiation-induced dysbiosis.

4. Safety in compromised hosts: Severe neutropenia or steroid-refractory colitis may preclude use of live biologic therapies; yet these are precisely the patients with the greatest unmet need. Post-biotic or phage-based options could fill this gap, but they lack human data (32).

5. Regulatory and manufacturing hurdles: Inter-continental heterogeneity in oversight complicates global trials and supply chains. Consensus on minimalquality attributes —viable-count thresholds, contaminant screening, and potency assays— is overdue (42).

6. Equity and accessibility: High-cost LBPs and personalised diet regimens risk widening disparities, especially in low-resource settings where CRC burden is rising (43). Affordable, shelf-stable post-biotics may offer scalable solutions.

Research Priorities (Table 5): standardised longitudinal sampling, functional rather than taxonomic biomarkers, platform trials integrating microbiota arms, and mechanistic dissection of tumour-microbe-host genomics to inform combinatorial regimens.

Clinical and Research Consequences

Practical steps now include antibiotic stewardship, dietitian-guided fibre optimisation, and selective enrolment in trials of FMT, LBP, or postbiotics.

Table 5. Priority knowledge gaps and research agenda

Gap	Consequence	Proposed solution
Taxonomy-centric biomarkers lack external validity	Conflicting predictive taxa	Shift to functional gene & metabolite signatures; establish shared analytic pipelines
Donor selection for FMT is empirical	Variable efficacy & safety	Define potency assays (inosine, SCFA output); HLA-matched or synthetic consortia trials
Regulatory heterogeneity (FMT vs. LBP)	Slow global trial rollout	Harmonise classification by viability & manufacturing control; engage ICMRA working group
Access in low-income regions	Widening survival disparities	Develop shelf-stable post-biotics; open-source metagenomic datasets for local validation

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Embedding microbiota stewardship in routine care

Checkpoint timing: In mCRC, PD-1 or PD-1/CTLA-4 therapy is typically initiated after failure of fluoropyrimidine-based chemotherapy. Because antibiotic exposure within 60 days of ICI start doubles the risk of early progression (10), multidisciplinary tumour boards should review antimicrobial prescriptions and, where possible, defer elective courses until after two ICI cycles. When antibiotics are unavoidable, agents with minimal activity against anaerobic bacteria (e.g., fosfomycin) are preferred over broad-spectrum β-lactams.

Dietary counselling: A registered dietitian can deliver a high-fibre, plant-forward diet that enriches *Ruminococcaceae* and Akkermansiaceae, both are linked to superior ICI outcomes (15,16). Practical targets—≥30 g/day total fibre and ≥5 different fruits and vegetables daily—fit within enhanced recovery protocols for colorectal surgery.

Patient-selection algorithm for modulation strategies

Baseline stool sampling (qPCR five-gene panel or 16S/shotgun sequencing where available) allows stratification into three tiers:

Tier	Microbiota features	Recommended action
Green	High α-diversity, responder taxa ≥75th centile	Proceed with ICI alone; reinforce diet
Yellow	Mixed profile or recent antibiotic exposure	Consider synbiotic or fibre preload; enrol diet-optimisation trials
Red	Dominant *Fusobacterium*, low diversity, antibiotic course <60 d	Offer FMT/LBP trial or compassionate-use post-biotic

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This flow is being prospectively evaluated in the adaptive FMT study NCT04988867 (11).

Clinician's playbook: Microbiota-guided ICI in CRC (practical steps)
1) When to sample. Collect baseline stool before the first ICI; repeat collection if antibiotics are administered within 60 days.

2) How to stratify fast. Use a 5-gene stool qPCR or 16S/shotgun (if available).

• Green (high α-diversity; responder taxa ↑) → ICI; reinforce fibre (≥30 g/day).

• Yellow (mixed profile/recent antibiotics) → preload synbiotic/fibre 2-4 weeks; avoid broad anaerobe-killing antibiotics unless essential.

• Red (*Fusobacterium* dominance; low diversity; recent broad antibiotics) → FMT/LBP trials or post-biotics when live products are unsuitable.

3) Feasibility & access. qPCR fits pathology workflows, dietitian counselling is provided via ERAS, LBP/FMT are evaluated mainly via trials, and butyrate/inosine are lower-cost adjuncts.

4) Document confounders. Diet, PPIs, bowel prep, tumour sidedness.

Surgical and interventional radiology implications

Preoperative FMT or LBP is feasible before metastasectomy or liver-directed therapies, provided that a seven-day window for engraftment is available. Pasteurised *A. muciniphila* (MucT^{TM}) does not increase anastomotic leak rates in mouse colorectal resection models and is undergoing phase I safety assessment in perioperative CRC (40). Surgeons should liaise with microbiome teams to coordinate bowel preparation, as polyethylene glycol lavage transiently reduces engraftment by approximately 40% (35).

Trial-design recommendations

Endpoints: Beyond RECIST response, microbiota engraftment kinetics, SCFA and inosine levels, and immune-cell spatial profiling were included to establish causal mediation (9).

Randomisation strata: Location (right versus left colon) and prior radiotherapy confound the baseline microbiota and should be balanced across study groups (36).

Control arm choice: Given the antibiotic confounding, "ICI + standard care" must specify restricted antimicrobial use or implement dynamic covariate adjustment (10).

Manufacturing and regulatory road map

Consortia such as LBP already meet the EMA/FDA live-biotherapeutic product guidance, including whole-genome sequencing, potency via SCFA output, and absence of antimicrobial-resistance genes (37). National agencies could fast-track LBPs via "breakthrough designation" if phase II response rates exceed 20% in MSS mCRC, analogous to prior dMMR approvals.

Equity, cost and global applicability

Current LBP courses are priced at US$ 6.000–8.000—comparable to one month of pembrolizumab, but untenable for low-income settings. Shelf-stable butyrate or inosine capsules (approximately US $80/month) have shown preliminary efficacy (32) and may help bridge this gap. Global academic consortia should deposit anonymised metagenomic and clinical data into the International Cancer Microbiome Portal to democratise biomarker discovery (34).

CONCLUSION

Checkpoint blockade is transformative in dMMR CRC but not in most MSS tumours. Microbiota modulation offers actionable interventions to sustain durable benefits.

Checkpoint blockade transforms dMMR CRC, yet remains ineffective for the MSS majority. Converging mechanistic, translational, and early clinical data demonstrate that the gut microbiota is a central—crucially actionable—determinant of therapeutic success. Beneficial commensals such as *Akkermansia muciniphila*, *Bacteroides fragilis*, and SCFA-producing *Ruminococcaceae* prime dendritic cells to produce IL-12, enhance Th1 polarisation, and reinvigorate exhausted $CD8^+$ T-cells, whereas dysbiosis driven by broad-spectrum antibiotics, Western diets, or *Fusobacterium nucleatum* fosters resistance (5,6,21). Microbiota-guided interventions—ranging from donor-screened FMT and multi-strain LBPs (11,31) to fibre enrichment, targeted bacteriocins and metabolite supplementation (16,18,32)—offer tractable avenues to "re-arm" checkpoint therapy in MSS disease.

Translating these insights into routine practice demands standardised sampling, functional (not merely taxonomic) biomarkers, and harmonised manufacturing quality. Antibiotic stewardship, dietitian-led fibre optimisation and early enrolment in microbiota-modulation trials constitute pragmatic first steps. Ultimately, a precision-microbiome framework that aligns tumour genomics, host immunity, and commensal functionality could extend durable immunotherapy benefit to the vast majority of CRC patients who currently fall outside the dMMR niche.

The next decade should witness integration of microbiota indices into treatment algorithms, regulatory approval of the first LBPs, and equitable access to cost-effective postbiotics—transforming what is now an experimental adjunct into a cornerstone of CRC care.

Ethics

Acknowledgments

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Footnotes

Author Contributions

Concept - T.Q., Z.S.A.A.; Design - T.Q., Z.S.A.A.; Data Collection or Processing - T.Q., Z.S.A.A., L.Q.; Analysis or Interpretation - T.Q., Z.S.A.A., L.Q.; Literature Search - T.Q., Z.S.A.A., L.Q., C.Y.; Writing - T.Q., Z.S.A.A., L.Q., C.Y.

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How is GIST to be pronounced? Like a ginger

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Dear Editor,

Gastrointestinal stromal tumors (GISTs) are neoplastic diseases with malignant potential, and their management is of considerable importance to oncological care providers. Despite significant advancements, a consensus regarding the optimal treatment of GISTs has yet to be fully established. This ongoing uncertainty continues to attract clinical attention, as evidenced by the number of related articles published in this journal (1,2).

This brings me to a lighter, albeit intriguing, observation: How do readers pronounce the term "GIST" when they first encounter it? Personally, as a Japanese surgeon, I have consistently pronounced it as "Jist," with the initial syllable "GI" sounding like "gih." However, over the course of my career, I have noticed that a significant number of professionals pronounce "GI" as "gui" instead. This variation is not confined to a single field; I have encountered it in surgery, internal medicine, pathology, and even basic science disciplines.

Which pronunciation is correct: "Jist" or "Guist"? Interestingly, the English word gist—spelled identically—means "the main point" or "essence," and is pronounced /dʒɪst (3). This would seem to support the "Jist" pronunciation.

Although the "Jist" camp appears to have the upper hand, uncertainty remains. One might reasonably ask: If gift is pronounced /gɪft/, shouldn't GIST logically be /gɪst/? This question prompted me to examine how the "gi" combination is generally pronounced in English, leading me on a brief exploration of linguistic history (4). Here is what I found:

- The letter *g* was originally pronounced as a hard "g" (as in *go*) in Latin.
- Over time, when followed by e or i, it often shifted to a soft "g" sound—ginger being a classic example.
- Words such as get and give retain the hard "g," but they are exceptions; gift also falls into this category.
- To preserve the hard "g" before an e or i, English often inserts a u, as seen in guilty or guess.

Based on these linguistic patterns, the pronunciation "Jist" for GIST is both defensible and phonetically reasonable. Having considered the matter in some depth, I now feel confident in referring to the tumor as "Jist." Admittedly, it can require a bit of courage to say "Jist" after a colleague has confidently said "Guist," but I am prepared to summon that courage and declare—perhaps proudly, and with a slightly smug smile—"Jist."

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