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FROM THE EDITOR-IN-CHIEF'S DESK

The weight of summer's end: A surgeon's emotional landscape

The end of summer is a very complex and deeply experience. It is such a time blending the farewell with the promise of a new beginning. While humans may feel a sense of loss for the sun-filled days and the freedom it represents, this transition offers a big chance for reflection and a preparation for what lies ahead. The beginning of the season is a burst of energy and possibility, its conclusion arrives with a more subdued grace: The frantic spirit of June and July gives way to a quieter mood as August draws to a close. The romanticization of summer overlooks the psychological challenges that can accompany the season's changes. The change is marked by more than a drop in temperature; it is an emotional shift, a collective feeling of wistfulness as we prepare for the routines of the autumn.

There is a unique and often bittersweet quality to the summer months for a surgeon. While the world may slow down for a summer holiday, the hospital does not. The surgeon's summer is a testament to our dedication—a season where the pursuit of personal well-being is always secondary to the ultimate responsibility of saving lives. So called the "summer blues" are a valid and complex emotional experience that challenges the traditional narrative of the season as a time of pure joy. Our life is defined by a rigid, demanding and relentless schedule. The precision and focus that we require in the operating theatre demand a level of psychological and physical energy that leaves a tiny room for spontaneity. I think that the summer, with the promise of a vacancy and temporary loosening of our professional ties, is not just a season but a vital oasis. The months that we left behind represent a brief window to reconnect with the others, or simply decompress from the massive stress of our daily routine. As the autumn approaches and our administrative/academic calendars fill up again, the surgeons must prepare to leave the oasis behind and reenter a world where our every decision carries an immense gravity.

On the other hand, for a patient undergoing a major surgical procedure in the summer, that is a deeply personal and often challenging experience that runs counter to the season's typical narrative. It causes the isolation and frustration of being unable to participate in the activities that others enjoy. The recovery from surgery inherently involves a period of confinement and limited mobility. While the friends are on vacation, the surgical patient is often confined to bed-rest, managing pain and adhering to a strict regimen of rest. This experience creates a unique emotional and physical landscape, forcing a redefinition of what the season means and testing an individual's resilience in the face of unforeseen challenges. The sunshine that once symbolized freedom can instead become a cruel reminder of what has been lost, a constant presence outside the window that highlights one's own stasis. It is at this tough intersection that the deliberate practice of surgical healing, both physical and emotional, becomes a very crucial tool for navigating these challenges.

Eventually, the summer months feel like a collective exhale for a fully recovered patient and a fatigued surgeon, however, the academic profession rarely affords such a complete pause. Hence, our journal strives to be a constant, a source of scientific nourishment and professional support that transcends the seasons. In the current issue, we are featuring a range of articles designed to both challenge and inspire. We are so honored to be a part of the professional journey and look forward to the contributions and insights that will shape the future of surgery.

As always, thanks to our readers for their support.

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

EDITORIAL
Turk J Surg 2025;41(3):216-218

Pilonidal disease: Gaps in the guidelines and future perspectives

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INTRODUCTION

Pilonidal disease (PD) is an increasingly common condition that predominantly affects the young population. The variety of treatment modalities described in the literature makes it nearly impossible to design a study capable of definitively identifying the optimal method. As a result, treatment strategies are broadly categorized into minimally invasive and excisional approaches, with the choice often tailored to the severity and complexity of the disease on an individual basis.

Currently, four major guidelines and consensus reports have been published on PD: The American (1), German (2), and Italian (3) guidelines, as well as the most recent guideline from the European Society of Coloproctology (ESCP) (4) in 2024. While these guidelines share certain points of agreement, they also diverge on several issues, and most of their recommendations are based on expert opinion or very low levels of evidence. Furthermore, many questions frequently encountered by surgeons in daily practice are either not addressed or remain unanswered in these guidelines.

Here, we explore some of these critical gaps:

Disease Classification and Treatment Options

The only meta-analysis on classification, by Beal et al. (5), concluded that none of the eight existing classification systems can be recommended for routine use, as none have been validated in large series or compared with each other. These systems differ in their consideration of disease presentation, recurrence, anatomical location, and patient-related factors. Current guidelines generally divide PD into "simple" and "complex" categories, with treatment options determined accordingly. However, the criteria for distinguishing between simple and complex disease are left to the surgeon's subjective assessment.

Among available evidence, the ESCP guideline provides the most practical treatment algorithm: minimally invasive techniques for simple disease, and excisional procedures for complex cases (4). For defining simple versus complex disease, Tezel's (6) navicular area classification offers a useful framework: Simple disease is limited to the navicular area with minimal extension, while complex disease extends beyond this area or represents persistent/recurrent PD. Both classification and management of PD remain areas in need of further research. Surgeons should utilize at least one of the existing classification systems to document and evaluate their outcomes, thereby contributing to future validation studies.

Management of Acute Abscess and the Need for Definitive Treatment

For abscesses, incision and drainage are the primary treatments regardless of location. However, in PD, clinical practice varies widely. The optimal site for

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drainage is debated: One study found that midline drainage led to delayed healing and advocated for lateral incisions (7), while others argue that midline approaches directly target the disease. Some surgeons recommend enlarging existing pits or connecting them. In Türkiye, the common practice is to drain from the point of maximal fluctuation (8). Needle aspiration is another controversial approach; one study reported 90% healing with needle aspiration and antibiotics (9). Neither the Italian nor German guidelines specify details regarding the site or technique of drainage (2,3). Until higher-level evidence emerges, the ESCP guideline's recommendation appears most reasonable: Drainage and debridement via a lateral incision large enough to allow proper cleaning of the cavity (4).

All guidelines advocate for definitive treatment after acute inflammation heals (1-4). This is largely based on a meta-analysis by Stauffer et al. (10), which reported a 40% recurrence rate at 60 months post-drainage. However, a national audit from the Netherlands found only a 9% recurrence rate at 12 months, challenging the necessity of elective surgery for all patients (11). Notably, Stauffer et al.'s (10) meta-analysis showed that 60% of patients healed with drainage alone. Given these findings, the need for elective surgery in asymptomatic patients post-drainage is questionable. Moreover, minimally invasive interventions such as unroofing, phenol application, and EPSIT are increasingly performed during abscess drainage with a simultaneous curative intent (8), further complicating the issue. All classification systems define patients without symptoms as asymptomatic PD, for which no guideline recommends intervention (5). I believe that treatment, especially excisional surgery should not be performed unless symptoms recur.

Hair Removal

The Italian guideline recommends epilation for patients with dense hair, but does not specify how to assess hair density, when to begin hair removal, how long to continue, or which methods to use (3). The ESCP guideline states that pre- and postoperative hair removal does not affect recurrence (4). Electron microscopy studies by Doll's group (12) have shown that hairs isolated from pilonidal cysts are often transported from other parts of the body—most commonly the occipital region. Both a meta-analysis (13) and a review (14) have reported a reduced recurrence with laser depilation, though this recommendation has not yet been incorporated into guidelines. Another study found that individuals with denser body hair are more prone to hair entrapment in the natal cleft, which may explain the relationship between hair density and PD risk (15). Given these findings, regular hygiene measures—such as cleaning the natal cleft, daily showers, and especially showering after haircuts—are advisable. Laser epilation may help reduce hair and debris entrapment, but further studies are needed before it can be routinely recommended. More research is required to clarify the impact of hair removal practices commonly used in clinical practice.

Postoperative Wound Care and Activity Restrictions

There are no specific guideline recommendations regarding wound care or dressing after either minimally invasive or excisional treatment for PD, nor are there prospective studies addressing these issues. In practice, some surgeons advise avoiding water contact after excisional procedures, particularly when drains are present, while others recommend daily showers. Although there is no direct evidence for PD, wound care protocols for other body regions may be applicable: dressings for the first two days until epithelialization, followed by daily showers. After minimally invasive procedures, daily showers and covering the area with gauze until discharge ceases may be appropriate. More research on postoperative wound care for PD is needed.

There is also no data regarding restrictions on sitting or sleeping positions after excisional procedures. Some surgeons restrict sitting after flap procedures, encourage supine positioning to reduce seroma formation, or recommend prone positioning to protect flap circulation. This area requires further study. My personal view is that there is no need to restrict sitting or sleeping positions, but patients should avoid cycling and high-impact sports (such as football or basketball) that may increase the risk of falls.

CONCLUSION

Current guidelines on PD do not provide clear recommendations regarding classification, acute abscess management, hair removal, or postoperative care. Considering the high prevalence of this disease especially in Türkiye, and its increasing incidence worldwide, future scientific studies should focus on addressing these conflicting and unresolved issues.

Keywords: Pilonidal disease, proctology, abscess

Footnotes

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REVIEW
Turk J Surg 2025;41(3):219-226

Bariatric surgery outcomes in obese adults with cognitive impairments: A systematic review

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ABSTRACT

Obesity is highly prevalent among individuals with cognitive impairments, yet bariatric surgery is often underutilized in this population due to concerns regarding adherence and safety. The aim of this review is to evaluate the outcomes of bariatric surgery in obese adults with cognitive impairments, focusing on weight loss, cognitive function, general health, and postoperative risks. A systematic review of 11 studies was conducted, including case reports, cohort studies, and pilot trials that investigated bariatric surgery outcomes in adults with intellectual disabilities, neurodevelopmental disorders, or acquired cognitive dysfunction. Outcomes included excess weight loss (EWL), cognitive changes, comorbidity resolution, and postoperative complications. Most studies reported significant weight loss, although slightly lower than in neurotypical populations (EWL ranging from 31.1% to 90%). Cognitive improvements were observed in domains such as memory and executive function within weeks after surgery. Bariatric surgery also led to notable improvements in comorbidities such as diabetes and hypertension. However, risks included nutritional deficiencies and poor adherence, particularly in patients with low preoperative cognitive function. Strong caregiver support and structured follow-up programs were key predictors of long-term success. Bariatric surgery can be a safe and effective intervention for adults with cognitive impairments when tailored support systems are implemented. Cognitive screening and personalized postoperative care are essential to optimize outcomes.

Keywords: Bariatric and metabolic surgery, gastrointestinal surgery, minimal invasive surgery

INTRODUCTION

Bariatric surgery is a well-established intervention for severe obesity, providing significant and sustained weight loss while improving metabolic health and reducing obesity-related comorbidities such as type 2 diabetes, hypertension, and obstructive sleep apnea (1). Beyond these physical health benefits, emerging evidence suggests that bariatric surgery may also influence cognitive function, as obesity is increasingly recognized as a risk factor for neurocognitive decline (2). Obesity is notably prevalent among individuals with non-acquired cognitive impairments, such as intellectual disabilities, neurodevelopmental disorders, and neurodegenerative conditions (3). Despite the known benefits of bariatric surgery in the general population, its effectiveness and safety in cognitively impaired patients remain a subject of debate (4). Individuals with pre-existing cognitive impairments, such as those with intellectual disabilities or psychiatric conditions, may experience additional challenges in weight management, adherence to dietary recommendations, and long-term lifestyle changes following surgery (5). While some studies indicate that bariatric surgery can lead to improvements in cognitive function through mechanisms such as reduced systemic inflammation and enhanced cerebral oxygenation, concerns remain regarding postoperative adherence and the risk of nutritional deficiencies that could negatively impact cognition (5). Understanding the complex relationship between bariatric surgery and cognitive function is essential for optimizing patient outcomes, particularly for those with cognitive impairments.

Clinical and Research Consequences

A comprehensive literature search was conducted using Scopus, Web of Science, and Medline to identify studies on bariatric surgery outcomes in obese adults with cognitive impairments that were published over the last 15 years. Keywords such as "bariatric surgery", "cognitive impairment", "intellectual disability", and "weight loss" were used to ensure a broad yet relevant selection of studies. Boolean operators

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(AND, OR) were applied to refine the search. The initial search yielded 241 studies. After applying the inclusion and exclusion criteria, 11 studies remained for final analysis, all of which were published in English (Table 1).

Studies were included if they were published in the last 15 years, focused on adults aged 18 years or older, and were written in English. Eligible studies examined bariatric surgery outcomes in patients with cognitive impairments, including intellectual disabilities (e.g., Down syndrome), neurodegenerative disorders (e.g., Alzheimer's, Parkinson's), or acquired cognitive dysfunction (e.g., traumatic brain injury, stroke). Studies had to report at least one of the following: Weight loss outcomes, metabolic improvements, cognitive function changes, postoperative adherence, or psychological effects.

Studies were excluded if they focused only on cognitively normal patients, were review articles or editorials, or lacked primary data. Data extraction focused on study design, sample characteristics, type of bariatric procedure, weight loss outcomes, metabolic improvements, cognitive function assessments, postoperative adherence, and complications (Figure 1).

A qualitative synthesis was conducted to summarize findings, and all included studies were published in high-quality, peer-reviewed journals. This systematic approach ensured a focused and high-quality evaluation of bariatric surgery outcomes in obese adults with cognitive impairments.

Several studies demonstrated that bariatric surgery results in clinically significant weight loss in obese individuals with cognitive impairments, though outcomes may vary based on cognitive capacity and surgical approach.

In Cazzo et al. (6), two patients, one with Prader-Willi syndrome and another with Down syndrome, achieved 55% and 90% excess weight loss (EWL), respectively, one year after surgery. Daigle et al. (7) reported a mean 31.1% EWL at an average follow-up of 33.7 months in a cohort of six patients with lifelong cognitive impairment, although individual results ranged widely.

Heinberg and Schauer (8) described a patient with borderline intellectual functioning who maintained 74% EWL over 4.5 years. This was attributed to structured pre- and post-operative support. Similarly, Vermeer et al. (9) showed that patients with cognitive or psychiatric comorbidities achieved an average of 27.4% total weight loss over four years, slightly less than the general population but still clinically successful.

Short-term outcomes also reflected consistent weight reduction. Spitznagel et al. (5) reported 6.6% to 16.2% total weight loss within 4-6 weeks postoperatively. Another longitudinal study found that patients' body mass index decreased from 45.11 to 31.69 kg/m^2 over 36 months, with early cognitive performance (e.g., memory, working memory, and generativity) predicting long-term success (10).

Across these studies, better preoperative or early postoperative cognitive function was consistently associated with superior weight loss outcomes and long-term weight maintenance (10).

Studies have demonstrated significant improvements in metabolic health following bariatric surgery, including diabetes remission, improved cardiovascular markers, and reduced inflammation. This is reinforced by the Cazzo et al. (6) study, which showed significant improvements in obesity-related conditions for the two reported cases. The Prader-Willi syndrome patient, who previously had impaired glucose tolerance and a walking disability, experienced complete resolution of impaired glucose tolerance and improved mobility. The patient with Down syndrome, diagnosed with hypertension, saw resolution of his high blood pressure post-surgery. Both individuals also exhibited improvements in lipid profiles, such as reduced low-density lipoprotein and triglyceride levels and increased HDL cholesterol, suggesting that bariatric surgery can provide broad health benefits beyond weight loss even in cognitively impaired individuals (6).

However, cognitive impairments may influence the management of these health improvements. Individuals with poorer executive function and memory may struggle with medication adherence, dietary compliance, and medical follow-ups, potentially affecting long-term outcomes (7). Spitznagel et al. (5) further supports this, finding that while bariatric surgery is associated with improvements in type 2 diabetes, hypertension, and dyslipidemia, low adherence rates post-surgery such as poor dietary habits, inadequate physical activity, and insufficient protein intake can hinder success, particularly among those with cognitive dysfunction.

Bianciardi et al. (10) also confirmed improvements in obesity-related comorbidities, including hypertension, diabetes, and sleep apnea. However, patients with preoperative binge eating disorder exhibited a greater risk for long-term weight regain, highlighting the need for ongoing behavioral interventions beyond the first year following surgery (10).

Another study emphasized that patients with lower cognitive function may struggle to maintain lifestyle changes, which could lead to suboptimal outcomes. Approximately 16.2% of participants experienced some weight regain between 12 weeks and 36 months, reinforcing the importance of cognitive capacity in sustaining health benefits (11).

Daigle et al. (7) reported that patients with cognitive impairment often present with multiple obesity-related comorbidities, and those with greater weight loss were more likely to experience comorbidity resolution. Importantly, a strong social support system was found to enhance postoperative adherence, including dietary restrictions and follow-up attendance (7).

Table 1. Includes all studies

Study title	Number of patients	Type of bariatric surgery	Type of cognitive disorder	BMI before surgery	BMI after surgery	Weight reduction (%)	Post-op complications
Spitznagel et al. (5)	37	LRYGB	Cognitive impairment affecting adherence (attention, executive function, memory)	45.59	Not provided	11.24%	Nausea (5), Infection (2), Stricture (1), Anemia (1)
Cazzo et al. (6)	2 (case report)	Biliopancreatic diversion (1), RYGB (1)	Severe cognitive impairment (Prader-Willi syndrome, Down syndrome)	55 / 41.5	38.5/26.7	55%/90% EWL	No significant complications
Daigle et al. (7)	6	RYGB (2), Sleeve (3), Adjustable Band (1)	Nonacquired cognitive impairment (trisomy 21, unknown causes)	49.4	41	31.1% EWL	No significant complications, 1 readmission (fever)
Heinberg and Schauer (8)	1 (case study)	RYGB	Borderline intellectual disability	47.9	31.2 (4.5 years)	74% EWL (2 years)	No complications, improved sleep apnea, hyperlipidemia
Vermeer et al. (9)	2525 (163 psychiatric group)	Not specified (likely RYGB)	17.9% had cognitive impairment (also mood disorders, PTSD, ADHD)	Not provided	Not provided	Psychiatric group: 27.4% TWL (1 yr), 21.6% (4 yrs)	Psychiatric group had lower weight loss
Bianciardi et al. (10)	78	Mostly sleeve gastrectomy (82%)	Cognitive impairment (executive function, memory) & BED	43.15	Not explicitly mentioned	58.13% (1 year), 54.83% (4 years)	Patients with BED had poorer weight loss
Spitznagel et al. (11)	55	Mostly RYGB (1 gastric band)	Cognitive impairment affecting memory, executive function, and adherence	45.11	31.69	69% lost >25% weight at 36 months	Not explicitly detailed
Alosco et al. (12)	50	Mostly RYGB (1 gastric band)	Cognitive impairment (attention, executive function, memory)	46.61	32.35	Not explicitly mentioned	Weight regains (24-36 months), decline in attention
Manderino et al. (13)	116	Bariatric surgery candidates (type not specified)	Cognitive dysfunction (emotion recognition)	46.29	Not provided	Not provided	Not applicable (pre-surgery study)
Custers et al. (14)	133	RYGB	Obesity-related cognitive impairment	Not provided	Not provided	Not explicitly mentioned	42.9% cognitive improvement at 24 months, brain structure changes in temporal lobe
Tucker et al. (15)	6 bariatric patients, 10 normal-weight controls, 7 reference controls	Sleeve gastrectomy	Obesity-associated cognitive impairment	41.9±3.9	Not explicitly mentioned	Significant weight loss observed (exact % not stated)	17% cognitive improvement at 2 weeks, 21% at 14 weeks; improved macrovascular function but no CVR change

BMI: Body mass index, BED: Binge eating disorder: RYGB: Roux-en-Y gastric bypass, CVR: Cerebral vascular reactivity, LRYGB: Laparoscopic Roux-en-Y gastric bypass, PTSD: Post-traumatic stress disorder, ADHD: Attention deficit hyperactivity disorder, EWL: Excess weight loss.

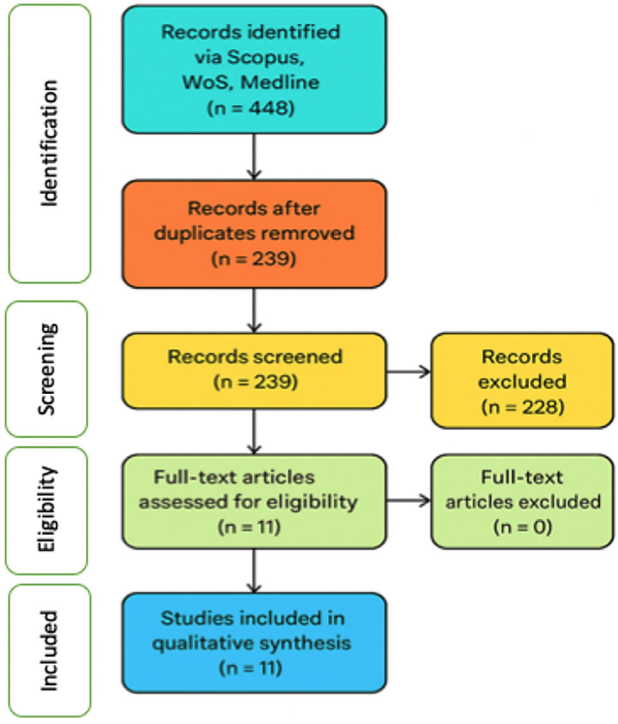

Figure 1. The process for selecting the included studies.

Similarly, Heinberg and Schauer (8) documented significant resolution or improvement in sleep apnea, hyperlipidemia, asthma, and acid reflux. Their case also showed reduced seizure frequency and emphasized the value of structured education and monitoring in supporting cognitively impaired individuals post-surgery.

Vermeer et al. (9) found that while the psychiatric cohort including those with cognitive impairment had slightly smaller improvements in physical health-related quality of life compared to the general population, outcomes were still clinically significant. Interdisciplinary support was critical in enhancing long-term health outcomes.

Finally, Alosco et al. (12) found improvements in comorbidities such as type 2 diabetes and hypertension, along with reduced use of antihypertensive medications. Neuroimaging results suggested structural brain changes, including increased cortical thickness and vascular efficiency, pointing to possible neuroprotective effects. However, reductions in gray matter and cerebral blood flow in some areas suggest that these changes may be due to metabolic shifts rather than direct cognitive benefits (13,14).

The study by Tucker et al. (15) examined the effects of bariatric surgery on cerebral vascular reactivity (CVR) and cognitive function in severely obese individuals. Obese patients demonstrated lower cognitive function than normal-weight controls prior to surgery, but cognitive performance improved by 17% at two weeks and 21% at 14 weeks post-surgery. Although these cognitive gains were not directly linked to changes in CVR or middle cerebral artery (MCA) vasodilation, the elimination of preoperative MCA vasoconstriction in 60% of patients suggests some macrovascular improvement. The findings imply that metabolic or hormonal changes may contribute to early cognitive recovery, though the exact mechanisms remain uncertain (15,16).

Manderino et al. (13) explored preexisting cognitive deficits among bariatric surgery candidates, identifying impairments in executive function, memory recall, and attention switching. These deficits were associated with poorer emotion recognition, potentially affecting psychological well-being and social interactions. The study raises questions about whether individuals with such impairments may experience cognitive improvement post-surgery or continue to struggle in these areas.

Similarly, Spitznagel et al. (11) found that 5.3% of bariatric candidates exhibited clinically significant cognitive impairments, and subclinical deficits were common in memory, attention, and executive function. These impairments were associated with lower adherence to postoperative guidelines. The study emphasizes that early postoperative success is more influenced by preoperative cognitive status than by potential post-surgical improvements (5).

Bianciardi et al. (10) also highlighted the importance of preoperative executive function in long-term weight management. Cognitive deficits in planning, problem-solving, and impulse control were linked to maladaptive eating behaviors and lower adherence to postoperative recommendations. However, the study did not measure postoperative cognitive change, leaving the question of surgery-induced cognitive improvement open.

Further evidence of cognitive enhancement is presented in a study showing significant improvements in memory and executive function at 12 weeks post-surgery, with continued benefits up to 36 months. Improvements in memory and executive function were observed up to 36 months post-surgery. Nonetheless, the study stresses that early postoperative cognitive performance is a strong predictor of long-term success, indicating a need for additional support for patients with lower baseline function (11).

The study by Cazzo et al. (6) reports that both cognitively impaired patients recovered without major postoperative complications. Neither the patients nor the control group experienced protein-calorie malnutrition, a common concern following procedures like biliopancreatic diversion or Roux-en-Y gastric bypass. Strong caregiver support was identified as essential in ensuring adherence to dietary guidelines and follow-up care, reinforcing

the importance of long-term monitoring to sustain health outcomes and prevent malnutrition-related issues.

While Manderino et al. (13) does not focus on physical complications, it highlights psychological risks associated with bariatric surgery, particularly in individuals with cognitive impairments. These patients may be more vulnerable to depression, anxiety, and social withdrawal, which may worsen after surgery due to changes in body image and impaired emotion recognition. This underscores the need for psychological screening and postoperative support.

Spitznagel et al. (5) link cognitive dysfunction with poor adherence to key postoperative guidelines, including protein intake, vitamin supplementation, and physical activity. Although most early physical complications (e.g., nausea, infections, anemia, and mild strictures) resolved by the time of follow-up, the study suggests that cognitive impairments increase the risk for nutritional deficiencies and weight regain. Tailored interventions, such as structured reminders and simplified plans, may help mitigate these risks.

Bianciardi et al. (10) also underline the need for ongoing mental health assessment post-surgery. Although psychopathology was not directly associated with weight loss outcomes, the risk of depression and self-harm remains elevated, particularly after the initial weight loss period. The study also notes that older patients tend to achieve less effective outcomes, possibly due to longstanding comorbidities and reduced metabolic responsiveness (10).

Additional findings confirm that cognitive impairments, especially in memory and executive function, can hinder adherence to dietary and exercise regimens, increasing the likelihood of nutritional complications and suboptimal long-term outcomes. These patients may require structured, individualized support to manage their postoperative care effectively (11).

Daigle et al. (7) reported no major complications or mortality in their cohort, though one patient was readmitted briefly for a postoperative fever. The study highlights that patients with lower independent functioning may be at higher risk for poor outcomes, emphasizing the importance of careful patient selection and comprehensive support systems (7).

Heinberg and Schauer (8) likewise observed no major surgical complications. However, their case required more frequent follow-ups, and they initially faced challenges with dietary compliance. Success was ultimately achieved through structured, ongoing support. The study also raises ethical considerations regarding informed consent and the suitability of bariatric surgery in patients with intellectual disabilities, a group often excluded from such interventions (8).

This review has examined the outcomes of bariatric surgery in cognitively impaired adults with obesity, focusing on studies published over the past 15 years, in light of advancements in surgical techniques during this period. In contrast to previous reviews, which have included both adult and pediatric populations and incorporated studies regardless of publication date, the present analysis provides a more focused and contemporarily relevant synthesis of the evidence (17,18).

Most studies report clinically significant reductions in excess weight in cognitively impaired patients after bariatric surgery. However, the degree of weight loss tends to vary based on the type and severity of cognitive impairment, the presence of structured support systems, and the patient's baseline executive functioning (6,9,10). Patients with higher levels of executive function particularly in areas such as impulse control, attention, and planning achieve greater weight loss and are more likely to maintain it over time (7,10,15).

In comparison to behavioral-only interventions, as highlighted in Spanos et al. (18), surgical interventions appear to offer greater and more sustained weight loss in patients with obesity and intellectual disabilities. While Spanos emphasized lifestyle-based strategies, our review demonstrates that when surgical interventions are delivered within a structured and supportive framework, they can yield favorable outcomes even in cognitively vulnerable populations. Thus, a multidisciplinary and individualized approach remains essential to success.

Emerging evidence suggests that bariatric surgery may lead to improvements in cognitive function, even among individuals with pre-existing cognitive impairments. Several studies included in this review observed enhancements in domains such as memory, executive function, and attention, beginning as early as two weeks post-surgery and extending up to three years in some cases (10,11,13,15). These improvements are particularly relevant given the strong association between obesity, systemic inflammation, insulin resistance, and cerebral perfusion, all of which are known contributors to cognitive decline (2,12).

The mechanisms underlying postoperative cognitive improvements are not yet fully understood, but several hypotheses have been proposed. These include increased cerebral oxygenation, improved vascular reactivity, reduced levels of pro-inflammatory cytokines, and better metabolic regulation following significant weight loss (12,15,16). In some neuroimaging studies, structural brain changes such as increased cortical thickness and improved white matter integrity were documented, further supporting the possibility of neuroplastic recovery (16).

Importantly, the degree of cognitive improvement appears to be modulated by baseline cognitive status. Patients with milder impairments or borderline intellectual functioning

may experience more pronounced cognitive gains, likely because they are better able to engage with postoperative recommendations and benefit from enhanced metabolic health (5,11). Conversely, patients with more severe intellectual disabilities may experience stabilization rather than dramatic improvement, which is still a valuable outcome in preventing further decline.

However, the literature also highlights significant variability in cognitive outcomes. Some studies reported minimal or no improvement in certain subgroups, while others warned of possible neuropsychiatric risks such as mood instability or poor adjustment to body image changes postoperatively (7,8). These mixed findings underscore the importance of individualized cognitive screening both before and after surgery, along with continuous psychosocial support throughout the recovery process.

While Thiara et al. (17) demonstrated consistent cognitive improvements across psychiatric populations after bariatric surgery, their findings also emphasized the need to distinguish between neurodevelopmental conditions and acquired cognitive dysfunctions, as the trajectories of recovery may differ. Our review supports similar conclusions, showing that surgery-related cognitive benefits are most pronounced when paired with structured postoperative care and close follow-up.

Overall, the evidence supports the notion that cognitive improvement is possible, and in some cases likely, following bariatric surgery in cognitively impaired individuals. Nevertheless, more research, particularly longitudinal studies with standardized neuropsychological assessments, is needed to fully characterize the nature, timeline, and sustainability of these cognitive changes.

While bariatric surgery is generally considered safe, cognitively impaired patients face unique risks that can affect both surgical outcomes and long-term health. The most frequently reported complications in this population include nutritional deficiencies, psychological distress, poor adherence to postoperative guidelines, and a higher likelihood of weight regain (7,8,11).

Patients with intellectual or neurocognitive impairments may struggle to fully understand and comply with complex dietary instructions, supplement regimens, and physical activity recommendations required after surgery. Cognitive deficits in memory, planning, and attention can make it difficult to maintain consistent protein intake, vitamin supplementation, or hydration, putting patients at increased risk for complications such as anemia, vitamin B12 deficiency, and dehydration (5,7).

In addition to physical complications, several studies reported elevated rates of emotional and behavioral disturbances postoperatively. These include mood swings, depressive symptoms, anxiety, and difficulty adjusting to rapid body image changes (7,8). Emotion regulation can be particularly challenging for patients with pre-existing psychiatric comorbidities or impaired emotion recognition, which are common in this population.

While most studies in this review reported low rates of major surgical complications, such as infections or anastomotic leaks, the risk of long-term non-adherence remains one of the most significant concerns. This is especially critical because postoperative success in bariatric patients is highly dependent on sustained lifestyle changes, which require cognitive engagement and behavioral consistency (5,8,11).

Caregiver involvement emerged as a protective factor across multiple studies. Patients who received daily support such as meal preparation, medication reminders, and transportation to follow-up visits had fewer complications and better adherence to care protocols (7,11). These findings are consistent with previous literature on neurodevelopmental and psychiatric populations, where structured support systems have repeatedly been shown to mitigate adverse outcomes and enhance treatment adherence (14,19). In contrast, patients lacking consistent supervision or structure were more vulnerable to both physical and psychological setbacks.

Interestingly, a few studies reported lower-than-expected complication rates in some cognitively impaired patients, particularly when robust support systems were in place. For example, Vermeer et al. (9) noted that despite psychiatric comorbidities, patients achieved clinically meaningful weight loss with limited complications. Similarly, Heinberg and Schauer (8) documented successful long-term outcomes in a patient with borderline intellectual functioning, suggesting that individual and environmental factors may offset some of the risks typically associated with cognitive impairment.

Ethical and legal considerations also arise in this context, particularly regarding informed consent. Some patients may lack the cognitive capacity to fully understand the nature, risks, and long-term requirements of bariatric surgery. In these cases, a multidisciplinary team including psychologists, legal guardians, and ethics consultants should be involved to ensure that decisions align with the patient's best interests and respect their autonomy (8).

Despite these concerns, it is important to note that mortality rates in this population remain low and are generally unrelated to the surgical procedure itself (9). With the implementation of tailored education, structured postoperative plans, and ongoing monitoring, many of these risks can be successfully mitigated.

Study Limitations

This review has several limitations. First, there is a small number of eligible studies, because most are case reports or pilot studies, with limited statistical power, precluding a meta-analysis.

Additionally, the heterogeneity of cognitive impairments, including Prader-Willi syndrome, Down syndrome, and acquired impairments, limits the ability to make uniform comparisons. Most of these reports have short follow-up durations, and long-term cognitive and metabolic outcomes beyond 3-4 years remain unknown. Additionally, most of the data originate from Western countries, which may limit the generalizability of findings to other populations.

Recommendations

To optimize bariatric surgery outcomes in adults with cognitive impairment, several integrated strategies are recommended. All candidates with known or suspected cognitive deficits should undergo a comprehensive preoperative neuropsychological evaluation. This allows clinicians to identify impairments such as executive dysfunction or memory issues that may affect the patient's ability to adhere to postoperative instructions and sustain long-term lifestyle changes.

The surgical process should be guided by a multidisciplinary team composed of bariatric surgeons, psychologists, dietitians, primary care providers, and, when necessary, legal or ethical consultants. This collaborative approach ensures that the medical, cognitive, and psychosocial complexities of each patient are thoroughly addressed. Preoperative education must be tailored to the cognitive level of the patient, using simplified language, visual aids, repetition, and active caregiver involvement to enhance comprehension and retention.

Postoperative care should be highly structured, featuring regular follow-up appointments, clear and written instructions for medications, diet, and physical activity, and an emphasis on consistency. A responsible caregiver plays a crucial role in supporting the patient through this process. Caregivers should receive training and guidance on tasks such as managing medications, planning meals, and coordinating follow-up visits.

Ongoing psychological monitoring is essential, as individuals with cognitive impairments may be at increased risk for emotional distress, body image dissatisfaction, and social isolation following surgery. Access to mental health services should be integrated into postoperative care to support emotional well-being. For patients with limited decisional capacity, ethical safeguards must be in place. This may include legal guardianship, and consultation with ethics committees to ensure informed consent is valid and that the decision to proceed with surgery aligns with the patient's best interests.

Finally, future research should focus on conducting longitudinal studies and randomized controlled trials to investigate the long-term metabolic, psychological, and cognitive outcomes of bariatric surgery in this population. Such research is essential to inform clinical practice and enhance the safety and efficacy of surgical interventions for cognitively impaired individuals.

CONCLUSION

Bariatric surgery is an effective intervention for weight loss and metabolic health improvements, but its success is highly dependent on patient adherence and cognitive capacity. Patients with intellectual disabilities can benefit significantly from surgery, but they require additional support, structured lifestyle modifications, and long-term monitoring to optimize outcomes. Future research should focus on tailored interventions that enhance adherence and minimize cognitive and psychological barriers to success.

Footnotes

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ORIGINAL ARTICLE
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Computed tomography defined body composition may predict postoperative outcomes and prognosis following gastric cancer surgery

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ABSTRACT

Objective: Loss of muscle mass (sarcopenia) and impaired muscle quality (myosteatosis) associated with poor surgical outcomes. This study aimed to evaluate the impact of sarcopenia and myosteatosis on postoperative short-term outcomes and prognosis in patients with gastric cancer.

Material and Methods: Patients who underwent gastric cancer surgery and had abdominal computed tomography (CT) imaging were included in the study. Skeletal muscle index (SMI) and skeletal muscle density (SMD) were calculated using CT images. Patients were divided into groups based on previously established threshold values: Those with low SMI (indicating sarcopenia) versus those with normal SMI, and those with low SMD (indicating myosteatosis) versus those with normal SMD. Demographics, clinicopathologic characteristics, postoperative outcomes, and survival data were extracted from prospective database.

Results: Among the 237 patients, 87 patients (36.7%) had sarcopenia and 139 patients (58.6%) had myosteatosis. Patients with myosteatosis were characterized by older age, poorer preoperative nutritional status, inferior performance status, and extended hospital stays. Higher severe complication incidence was observed among patients with myosteatosis (18% vs. 10.2%, p=0.09). Overall survival of patients with sarcopenia or myosteatosis was significantly lower than that of patients with a normal SMI or SMD (p=0.03, p<0.001 respectively). Myosteatosis was identified as an independent risk factor for overall survival in multivariate analysis (hazard ratio: 2.20, 95% confidence interval: 1.26-3.86, p=0.006).

Conclusion: This study indicated sarcopenia or myosteatosis is associated with reduced overall survival. Although there were no significant difference severe complication rates are higher in patients with low SMD than in patients with normal SMD, and reporting of SMD from preoperative CT should be considered in preoperative evaluation.

Keywords: Body composition, gastric cancer, sarcopenia, myosteatosis, skeletal muscle index, skeletal muscle density

INTRODUCTION

Gastric cancer is the sixth most prevalent cancer and the third most common cause of cancer-related death worldwide (1). Despite the development of multimodal therapy, surgical therapy is still the primary treatment for gastric cancer. Radical gastrectomy is a complex surgical procedure associated with high morbidity. Approximately 21% of all gastric cancer patients who undergo surgical resection develop a postoperative major complication such as infection, anastomotic leakage, hemorrhage, or organ dysfunction (1-3). Although a few risk factors for postoperative complications and prognosis have been identified, such as age, body mass index (BMI), malnutrition, anemia, presence of comorbidities, and tumor stage, these factors do not entirely clarify the observed wide disparity in postoperative outcomes after gastrectomy (4). Recently, there has been a rising interest in the association between body composition and postoperative outcome (5). Predicting the risk of postoperative complications might help improve the patient's condition preoperatively or avoid surgery in high-risk patients (4).

Sarcopenia is a clinical condition defined as the generalized loss of skeletal muscle mass, strength, and quality (1,6). The other pathologic pattern related to reduced muscle quality is myosteatosis. It is characterized by increased fat infiltration in muscle, which causes reduced muscular strength and subsequently limits physical activity (4,7,8). Although the reasons for sarcopenia are not entirely known, it often occurs due to aging, physical inactivity, malnutrition, and malignancy (7,9,10). Particularly in

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cancer patients, excessive systemic inflammatory response and the insulin resistance, protein hypercatabolism, and metabolic changes caused by it are considered to be responsible (11,12). Furthermore, several studies have reported that insufficient energy and protein intake are independent risk factors for sarcopenia. When considering gastric cancer patients, poor oral intake can lead to severe nutritional depletion compared to other cancer patients (11). The routine uses of computed tomography (CT) in the staging of malignancies and improvements in computer software for CT-based body composition analysis have enabled the measurement of muscle mass and its fat content non-invasively, eliminating extra imaging modalities (13). CT-based sarcopenia is diagnosed using two objective criteria: The skeletal muscular index (SMI) and skeletal muscular density (SMD). While the low SMI reflects loss of muscle mass, the low SMD has been known to reflect increased muscle lipid content, indicating sarcopenia in CT imaging (14). The preceding studies have reported that sarcopenia is associated with increased postoperative complication rates and poor prognosis, especially in colorectal, endometrial, pancreatic, and hepatic surgery (15-18). However, there is uncertainty about postoperative outcomes of patients with gastric cancer, and controversies continue in the literature (9,10). While some studies report adverse effects on both early postoperative outcomes and prognosis, others report that sarcopenia does not have any effect (1). Moreover, no study has evaluated the effect of both SMI and SMD on postoperative outcomes and prognosis after radical gastrectomy.

We aimed to search for SMI and SMD values for the diagnosis of sarcopenia in CT images in our series and to determine whether they have an impact on postoperative short-term results and prognosis in patients with gastric cancer.

MATERIAL and METHODS

Study Populations

Prospective data from 407 consecutive patients with gastric cancer who underwent radical gastrectomy in January 2017 and December 2020 were analyzed retrospectively. After excluding 170 patients who did not meet the study criteria, a total of 237 patients enrolled in the study.

Inclusion criteria were age older than 18 years, histologically proven gastric adenocarcinoma, and the availability of CT and positron emission tomography (PET) imaging taken within 15 days before surgery. Patients who were younger than 18 years old, had American Society of Anesthesiologists physical status (ASA-PS) 4, had metastatic disease, or had undergone palliative resection and who were followed up in a postoperative intensive care unit were excluded. Patients with insufficient follow-up information whose CT or PET/CT images were unavailable or of poor quality for the third lumbar vertebra skeletal muscle mass index measurement were also excluded. All surgical procedures were conducted by experienced general surgeons, using a standardized surgical technique. Also, a standardized D1 plus lymphadenectomy was carried out in conjunction with radical gastrectomy for all patients.

The Ethics Committee of Marmara University approved the study protocol (date: 05.03.2021, no: 09.2021.248). Written informed consent was obtained from all patients participating in the study.

CT-Based Skeletal Mass Measurements

The measurements were performed on the local PACS (Infinitt, Infinitt Healthcare, Seoul, South Korea).

Skeletal muscle mass is mainly calculated from the total volume of the abdominal muscle on a CT image, generally at the level of the third lumbar vertebra. It was normalized by dividing the measured area (cm^2) by the square of the patient's height (m^2), (SMI). A scale of pre-defined thresholds has been reported in studies from various populations. SMI <52.4 cm^2/m^2 in men and SMI <38.5 cm^2/m^2 in women were considered sarcopenic (19). Patients were divided into a low SMI group and a low SMD group according to the sarcopenia threshold value.

The skeletal muscle density (SMD) can also be calculated from the CT images, and low SMD values support the diagnosis of myosteatosis radiologically. It is defined by mean muscle attenuation under a specified threshold as described in the literature. It was measured in Hounsfield unit (HU) at the level of the third lumbar vertebra, similar to measurements used for sarcopenia. (13) It was derived by averaging HU radiodensity for the total sectional skeletal muscle. Although no universally accepted thresholds exist for defining SMD, the cutoff points for SMD were determined from previous studies as 41 cm^2/m^2 and 33 cm^2/m^2 for BMI less than 25 and BMI ≥25 patients, respectively (20,21). The patients were divided into a low SMD group and a normal SMD group according to the myosteatosis threshold values.

Data Collection

Patient demographics (including age, sex, BMI, performance status, nutritional status, and comorbidities), histopathologic features of tumors (such as localization, TNM stage, grade, and lymphovascular invasion), operative outcomes, postoperative complications, and lengths of hospital stay were retrieved from a prospectively maintained database. ASA-PS was used to classify patients' performance status. The prognostic nutritional index (PNI) was used to determine patients' nutritional status. The SMI and SMD were computed in preoperative body/abdomen CT examinations. The Clavien-Dindo classification was used to evaluate postoperative complications. Severe complications were defined as greater than or equal to Clavien-Dindo grade 3a. Perioperative mortality was defined as death within 30 days

of the operation. Overall survival (OS) was defined as the time from surgery until death or loss of follow-up.

Statistical Analysis

The statistical analyses were performed with SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Normally distributed data will be expressed using the mean ± standard deviation, and non-normally distributed data, will be expressed using the median (range) values. Chi-square and Fisher's exact tests will be used to compare categorical data. Student's t-test was used to compare parametric data, and the Mann-Whitney U test was used to compare non-parametric data. The Kaplan-Meier method was used in survival analysis, and the log-rank test was used in univariate analysis. Cox regression models were created with variables that were statistically significant or close to significant ($p<0.05$) in univariate analysis to determine independent prognostic factors for survival. The confidence interval for statistical significance will be accepted as 95%, with a two-tailed p-value <0.05.

RESULTS

Patient Characteristics

Two hundred thirty-seven of 407 curatively treated patients were enrolled in the study. One hundred seventy patients were excluded because the reasons for exclusion included preoperative CT examinations not being available (n=74), metastatic disease (n=64), palliative resection (n=15), benign diseases (n=8), other malignancies (n=7), and ASA 4 patients (n=2). The mean patient age was 61.5±11.5 years; 153 (64.5%) patients were male, and 84 (35.4%) were female. The clinicopathologic features of patients are detailed in Table 1.

Relationship Between Patient Characteristics and Sarcopenia

Eighty-seven (37%) patients have a low SMI values. The male sex and lower BMI were significantly associated with the low SMI group (p=0.0001 and p=0.0001, respectively). The low SMI group included more ASA 2 patients than the normal SMI group (p=0.03). When comparing normal SMI patients to those with proximal-located tumors, patients with proximal-located tumors had a low SMI (p=0.01). Also, the prevalence of low SMI status was found to be significantly higher in patients receiving neoadjuvant treatment. However, age and PNI were not different between the two groups. No surgical or pathological characteristics differed between low SMI and normal SMI groups (Table 2).

Relationship Between Patients' Characteristics and Myosteatosis

One hundred and thirty-nine (58%) of the patients have low SMD values. The older age, higher ASA score, and presence of comorbidities was significantly higher in the low SMD group (p=0.0001, p=0.001, and p=0.0001, respectively). While the PNI mean value was lower in the low SMD group (p=0.001), the hospital stay was also longer in this group (p=0.001) (Table 2).

Short-term Surgical Complications

Regarding short-term surgical outcomes, 62 patients (26%) experienced postoperative complications. While 27 of them (11.3%) involved minor complications, 35 (14.7%) were major complications (greater than or equal to Clavien-Dindo grade 3a). Among patients with major complications, eight (3.4%) died due to complications. There were no significant differences in the rates of major and minor complications in patients with low SMI compared to other patients with normal SMI. Although patients with low SMD experienced approximately twice as many major complications when compared to those with normal SMD, the difference was not statistically significant (p=0.09). Also, although perioperative mortality rates were higher in patients with low SMI (4.6%) and low SMD (5%) compared to those with normal SMI (2.7%) and normal SMD (1%), the difference did not reach statistical significance (p=0.4 and p=0.08, respectively). The length of hospital stay was significantly higher in the low SMD group, but there was no significant difference between low SMI, and normal SMI groups (Table 2). Low SMD was significantly correlated with a higher length of hospital stay (p=0.0001).

Table 1. Clinicopathologic features of all patients

Parameters	All patients (n=237)
Age, years, mean ± SD	61.5±11.5
Sex, n (%) Male Female	 153 (64.6) 84 (35.4)
BMI, kg/m^2, median (range)	25 (16-43.1)
SMI, cm^2/m^2, mean ± SD	50.1±8.8
SMD, HU, mean ± SD	35.4±8.4
ASA-PS score, n (%) I II III	 93 (39.2) 85 (35.9) 59 (24.9)
Neoadjuvant treatment, yes, n (%)	44 (18.5)
Differentiation, n (%) Differentiated Undifferentiated	 74 (31.2) 154 (65)
Stage, TNM, n (%) I II III	 52 (21.9) 50 (21.1) 135 (57)
Complications, CD ≥3a, n (%)	35 (14.8)
Length of the hospital stay, median (range)	7 (1-56)
Overall survival rates, months, mean ± SD	32.7±1.3

SD: Standard derivation, BMI: Body muscle index, SMI: Skeletal muscle index, SMD: Skeletal muscle density, HU: Hounsfield unit, ASA-PS: American Society of Anesthesiologists physical status, CD: Clavien-Dindo classification.

However, no significant correlation existed between length of hospital stay and SMI (Figure 1).

Survival Analysis

The median follow-up was 15 (0-47) months. The OS of patients with a low SMI was significantly lower than that of patients with a normal SMI (28 vs. 34 months, p=0.03). Similarly, regarding SMD, there was a significant difference between the normal and low groups in the survival analysis (36 vs. 29 months; p=0.0007) (Figure 2). Univariate analysis showed that low SMI and SMD, ASA-PS score, and poor pathologic features (higher stage, poor differentiation, presence of lymphovascular and perineural invasion, and positive resection margin) were significant risk factors for overall survival. However, in the multivariate analysis, low SMD, high ASA-PS score, and positive resection margin were significant risk factors for OS (Table 3).

DISCUSSION

Although many risk factors for postoperative complications and prognosis have been identified in patients with gastrointestinal cancers, these factors do not entirely clarify the observed wide disparity in postoperative outcomes and prognosis after surgical treatment. There has been a rising interest in finding preoperative predictive factors in patients with gastrointestinal cancer; the body composition of patients is one of the leading research topics.

Sarcopenia has been described as low muscle mass, poor muscle strength, and weak physical performance by the

Table 2. Comparison of patients regarding skeletal muscular index (SMI) and skeletal muscular density (SMD)

Parameters	SMI		p-value	SMD		p-value
	Low SMI (n=87)	Normal SMI (n=150)		Low SMD (n=139)	Normal SMD (n=98)	
Age, years, mean ± SD	62.9±12.9	60.6±10.7	0.1	64.9±10.1	56.6±11.7	0.0001
Sex, n (%) Male Female	 70 (80.5) 17 (19.5)	 83 (55.3) 67 (44.7)	0.0001	 83 (59.7) 56 (40.3)	 70 (71.4) 28 (28.6)	0.06
BMI, kg/m^2, median (range)	23.6 (16-36.3)	26.2 (17.3-43.1)	0.0001	24.2 (16.1-40)	25.7 (16-43.1)	0.1
PNI, median (range)	46.5 (26.5-64.5)	48 (27-63)	0.3	47 (26.5-64.5)	48.7 (31.5-62)	0.007
ASA-PS score, n (%) I II III	 52 (34.7) 63 (42) 35 (23.3)	 41 (47.1) 22 (25.3) 24 (27.6)	0.03	 48 (34.5) 44 (31.7) 47 (33.8)	 45 (45.9) 41 (41.8) 12 (12.2)	0.001
Comorbidities, yes, n (%)	41 (47.1)	76 (50.7)	0.5	83 (59.7)	34 (34.7)	0.0001
Neoadjuvant treatment, yes, n (%)	22 (25.3)	22 (14.7)	0.04	29 (20.9)	15 (15.3)	0.2
Differentiation, n (%) Differentiated Undifferentiated	 24 (28.6) 60 (71.4)	 50 (34.7) 94 (65.3)	0.3	 45 (33.6) 89 (66.4)	 29 (30.9) 65 (69.1)	0.6
Stage, TNM, n (%) I II III	 14 (16.1) 18 (20.7) 55 (63.2)	 38 (25.3) 32 (21.3) 80 (53.3)	0.2	 33 (23.7) 29 (20.9) 77 (55.4)	 19 (19.4) 21 (21.4) 58 (59.2)	0.7
Localization, n (%) Upper Middle Lower Whole	 21 (24.1) 36 (41.1) 21 (24.1) 9 (10.3)	 38 (25.3) 39 (26) 63 (42) 10 (6.7)	0.01	 38 (27.3) 42 (30.2) 49 (35.3) 10 (7.2)	 21 (21.4) 33 (33.7) 35 (35.7) 9 (9.2)	0.7
Surgery type, n (%) Total Subtotal	 37 (42.5) 50 (57.5)	 56 (37.3) 94 (62.7)	0.4	 57 (41) 82 (59)	 36 (36.7) 62 (63.3)	0.5
Complications, CD ≥3a, n (%)	17 (19.5)	18 (12)	0.1	25 (18)	10 (10.2)	0.09
Length of the hospital stay, median (range)	5 (3-41)	5 (1-56)	0.7	6 (1-41)	5 (3-56)	0.001
Overall survival rates, months, mean ± SD	28.3±2.3	34.7±1.6	0.03	29.9±1.8	36.3±1.8	0.007

SD: Standard derivation, BMI: Body muscle index, SMI: Skeletal muscle index, SMD: Skeletal muscle density, PNI: Prognostic nutritional index, ASA-PS: American Society of Anesthesiologists physical status, CD: Clavien-Dindo classification.

European Working Group on Sarcopenia in Older People and the Asian Working Group for Sarcopenia (22,23). Sarcopenia working groups recommended the hand grip strength test to measure muscle strength in sarcopenia diagnosis (22). Then, it has been reported that measuring increased intramuscular lipid content, called myosteatosis, which contributes to muscle weakness, gives more objective information about muscular strength (14). The routine uses of CT in the staging of malignancies and

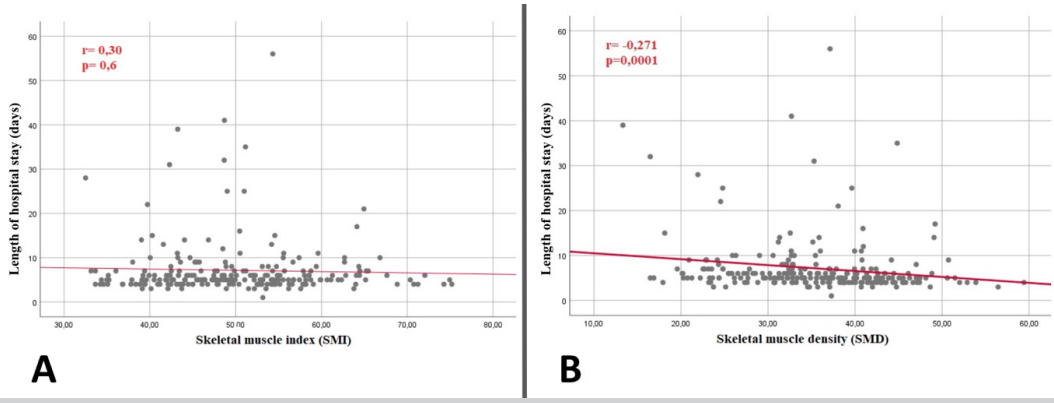

Figure 1. Correlation analyses with Spearman's Rho test: A: between SMI and length of hospital stay, B: between SMD and length of hospital stay.
SMI: Skeletal muscle index, SMD: Skeletal muscle density

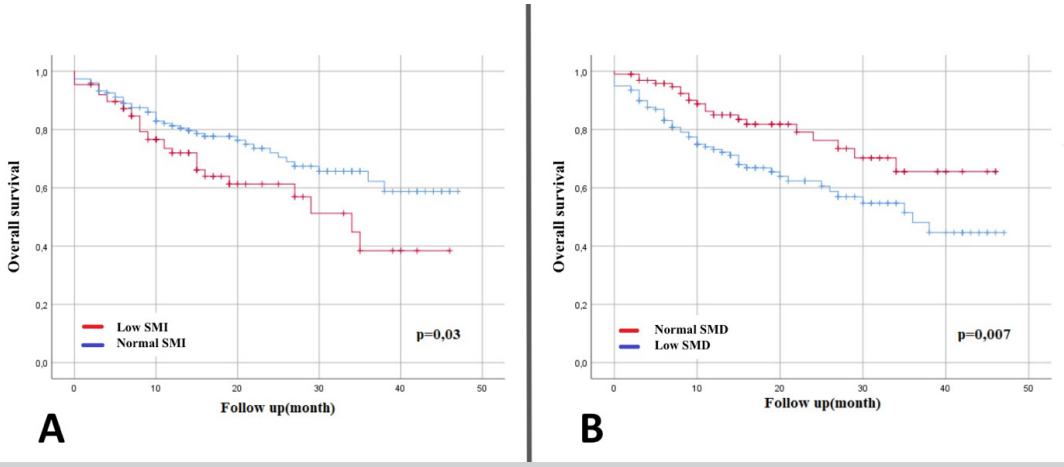

Figure 2. Kaplan-Meier survival Logrank analyses. Patients with low SMI (A) and low SMD (B) have poorer overall survival compared to patients with normal SMI and SMD.
SMI: Skeletal muscle index, SMD: Skeletal muscle density

Table 3. Univariate and multivariate analyses of variables that predict overall survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
SMI (low/normal)	1.63	1.01-2.62	0.04	1.24	0.74-2.07	0.3
SMD (low/normal)	1.98	1.18-3.33	0.009	2.20	1.26-3.86	0.006
ASA-PS score (I/II/III)	1.84	1.04-3.25	0.03	2.07	1.10-3.88	0.02
TNM stage (I/II/III)	3.89	1.77-8.56	0.001	2.63	0.89-7.75	0.07
Differentiation (well/poor)	2.85	1.46-5.58	0.002	1.96	0.92-4.17	0.07
Lymphatic invasion (yes/no)	2.46	1.13-5.39	0.02	0.60	0.21-1.65	0.3
Vascular invasion (yes/no)	2.70	1.56-4.66	0.0001	1.31	0.67-2.54	0.4
Perineural invasion (yes/no)	2.73	1.49-4.99	0.001	1.20	0.56-2.58	0.6
Resection margin (positive/negative)	4.21	2.58-6.84	0.0001	3.45	1.95-6.10	0.0001

HR: Hazard ratio, CI: Confidence interval, SMI: Skeletal muscle index, SMD: Skeletal muscle density, ASA-PS: American Society of Anesthesiologists physical status.

improvements in computer software to establish CT-based body composition analysis has enabled measuring muscle mass and its fat content non-invasively and eliminated the need for extra imaging modalities (13,24). Previous studies have reported that sarcopenia is associated with increased postoperative complication rates, excess chemotherapy toxicity, and poor prognosis, especially in colorectal, endometrial, pancreatic, and hepatic surgery (15-18,25). However, when considering patients with gastric cancer, although some studies reported that it has adverse effects on both early postoperative outcomes and prognosis, others reported that it does not have any effect. Therefore, there is uncertainty about postoperative outcomes regarding patients with gastric cancer. Two objective criteria for the diagnosis of CT-based sarcopenia are SMI and SMD. While the low SMI reflects loss of muscle mass, the low SMD reflects increased muscle lipid content, indicating sarcopenia in CT imaging (14). Although there are many studies on SMI and SMD in the literature, it is not fully understood which one better reflects patients' physiological reserve capacities or whether they affect postoperative results, especially in elderly patients. On the other hand, as far as we know, no study has evaluated the effect of both SMI and SMD on postoperative outcomes and prognosis after radical gastrectomy. In the present study, we aimed to assess SMI and SMD values for the diagnosis of sarcopenia in CT images from our series and determine whether they have an impact on postoperative short-term results and prognosis in patients with gastric cancer.

Sarcopenia is an age-related syndrome that usually starts in the fifth decade of life and progresses at a rate of 0.8% annually (26). In our study, the age of incidence of sarcopenia was the seventh decade of life. According to low SMI and low SMD, the mean ages of sarcopenia were 62 and 64 years, respectively. Both parameters of sarcopenia are consistent with other studies in the literature. The total muscle mass in the body is different between males and females. Thus, SMI measurements can be more sensitive in males than SMD measurements. Sarcopenia is not limited to individuals who appear weak or slim. Indeed, our study population was characterized by body weights with a mean BMI (23-26 kg/m^2), the upper limit of average weight, bordering on overweight. Our findings support that theory because patients with a normal BMI show low SMI and low SMD values, which describe sarcopenia. Typical or near-normal fat tissue may cause misperception (15). Adequate protein intake is crucial for maintaining muscle mass and is expected to be reflected in the PNI (1). In patients with gastric cancer, poor oral intake due to dysphagia, obstruction, or nausea can induce more severe nutritional depletion compared to patients with other types of malignancy. In our series, the patients with low SMD have a significantly lower mean value of PNI. Factors such as age, comorbidity, and frailty are considered some of the main reasons for referrals from other centers to tertiary hospitals. Since our center is a tertiary hospital, most patients have ASA-PS II and ASA-PS III scores. We have excluded ASA-PS IV and above patients from the study. The physical disability caused by the comorbidity will lead to muscle weakness. The low SMI and SMD values of our patients with ASA-PS II/III scores may be related to this. We found no relationship between muscular parameters, tumor stage, and tumor differentiation grade. Patients with distal gastric tumors have significantly lower SMI levels without affecting SMD. We were unable to comment on the reasons for this result.

Postoperative complications continue to exist substantially in older adults because of comorbidities and the decline of functional reserve associated with aging (26). Recently, some studies have reported that sarcopenia may be one of the most critical factors affecting postoperative complications in older people (26-29). However, other studies could not show a relationship with short-term outcomes; nonetheless, a significant relationship was found with long-term survival (1,11,30,31). Our study revealed no significant differences between SMI and SMD values with respect to major postoperative complications (p=0.1, p=0.09, respectively). However, there was a significant difference between low SMD and normal SMD values in the length of hospital stay (p=0.01). Joglekar et al. (29) reported that muscle density, but not muscle mass, is a significant predictor of major postoperative complications in pancreatic cancer. Although there were no significant differences, in line with this information, the major complication rates in our study were higher in patients with low SMD than those with higher SMD. These results explain why patients with low SMD have statistically significant longer hospital stays. Our series showed a significant reduction in OS in patients with both low SMI and low SMD. This finding is consistent with other studies that have also been reported by oncologic cohort groups in the literature (9,32). While Murnane et al. (32) attributed that result to the relationship between anastomotic leakage and myosteatosis, some authors referred to the failure of postoperative adjuvant therapy due to chemotherapy toxicity caused by sarcopenia (25). Even though there were no significant differences, the major complication rates in our study were higher in sarcopenic patients than in non-sarcopenic patients. The other theory is that sarcopenia may be a reflection of the increased metabolic activity of a more aggressive tumor biology, and the increased metabolic activity leads to more major systemic inflammation and subsequently results in muscle wasting (27,33). We thought that all these reasons could affect the OS rates. Our univariate results found that low SMI, low SMD, ASA-PS score, TNM stage, differentiation grade, lymphovascular and perineural invasion, and a positive resection margin were associated with poor OS in patients with gastric cancer. In multivariate analysis, SMD,

ASA-PS score, and positive resection margin were found to be independent prognostic factors for OS.

Integrating SMD calculation into preoperative risk stratification and prognostic models may facilitate the identification of sarcopenic patients. Then, it can help select patients for nutritional support and physical activity to increase muscle strength before surgical treatment. This might be particularly suitable for patients with gastric cancer who require neoadjuvant chemotherapy. In a study that analyzed the change in body composition in patients after neoadjuvant chemotherapy for esophagogastric cancer, there was a statistically significant increase in the number of patients with sarcopenia post-chemotherapy (9,34).

Study Limitations

This study has several limitations. First, this retrospective, single-center study may exhibit selection bias. Second, minor and other complications, such as pulmonary, renal, and cardiac complications, were not recorded. It would have been better if we had recorded the length of stay in the intensive care unit, completion of adjuvant therapy, and disease-free survival. Therefore, a prospective multicenter and multidisciplinary study with a larger patient population may be necessary to clarify the relationship between muscular density and postoperative outcomes in specific subgroups of patients undergoing curative resection for gastric cancer.

CONCLUSION

This study demonstrated that, in patients undergoing curative resection for gastric cancer, there was a statistically significant association between myosteatosis and decreased overall survival. Even though there was no difference in muscular density, the major complication rates in our study are higher in patients with low SMD than in patients with normal SMD. Reporting of SMD from preoperative CT should be considered for patient preparation purposes.

Ethics

Ethics Committee Approval: The Ethics Committee of Marmara University approved the study protocol (date: 05.03.2021, no: 09.2021.248).

Informed Consent: Written informed consent was obtained from all patients participating in the study.

Footnotes

Author Contributions

Concept - A.A., T.K.U; Design - A.A., T.K.U; Materials - T.K.U., O.B., M.K.; Data Collection or Processing - A.A., O.B., M.K.; Analysis or Interpretation - A.A., T.K.U., O.B.; Literature Search - A.A., T.K.U.; Critical Review - A.A., T.K.U., A.E.A.; Writing - A.A., T.K.U., A.E.A.

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

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ORIGINAL ARTICLE
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Evaluation of quality of life in primary hyperparathyroidism patients: Pre- and post-parathyroidectomy outcomes in an Indian cohort

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ABSTRACT

Objective: Primary hyperparathyroidism (PHPT) is a common endocrine condition that causes hypercalcemia and other symptoms due to improper parathyroid hormone (PTH) secretion. With fatigue, bone pain, and neuropsychiatric difficulties, the disorder drastically lowers quality of life (QoL). This study uses Pasieka's parathyroid symptoms score to evaluate parathyroidectomy's impact on Indian PHPT patients' QoL.

Material and Methods: This 18-month prospective observational study was conducted at an Indian academic tertiary care facility. Parathyroidectomy was performed on 42 PHPT patients. Pasieka's parathyroid symptoms questionnaire and baseline clinical and biochemical parameters were completed preoperatively and three months postoperatively. The questionnaire uses a linear analog scale to assess 13 symptoms, including weariness, bone pain, mood issues, and cognitive issues.

Results: Preoperatively, patients demonstrated markedly increased calcium and PTH levels. Post-parathyroidectomy, notable enhancements were noted across various QoL dimensions. Significant reductions in bone pain, joint pain, weariness, and muscle weakness were seen ($p<0.001$). Neuropsychiatric symptoms, such as irritability and mood fluctuations, shown considerable improvement ($p<0.001$). Cognitive symptoms, including amnesia, exhibited some improvement, although dermatological symptoms such as itching and polydipsia were mitigated.

Conclusion: PHPT patients benefit greatly after parathyroidectomy in both physical and mental ways. In order to reduce the systemic effects of PHPT, surgery must be performed quickly. Parathyroidectomy improves patient well-being.

Keywords: Primary hyperparathyroidism, parathyroidectomy, quality of life, postoperative outcomes

INTRODUCTION

Primary hyperparathyroidism (PHPT) is caused by an intrinsic abnormality in one or more of the parathyroid glands, leading to inappropriate secretion of parathyroid hormone (PTH) independent of serum ionized calcium levels (1). As a result, patients with PHPT develop an altered calcium regulatory set point, maintaining elevated circulating calcium levels through increased renal calcium absorption, enhanced gastrointestinal absorption, and heightened osteoclastic activity in bone (2).

The diagnosis of PHPT is predominantly biochemical, marked by increased intact PTH levels and hypercalcemia in individuals with normal renal function (3). PHPT exerts considerable systemic effects, encompassing renal symptoms such as nephrolithiasis, nephrocalcinosis, renal tubular acidosis, nephrogenic diabetic insipidus, and both acute and chronic renal insufficiency (4). Bone-related problems, such as osteopenia and osteoporosis, are also common (5). Furthermore, PHPT is linked to a wide array of non-specific symptoms, such as cognitive deficits, fatigue, irritability, sleeplessness, digestive disorders, and musculoskeletal pain, all of which diminish quality of life (QoL) (6).

QoL evaluation in patients with PHPT is essential for understanding the disease's wider implications beyond biochemical irregularities. A variety of instruments exist for this objective, such as Pasieka's parathyroid symptoms score, the short-form

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health survey-36 (SF-36), the primary hyperparathyroidism quality of life questionnaire (PHPQoLQ), and the disease-specific quality-of-life questionnaire for patients with PHPT (7). Pasieka's parathyroid symptoms score is essential for assessing patient-reported outcomes post-parathyroidectomy (PTX), as it encompasses both physical and neuropsychiatric symptoms (8).

However, there is a paucity of data from India evaluating QoL in PHPT patients, despite differences in disease presentation, healthcare access, and treatment timelines compared to Western populations (9). Understanding patient-reported outcomes in this context is essential for guiding clinical decision-making and health policy.

Therefore, the aim of this study is to objectively assess the QoL in Indian patients with PHPT before and after curative parathyroidectomy using Pasieka's parathyroid symptoms score. This study provides valuable insight into the symptomatic burden of PHPT in an underrepresented population and highlights the tangible benefits of surgery beyond biochemical correction, contributing novel data to a globally relevant yet locally underexplored issue.

MATERIAL and METHODS

This prospective observational study was performed at an academic tertiary care institution in India over an 18-month period, from July 2019 to December 2020. Written informed consent was acquired from all participants. The study was approved by Institution Ethics Committee of Postgraduate Institute of Medical Education and Research, Chandigarh on March, 2021 under letter no. NK/6980/MS/175.

Patient Selection

Patients diagnosed with PHPT were included in the study. The inclusion criteria were persons with biochemically verified PHPT (elevated PTH levels alongside hypercalcemia). Exclusion criteria encompassed those with secondary or tertiary hyperparathyroidism, chronic kidney disease (stage 3 or above), or a history of neck surgery.

Data Collection and Preoperative Assessment

Prospective data collection included demographic information, medical history (including comorbidities), clinical manifestations of PHPT, and relevant biochemical, radiological, operative, and histological findings. All patients underwent parathyroid imaging, comprising of neck ultrasound and Tc-99m-sestamibi scans, to identify the afflicted gland(s).

Surgical Approach

Parathyroidectomy was conducted utilizing either a minimally invasive approach through a restricted cervical incision or via bilateral neck exploration, contingent upon preoperative imaging results and intraoperative evaluation.

QoL Assessment

All patients completed Pasieka's parathyroid symptoms questionnaire both preoperatively and at a three-month follow-up, which was originally developed in English. For patients who were not proficient in English, bilingual healthcare professionals assisted in translating the questionnaire into Hindi or other vernacular languages during the interview process. While this approach ensured patient comprehension, a formal forward-backward translation and validation process of the questionnaire in these languages was not performed. The questionnaire comprises 13 items assessing symptoms such as abdominal discomfort, bone pain, mood disorders, weakness, headaches, irritability, joint pain, exhaustion, amnesia, trouble standing from a seated posture, pruritus, and polydipsia. Symptoms were evaluated using a linear analog scale from 0 (absence of symptoms) to 100 (maximum severity), resulting in a cumulative score between 0 and 1300, based on multiple evaluations or a specified formula, not described here.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was employed to assess the distribution of continuous variables for normality. Continuous variables demonstrating normal distribution were expressed as mean ± standard deviation, while non-normally distributed variables, if any, were reported as median and interquartile range (IQR). Preoperative and postoperative comparisons of continuous variables were performed using the paired Student's t-test for normally distributed data and the Wilcoxon signed-rank test for non-parametric data.

Categorical variables were summarized as frequencies and percentages. Comparisons between categorical variables were conducted using the chi-square test or Fisher's exact test, as appropriate, based on the expected cell counts.

Effect sizes were calculated where relevant to assess the magnitude of differences observed. All statistical tests were two-tailed, and a p-value of less than 0.05 was considered statistically significant. Graphs and plots were generated to visualize the distribution of scores and, where applicable, changes in symptom severity over time.

RESULTS

The study included 42 patients with a mean age of 41.62±13.32 years (range: 18-72 years). The predominant age group among patients was 41-50 years, comprising 38.1%, while females represented 66.7% of the study cohort (Table 1). The average systolic and diastolic blood pressures were 130.60±11.27 mmHg and 77.74±6.64 mmHg, respectively. The average weight and height of the group were 69.95±11.81 kg and

161.07±5.85 cm, yielding a mean body mass index (BMI) of 26.60±3.15 kg/m^2. Over half of the patients (54.8%) exhibited a BMI within the overweight range (25.0-29.9 kg/m^2), while 14.3% were categorized as obese (BMI ≥30.0 kg/m^2) (Table 1).

Biochemical analyses indicated considerable abnormalities in calcium and phosphate metabolism preoperatively. The average serum calcium level was 2.80±0.30 mmol/L (range: 1.99-3.57 mmol/L), whereas the adjusted calcium level was 2.81±0.31 mmol/L (range: 2.20-3.65 mmol/L). The average serum phosphate level was 0.90±0.42 mmol/L, while the median (IQR) value of serum PTH levels was elevated to 237.50 (179.00-417.00) ng/L, with its extreme values reaching 2293.00 ng/L (Table 1).

PTX, patients demonstrated significant improvements in various aspects of health-related quality of life (HRQoL), particularly concerning musculoskeletal symptoms, neuromuscular function, fatigue, and mood (Table 2).

1. Musculoskeletal Manifestations: Patients experienced significant pain relief. Bone pain scores decreased from 40.71±19.68 to 15.71±5.9 (p<0.001), while joint pain scores dropped from 36.4320.82± to 15.24±5.52 (p<0.001). Joint pain reduction averaged -21.19±17.28, with reductions of up to -60.0. Abdominal pain also showed significant improvement, with scores declining from 30±20.12 to 13.33±6.5 (p<0.001), highlighting the clinical benefits of surgical intervention (Table 2).

Table 1. Summary of clinical details

Clinical parameters	Mean ± SD	Range	Frequency (%)
Age (years)	41.62±13.32	18.00-72.00	
Age distribution			
18-30 years			10 (23.8%)
31-40 years			7 (16.7%)
41-50 years			16 (38.1%)
51-60 years			6 (14.3%)
61-70 years			2 (4.8%)
71-80 years			1 (2.4%)
Gender			
Male			14 (33.3%)
Female			28 (66.7%)
Systolic BP (mmHg)	130.60±11.27	110.00-160.00	
Diastolic BP (mmHg)	77.74±6.64	70.00-90.00	
Weight (kg)	69.95±11.81	45.00-98.00	
Height (cm)	161.07±5.85	150.00-175.00	
BMI (kg/m^2)	26.60±3.15	20.00-34.50	
BMI distribution			
18.5-22.9 kg/m^2			4 (9.5%)
23.0-24.9 kg/m^2			9 (21.4%)
25.0-29.9 kg/m^2			23 (54.8%)
30.0-34.9 kg/m^2			6 (14.3%)
Investigations			
S. magnesium (mg/dL)	2.16±0.60	1.24-4.10	
S. calcium (mg/dL)	11.19±1.20	7.98-14.29	
S. albumin (g/dL)	3.95±0.44	2.89-4.77	
Corrected calcium (mg/dL)	11.21±1.22	8.80-14.60	
S. phosphate (mg/dL)	2.79±1.29	0.60-6.25	
S. PTH (pg/mL)	362.70±368.84	67.30-2293.00	
S. vitamin D (ng/mL)	32.17±18.79	9.75-93.40	
ALP (U/L)	213.03±182.20	63.00-737.00	

SD: Standard deviation, BMI: Body mass index, PTH: Parathyroid hormone, BP: Blood pressure, ALP: Alkaline phosphatase.

2. Neuromuscular Function and Fatigue: Fatigue and muscle weakness, common symptoms of hyperparathyroidism, have improved markedly. Fatigue scores reduced from 47.62±15.9 to 16.9±5.63 (p<0.001). Similarly, weakness scores improved from 45.71±20.62 to 17.38±5.87 (p<0.001) (Table 2). Patients reported better physical endurance and reduced difficulty in daily tasks. The ability to rise from a chair, a key mobility indicator, improved from 17.14±15.19 to 10.95±3.7 (p=0.003) (Table 2).

3. Neuropsychiatric and Cognitive Manifestations: Patients experienced significant reductions in irritability (27.38±17.54 to 14.05±7.34, p<0.001), mood fluctuations (18.57±13.36 to 11.43±3.54, p<0.001), and feelings of sadness (14.52±9.42 to 10.95±2.97, p=0.002) (Table 2). Headaches, another frequently reported symptom, decreased significantly from 25.71±20.02 to 13.1±6.04 (p<0.001), with an average reduction of 12.62±18.62 (Table 2).

Cognitive symptoms showed mild improvements. Forgetfulness scores decreased from 15±11.32 to 12.14±7.5, though the change was not statistically significant (p=0.110) (Table 2).

Dermatological and additional symptoms - Symptoms such as polydipsia and pruritus improved significantly. The feeling of thirst decreased, with an average change of -6.43±11.44. Pruritus symptoms were reduced significantly (Table 2).

4. Comprehensive Symptomatic Alleviation and Clinical Consequences: The postoperative changes in HRQoL underscore the substantial benefits of parathyroidectomy. The most significant improvements were observed in fatigue (-30.71±14.38), bone pain (-25.00±18.25), joint pain (-21.19±17.28), and weakness (-28.33±16.81), with some patients achieving total symptom relief (Tables 2, 3). While symptom relief varied among individuals, the overall trend highlighted the effectiveness of surgery in improving QoL.

DISCUSSION

Our study provides significant evidence that parathyroidectomy substantially improves the QoL in patients with PHPT. Using Pasieka's parathyroid symptoms score, we observed significant decreases in the severity of a wide range of symptoms within three months post-surgery. These findings corroborate past research highlighting the diverse advantages associated with surgical intervention in PHPT and emphasize the particular symptomatic improvements that reflect the experiences of patients in India.

Symptomatic Burden and Surgical Outcomes

PHPT is recognized for its diverse clinical presentations, including traditional symptoms like nephrolithiasis and osteoporosis, as well as more subtle signs such as fatigue, cognitive impairment, and irritability. Our investigation revealed that preoperative symptom scores identified fatigue, weakness, and bone pain as the most significant complaints. These findings correspond with previous research by Pasieka et al. (7) and others, which similarly highlighted fatigue and bone pain as defining characteristics of PHPT and key contributors to diminished QoL. A study by Pasieka et al. (7) indicated that 89% of patients with PHPT experienced fatigue, whereas 76% reported bone pain preoperatively,

Table 2. Summary of changes in individual parameter at 3 months after parathyroidectomy in 42 patients

HRQoL	Pre-operative Mean ± SD	Post-operative (after 3 months) Mean ± SD	p-value
Abdominal pain	30±20.12	13.33±6.5	0.000
Inability to move off a chair	17.14±15.19	10.95±3.7	0.003
Bone pain	40.71±19.68	15.71±5.9	0.000
Feeling thirsty	19.05±13.22	12.62±4.97	0.001
Feeling tired	47.62±15.9	16.9±5.63	0.000
Feeling weak	45.71±20.62	17.38±5.87	0.000
Feeling blue	14.52±9.42	10.95±2.97	0.002
Forgetfulness	15±11.32	12.14±7.5	0.110
Headache	25.71±20.02	13.1±6.04	0.000
Irritability	27.38±17.54	14.05±7.34	0.000
Itchy	15.95±13.26	11.19±3.28	0.011
Joint pain	36.43±20.82	15.24±5.52	0.000
Mood change	18.57±13.36	11.43±3.54	0.000

SD: Standard deviation, HRQoL: Health-related quality of life.

Table 3. Summary of change in HRQoL

Change in HRQoL (post-operative)	Mean ± SD	Min-max
Abdominal pain	-16.67±16.03	-60.0-0.0
Ability to move off a chair	-6.19±12.48	-60.0-0.0
Bone pain	-25.00±18.25	-70.0-20.0
Feeling thirsty	-6.43±11.44	-40.0-10.0
Feeling tired	-30.71±14.38	-50.0-10.0
Feeling weak	-28.33±16.81	-60.0-0.0
Feeling blue	-3.57±6.92	-30.0-0.0
Forgetfulness	-2.86±11.32	-40.0-40.0
Headache	-12.62±18.62	-60.0-30.0
Irritability	-13.33±16.48	-60.0-0.0
Itchy	-4.76±11.53	-50.0-10.0
Joint pain	-21.19±17.28	-60.0-0.0
Mood change	-7.14±12.15	-50.0-0.0

SD: Standard deviation, HRQoL: Health-related quality of life.

aligning with our findings on symptom prevalence. The post-surgical improvements observed in our study validate the results of prior research. A 2011 study by Wilhelm et al. showed that parathyroidectomy normalizes biochemical markers and significantly alleviates musculoskeletal and neuropsychiatric symptoms, often within a few months of surgery (10). Similarly, our study found that fatigue, weakness, and bone pain exhibited the most substantial reductions in symptom scores, with improvements of over 60% in these domains. This highlights the significance of parathyroidectomy as a conclusive procedure for both biochemical normalization and alleviation of symptoms.

Neuropsychiatric Enhancements and Ongoing Symptoms

Neuropsychiatric symptoms in PHPT, including depression, irritability, and memory loss, are often overlooked despite their significant impact on QoL. Our study noted significant post-surgical improvements in symptoms like irritability and mood swings, consistent with the findings of Roman (11), who documented substantial gains in emotional well-being after surgery. The improvement in symptoms like "feeling blue" and irritability aligns with the hypothesis that hypercalcemia-related neurochemical imbalances are reversible after surgery. However, certain symptoms in our cohort, such as forgetfulness and itchy skin, showed minimal improvement. This observation corresponds with other research, including a study by Westerdahl and Bergenfelz (12), which indicated that although parathyroidectomy efficiently alleviates symptoms directly related to hypercalcemia, symptoms with a multifactorial origin or less direct connection to parathyroid function may endure. Forgetfulness may be affected by age-related cognitive alterations or other concomitant conditions, highlighting the necessity for supplementary care techniques in addition to surgery.

Global Comparisons and Cultural Context

Our research provides significant insights into the global comprehension of PHPT, especially from an Indian viewpoint, where QoL data are limited. Studies conducted in Western populations, such as those by Szalat et al. (13) and VanderWalde (14), have consistently demonstrated QoL improvements after parathyroidectomy, with reductions in symptoms like fatigue, joint pain, and depression. These parallels emphasize the widespread advantages of parathyroidectomy among many populations, while also underscoring the necessity of regional studies, to include cultural and healthcare system disparities. In our investigation, the preoperative symptom load was significantly elevated, with mean scores for fatigue and bone pain surpassing those documented in comparable studies from Western nations. This gap may indicate postponed diagnosis and extended disease duration in Indian patients, potentially attributable to restricted awareness and access to specialized care. The increased symptom load highlights the critical necessity for prompt diagnosis and care in resource-limited environments.

Strengths and Novel Contributions

A principal strength of our study is its prospective design, facilitating a rigorous comparison of symptom profiles pre- and post-surgery. Furthermore, by employing disease-specific instrument such as Pasieka's parathyroid symptoms score, we obtained a detailed and thorough understanding of the clinical enhancements observed in PHPT patients. This methodology differentiates our research from others that have utilized generic QoL instruments, such as the SF-36, which may inadequately encompass the symptomatology specific to PHPT.

Our study's original contribution lies in its emphasis on an Indian cohort, offering context-specific data that were previously absent. With the growing recognition of PHPT in India due to enhanced diagnostic capabilities, our findings underscore the essential significance of parathyroidectomy in the management of this ailment and provide a standard for future studies in the area.

Study Limitations

Despite its strengths, our study has several limitations. The brief three-month follow-up duration may inadequately reflect the long-term advantages or possible symptom return following parathyroidectomy. Extended follow-up studies are essential to ascertain the sustainability of these enhancements and their effect on patients' overall QoL.

One of the key limitations of our study is that while the questionnaire was translated into the vernacular language with the assistance of bilingual healthcare professionals, a formal forward-backward translation and validation process was not performed. The single-center design and limited sample size restrict the generalizability of our results. Multicenter studies with larger cohorts could yield more extensive insights and facilitate subgroup analysis, including the effects of surgical procedures or variations in outcomes related to preoperative calcium levels. Ultimately, although Pasieka's parathyroid symptoms score serves as an effective instrument for evaluating disease-specific symptoms, the inclusion of other tools such as the PHPQoLQ or the SF-36 may yield a more comprehensive evaluation of patient outcomes.

CONCLUSION

The results of our research hold considerable significance for clinical practice. They underscore the significance of acknowledging the symptomatic burden of PHPT and the role of parathyroidectomy in attaining not just biochemical resolution, but also substantial enhancements in QoL. These findings should motivate doctors to emphasize early diagnosis and prompt surgical referral for symptomatic patients. The continuation of specific symptoms after surgery underscores the necessity for a multidisciplinary approach to patient care, incorporating supportive interventions like cognitive therapy or dermatological treatment where suitable.

Ethics

Ethics Committee Approval: The study was approved by Institution Ethics Committee of Postgraduate Institute of Medical Education and Research, Chandigarh on March, 2021 under letter no. NK/6980/MS/175.

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

Footnotes

Author Contributions

Concept – M.R., C.T., D.D., S.K.B.; Design – M.R., C.T., D.D.; Supervision – C.T., D.D., A.B., S.K.B.; Data Collection or Processing – M.R., D.D., M.T., S.K.B., A.B.; Analysis or Interpretation – M.R., M.T., S.V.P.; Literature Search – C.T., M.T., S.V.P.; Critical Review – A.B., S.K.B., D.D.; Writing – M.R., C.T.

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ORIGINAL ARTICLE
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A predictive tool for postoperative ileus after ileostomy closure: Model development and validation

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ABSTRACT

Objecitve: Postoperative ileus (POI) is a significant complication after ileostomy closure, which results in recurrent vomiting, dehydration, delay in starting enteral feeding, and even anastomotic breakdown. We aimed to develop a prediction model for POI occurrence after ileostomy closure.

Material and Methods: One hundred consecutive patients undergoing ileostomy closure were studied prospectively and data of various demographic and clinical variables were recorded in a predesigned proforma. The final prediction model was developed using logistic regression and internally validated in the next 50 patients.

Results: Factors associated with POI were age, body mass index, tobacco or alcohol addiction, comorbidity, anemia, thrombocytopenia, renal dysfunction, as shown by creatinine level, hypoproteinemia, hypernatremia, and hypokalemia. The mean score of those who developed POI was higher (p=0.002) than those who did not. A cut-off at score 8 had a sensitivity of 85.71%, specificity of 73.12%, and area under the curve was 0.8241 (SE 0.1123). The predictive model was validated in the next 50 consecutive patients and showed good sensitivity (80%) and specificity (93.3%).

Conclusion: Our predictive model can determine the occurrence of POI with accuracy.

Keywords: Ileostomy, ileostomy closure, stoma reversal, postoperative ileus, prediction model

INTRODUCTION

Defunctioning ileostomy (DI) is often performed after major elective colorectal surgeries or emergency surgeries involving the small intestine. Although considered a safety net, DI is not without its share of complications (1). Similarly, closure of DI is also associated with its own complications and even mortality (2-4). Postoperative ileus (POI), defined as delayed return of bowel activity for >3 days, is an important complication occurring in up to 4-20% of patients after DI closure (4-8). This may lead to vomiting, abdominal distention, delay in starting enteral feeds, and the risk of anastomotic disruption, and it is reported to be the most common cause of readmission within 30 days. Preventing POI is important given its associated morbidity and increased cost of care.

Many per-operative factors have been found to be associated with POI after ileostomy closure (8-14). However, there is a scarcity of studies from low- and middle-income countries (LMICs). This prompted us to study probable risk factors for POI and to develop and validate a prediction model for POI.

MATERIAL and METHODS

This study was conducted in the department of surgery of a tertiary teaching hospital in central India from September 2019 to December 2022. It was approved by the Institutional Ethics Committee of Netaji Subhash Chandra Bose Medical College Jabalpur (M.P.) (no: IEC/2019/9906, date: 09.12.2019).

Patients presenting for DI reversal, irrespective of the indication for creation, were prospectively enrolled in this study. Patients were optimized for fitness for surgery before planning closure of stoma. Patients with malignancy received either adjuvant chemotherapy or radiotherapy before closure.

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Prior to closure, a distal loop contrast study was performed to rule out any distal obstruction or leak. Preoperatively, distal loop wash was given with normal saline and enema administered rectally to clear off any inspissated mucus and fecoliths. Patient variables were recorded in a predesigned proforma and their association with POI was noted (Table 1).

All ileostomy closures were performed using the hand-sewn technique in two layers with silk 2-0 round body sutures by consultants. All patients received a dose of first-generation cephalosporin preoperatively as prophylaxis. A 32G intraperitoneal drainage tube was inserted in all patients, which was removed between the fifth and sixth post-operative days (POD).

Standard enhanced recovery after surgery protocols were applied during the post-operative period. Patients were observed for development of bowel sounds, time to start of liquid diet and progression to solids, development of vomiting, abdominal distention, or other complications like surgical site infection (SSI) and leak.

POI was defined as delay in the occurrence of intestinal motility presenting as an intolerance to oral food in absence of clinical or radiological signs of obstruction on or after POD 3 that either (a) required nasogastric tube insertion; or (b) was associated with two of the following: Nausea/vomiting, abdominal distention or the absence of flatus (4,8,13).

Statistical Analysis

Statistical analysis was done using SPSS (IBM Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29.0.2.0 Armonk, NY: IBM Corp).

Data analysis involved first univariate analysis to determine whether the variable has a significant effect on the outcome. These significant variables were later involved in multivariate regression analysis to determine the best combination of

Table 1. Patient variables, lab parameters and significance of their association with POI

Parameter		Total (n=100)	Non-POI (n=93)	Paralytic ileus (n=7)	p-value
Age	≤60 yrs	96	89	7	0.7466 (NS)
	>60 yrs	4	4	0	
Gender	Male	67	64	3	0.1601 (NS)
	Female	33	29	4	
BMI	≤18.5	28	23	5	0.0175 (S)
	>18.5	72	70	2	
Addiction	Alcohol	30	25	5	0.0242 (S)
	Tobacco/smoking	26	25	1	0.4133 (NS)
Comorbidity	Hypertension	5	5	0	0.6903 (NS)
	Diabetes	4	2	2	0.0237 (S)
	Tuberculosis	9	4	5	0.0001 (S)
	Chronic obstructive pulmonary disease	12	11	1	1 (NS)
	Any comorbidity	21	15	6	0.0014 (S)
	No comorbidity	79	78	1	
Nature of disease	Benign	87	80	7	0.5899 (NS)
	Malignant (adjuvant chemo/ radiotherapy)	13	13	0	
Pathology	Obstruction	53	48	5	0.4424 (NS)
	Perforation	47	45	2	
Duration before closure	≤3 months	35	33	2	1 (NS)
	>3 months	65	60	5	
SSI		17	10	7	0.0001
PONV		7	1	6	0.0001 (S)
Hospital stay during index surgery	≤10 days	92	90	2	0.0001 (S)
	>10 days	5	0	5	
Death		5	2	3	0.0012 (S)

POI: Postoperative ileus, BMI: Body mass index, SSI: Surgical site infection, PONV: Post-operative nausea and vomiting.

variables. Their cut-off values were determined using receiver operating characteristic (ROC) curves. The weighting scores were assigned to each variable based on its contribution in the multivariate analysis. The final score and cut-off were again determined using the ROC curve and a predictive tool was developed after performing multivariate analysis with various combinations of the above factors.

This predictive model was then subjected to validation in the next cohort of patients.

RESULTS

One hundred consecutive patients presenting for DI reversal were prospectively enrolled in this study. Most patients underwent emergency surgery for Typhoid intestinal perforation (n=80) Tubercular intestinal perforation (n=2), obstruction due to tuberculosis (n=3), or malignancy (n=2), while others had elective surgery for tubercular stricture (n=2) or malignancy (n=11) leading to stoma creation. Patients with malignancy did not receive neoadjuvant treatment.

Patient variables, lab parameters, and significance of their association with POI are shown in Table 1. Alcohol addiction and coexisting comorbidities such as diabetes and tuberculosis were associated with POI. Post-operative nausea and vomiting (PONV), hospital stay, and mortality were significantly higher in the POI group. A total of 7 patients developed POI; PONV was seen in 6 out of 7 patients; and 3 out of 7 patients died. Laboratory parameters and significance of their association with POI are shown in Table 2. Most variables had a significant association with POI; except the platelet count.

On regression analysis, among demographic factors, only body mass index (BMI) (higher odds for BMI ≤18.5) was found to be significantly associated with the occurrence of POI after DI closure (Table 3). Regression analysis showed a significant association between all preoperative lab parameters, the age of the patient, and the occurrence of POI (Table 4). Next, the ROC analysis was conducted to determine the optimal cut-off points for the significance of the variables found to have a significant impact on POI in the univariate analysis (Table 5). Scores were assigned to each factor, and weights were given according to their sensitivities. A prediction model was constructed by performing multivariate analysis with various combinations of the aforementioned factors plus platelet count, resulting in a minimum score of 2 and a maximum score of 12 (Table 6). The ROC analysis on the final scoring system revealed that the highest predictive value of the scoring system was at a cut-off of 7.5. As the scores were in non-decimal values, a cut-off

Table 2. Laboratory parameters and significance of their association with POI

Lab parameter	Ileus group (mean values)	Non ileus group (mean values)	Significance (p-value)
Hb	9.71±0.76	11.32±1.44	0.0044
TLC	14028.57±3176.85	8478.92 ±4351.35	0.0013
Platelets	2.45±0.95	2.77±0.99	0.4104
Albumin (g/dL)	2.62±0.50	3.09±0.25	<0.0001
Creatinine (g/dL)	1.54±0.72	1.07±0.41	0.0070
Sodium (MEq)	142±8.42	135.78±4.98	0.0032
Potassium (MEq)	2.78±0.52	3.57±0.81	0.0128

POI: Postoperative ileus, Hb: Hemoglobin.

Table 3. Significance of demographic factors, after regression analysis, with occurrence of POI

Factors		Odds ratio	p-value
Demography	Rural	1 (reference)	0.299
	Urban	0.41	
Sex	Male	1 (reference)	0.175
	Female	0.34	
Addiction of alcohol	No	1 (reference)	0.111
	Yes	3.96	
BMI	≤18.5	1 (reference)	0.042
	>18.5	0.17	
Time before stoma closure	≤3 months	1 (reference)	0.634
	>3 months	1.51	

POI: Postoperative ileus, BMI: Body mass index.

Table 4. Significance of preoperative lab parameters and age, after regression analysis, with occurrence of POI

Factors	Beta coefficient	Standard error	Z	p-value	95% CI	
					Lower	Upper
Age	-0.004	0.002	-2.01	0.047	-0.007	0.000
Hb	-0.039	0.016	-2.44	0.016	-0.071	-0.007
TLC	0.000	0.000	2.9	0.005	0.000	0.000
Platelets	0.053	0.022		0.021	0.008	0.097
Albumin	-0.337	0.079	-4.28	<0.0001	-0.493	-0.181
Creatinine	0.153	0.055	2.76	0.007	0.043	0.262
Sodium	0.014	0.005	3.01	0.003	0.005	0.023
Potassium	-0.077	0.031	-2.52	0.013	-0.138	-0.016

POI: Postoperative ileus, Hb: Hemoglobin, CI: Confidence interval.

Table 5. Empirical cut-point and sensitivity of significant factors for POI (from univariate analysis) after receiver operating curve analysis

Factors	Empirical cut-point	Sensitivity	Specificity	AUC
Age	19	86	14	50
BMI	20.45	29	58	43
Hb	9.9	86	10	48
TLC		100	86	93
Albumin	3.25	29	75	52
Creatinine	0.95	100	46	73
Sodium	142.5	86	85	85
Potassium	3.15	57	33	45

POI: Postoperative ileus, Hb: Hemoglobin, AUC: Area under the curve, BMI: Body mass index.

Table 6. Cut-off of various parameters used in score evaluation and allotting scores based on their weightage in scoring system for the prediction model (minimum score =2 and maximum score =12)

Parameters	Lower cut-off	Upper cut-off	Scores
Age	≤19	>19	1 & 2
BMI	<18.5	≥18.5	1 & 2
Alcohol addiction	Yes	No	1 & 0
Comorbidity	Yes	No	1 & 0
Hb	≤9.9	>9.9	0 & 1
Platelets	≤2.1	>2.1	0 & 1
Creatinine	≤0.95	>0.95	0 & 1
S. albumin	≤3.25	>3.25	0 & 1
Sodium	≤142.5	>142.5	0 & 1
Potassium	≤3.15	>3.15	0 & 1

BMI: Body mass index, Hb: Hemoglobin.

was set at score 8 with the sensitivity of 85.71%, the specificity of 73.12%, and the AUC was 0.8241 with SE of 0.1123. This means that the above factors contributed 82% towards POI occurrence (Figure 1).

When comparing the overall score of POI and non-POI groups, the mean score was significantly higher (8.29±1.70 vs. 6.28±1.40; t=3.23; p=0.002) in patients with POI. Sixteen patients had a score of >8; however, only 6 patients actually developed POI, 1 patient with POI had a score lower than 8. Out of 7 patients with POI, 6 (85.7%) had scores higher than 8. The sensitivity of the model in predicting POI was 85.71%; the specificity was 89.25% with an accuracy of 89%.

We validated prospectively this predictive model in the next 50 consecutive patients undergoing DI closure. A total of 7 patients had a score >8, of whom 4 actually developed POI. One patient with POI had a score less than 8; sensitivity of the model was 80% and specificity was 93.3% (Figure 2).

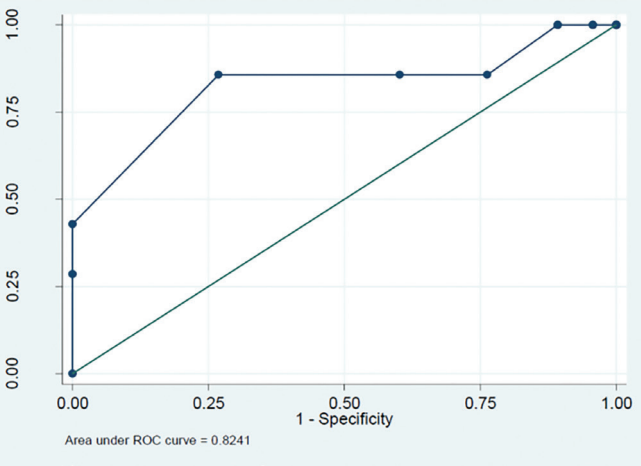

Figure 1. ROC of the predictive model.
ROC: Receiver operating characteristic

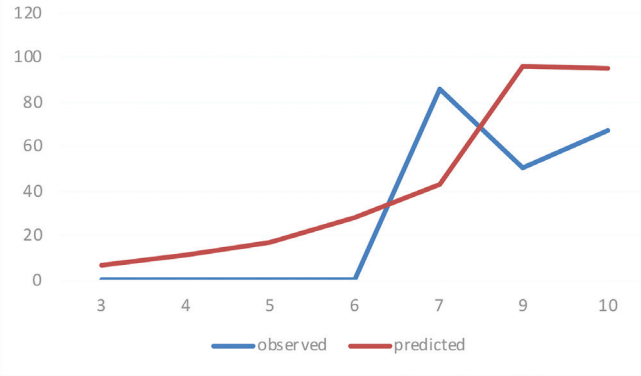

Figure 2. Comparison observed and predicted POI in the validation cohort.
POI: Postoperative ileus

DISCUSSION

POI is a common, challenging complication following ileostomy closure, which can delay patient recovery, increase hospital stay, and healthcare costs significantly. We constructed and internally validated a predictive model to assess POI risk in patients undergoing ileostomy closure. Our model, using logistic regression, identified age, BMI, addiction to alcohol, presence of comorbidities, anemia, thrombocytopenia, renal dysfunction, hypoproteinemia, hypernatremia, and hypokalemia: As key factors associated with POI. The model showed good accuracy, as demonstrated by an AUC of 0.8241 in the derivation cohort and robust sensitivity (85.71%) and specificity (73.12%) at a cut-off score of 8. Furthermore, internal validation in an independent cohort confirmed high predictive value (80% sensitivity, 93.3% specificity), suggesting that our tool could be reliably used to identify patients at heightened risk of POI.

DI is a prophylactic surgical step, that is added when there is a high risk of leakage after surgery for a distal ileal or colorectal pathology; hence prevention of leakage remains the focus of index surgery. However, the morbidity and mortality associated with the later closure of the DI is significant. POI merits attention not only because of its incidence (4-20%) but also because it has its own set of complications such as vomiting and abdominal distention, respiratory difficulties, delay in starting enteral feeds, risk of anastomotic disruption, and even death. POI remains poorly defined and needs an international consensus regarding definition, diagnosis, and treatment (15,16). Its prediction is of special interest because early identification and timely modification of associated factors may prevent its development. High-risk patients might benefit from extended and intensive observations in the hospital and could be offered early interventions (conservative or surgical), thereby potentially changing their outcomes (17). Incidence of POI was 7%, and 10%, respectively, in our derivation cohort and validation cohort.

Many associated risk factors, such as, older patients, high BMI, a >3-month interval for closure, hypertension, coexisting chronic obstructive pulmonary disease, tobacco addiction, and chemotherapy and radiotherapy that were found important in studies from developed countries, were not found significant in our study (8,11,17-19). Time interval for stoma closure was included in the univariate analysis, but it did not emerge as a statistically significant predictor of postoperative ileus. It could be because of the younger study population. Our patients were younger because DI was done most commonly for typhoid enteric perforations and tubercular obstruction or perforations. And even in this cohort, younger patients had a higher

incidence of POI. Similarly, we had more male patients, but the incidence of POI was higher (p= not significant) in females. Alcohol addiction was found to be a significant risk factor while tobacco addiction was not found to be one. The relationship between individuals with alcohol addiction and the occurrence of POI could not be found in any previous studies. Low BMI (<18.5) was a significant (p=0.0175) risk factor and can be considered a marker of nutritional status for our patients at the preoperative stage. In the majority (87%) of our cohort, DI was done for benign lesions; none of the remaining patients with malignant indications developed POI in spite of adjuvant chemotherapy and radiotherapy. In our cohort, more (9.4% vs. 4.25%, p= not significant) patients operated for an obstructive pathology developed POI than those operated for perforations. This may be of importance in view of our disease demography, and the exact causal relation is worth future study. Diabetes mellitus and tuberculosis were the two comorbidities associated with POI in our patients. Hypoproteinemia and Hypokalemia were common risk factors, as observed in previous studies (20,21). Patients with a hospital stay of more than 10 days at index surgery were found to have a higher incidence of POI, which may be due to surgical complications, e.g., leak, pelvic sepsis, etc., or medical conditions, e.g., pneumonia, sepsis, cardiac problems. Any intraperitoneal inflammation could lead to an increased likelihood of adhesions later (22,23). Duration between DI and its reversal has been known to affect incidence according to some, but not all, studies (8,24-26). However, it did not reach the significance level, unlike in our study.

Most of these differences can be explained by having a different patient cohort, and, in some cases, by having a smaller number of patients, which prevent the statistical difference from reaching a significant level.

An earlier prediction model developed in Canada included five variables: Increasing age, interval between ileostomy creation and closure, duration of surgery for ileostomy closure, ASA fitness grade, and underlying pathology/treatment (27). Again, the inherent differences between different patient cohorts substantiate the need for developing specific prediction tools for LMICs.

Study Limitations

Our study has some limitations: Factors like use of open vs. minimally invasive surgery, hand-sewn vs. stapler anastomosis, and a prophylactic drain could not be assessed because open surgery for index and stoma closure, hand-sewn anastomosis and a prophylactic drain were used in all our patients. Other missed factors included effects of efferent loop stimulation, epidural anesthesia, operation time, blood loss, post-operative opioid use, and probiotic stimulation. These limitations apart, implementing this predictive model in clinical settings could provide multiple benefits. First, it could facilitate preoperative counseling by giving clinicians a quantitative means to inform patients about their individual risk of POI. This risk-based approach can enhance shared decision-making and set realistic expectations about postoperative recovery. Second, high-risk patients could be triaged for preventive strategies, such as enhanced perioperative hydration, earlier initiation of gut motility agents, or other supportive measures aimed at mitigating POI risk. Moreover, resource allocation could be improved by focusing monitoring and resources on patients at greatest risk of prolonged hospital stays due to POI. This targeted approach could improve efficiency and reduce costs, aligning with modern healthcare objectives that emphasize resource optimization and cost-effectiveness (28,29).

While our model performed well in an internal validation cohort (Figure 2), external validation in larger and more diverse populations is essential to establish its generalizability across different healthcare settings. Future research aimed at external validation in varied clinical and geographical contexts is essential to strengthen the model's applicability and utility in broader surgical practice. All patients underwent open surgery with hand-sewn anastomosis. While this ensured consistency, it also limited applicability of the model in settings using different surgical techniques (e.g., minimally invasive or stapled closure). Moreover, the majority of patients had benign indications for ileostomy. This raises questions about whether the model would be applicable in malignant cases, especially those undergoing adjuvant therapies. This necessitates validation in these clinical contexts, including international cohorts. Further refinement may improve the predictive power of the scoring system. Future studies might also assess whether incorporating additional perioperative parameters—such as intraoperative fluid balance or early postoperative markers—could further enhance model performance. Moreover, prospective trials are needed to evaluate whether implementing this predictive tool and related interventions actually translates to reduced incidence of POI and improved clinical outcomes.

CONCLUSION

We have developed and internally validated a practical, predictive model for POI after ileostomy closure. By enabling early identification of high-risk patients, this model holds promise to improve preoperative planning, enhance patient counseling, and guide targeted interventions. Despite some limitations in generalizability and methodology, it provides a useful model for clinical practice, especially in LMIC settings.

Ethics

Ethics Committee Approval: It was approved by the Institutional Ethics Committee of Netaji Subhash Chandra Bose Medical College Jabalpur (M.P.) (no: IEC/2019/9906, date: 09.12.2019).

Informed Consent: Patients presenting for DI reversal, irrespective of the indication for creation, were prospectively enrolled in this study.

Footnotes

Author Contributions

Surgical and Medical Practices - A.V., D.K., A.K.; Concept - R.K., D.K., A.V.; Design - R.K., D.S., P.A.; Data Collection or Processing - A.V., A.K., D.K.; Analysis or Interpretation - A.V., A.K., D.K.; Literature Search - R.K., D.S., A.K.; Writing - A.B., D.S.

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

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ORIGINAL ARTICLE
Turk J Surg 2025;41(3):248-254

Factors affecting the formation of lymphedema due to breast cancer (Is primary systemic treatment an independent factor in the formation of breast cancer related lymphedema?)

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ABSTRACT

Objective: This study aimed to evaluate the local and systemic risk factors associated with breast cancer-related lymphedema (BCRL), with a focus on whether primary systemic treatment (PST), particularly taxane-based chemotherapy, is an independent risk factor.

Material and Methods: A prospective clinical study was conducted on 80 breast cancer patients discussed at our institution's weekly breast cancer council. Patients were grouped based on PST status. Clinical examinations and measurements were performed preoperatively and postoperatively at 1, 6, 12, 18, and 24 months. Only the operated arm was assessed using tape measurements and the truncated cone formula. Arm volumes were calculated, and lymphedema (LE) was diagnosed based on a volume difference (≥200 mL or ≥2 cm circumference).

Results: No statistically significant differences were found between PST and non-PST groups regarding age, body mass index, menopausal status, smoking, or tumor characteristics. LE was detected in 7 (8.8%) patients, all Stage 1. PST and taxane-based chemotherapy were not significantly associated with LE development. However, seroma presence (p=0.038) and axillary radiotherapy (p=0.043) were significantly associated with LE. Arm volume increase was most significant at 1 and 18 months postoperatively (p=0.055 and p=0.044, respectively).

Conclusion: PST, including taxane-based chemotherapy, does not appear to be an independent risk factor for BCRL. In contrast, postoperative seroma and axillary radiotherapy are significantly associated with LE development. Early identification and management strategies should target these modifiable factors to reduce the risk of LE.

Keywords: Breast cancer, primary systemic treatment, lymphedema, radiotherapy, sentinel lymph node biopsy, risk factors

INTRODUCTION

Breast cancer is the most prevalent malignancy among women. Increased survival rates due to early detection and systemic treatment have led to a rise in treatment-related complications, particularly lymphedema (LE), which is influenced by multiple factors, including obesity, surgical intervention, radiotherapy (RT), and possibly primary systemic treatment (PST), and significantly impairs quality of life (1). The role of PST, especially taxane-based regimens, in LE development remains controversial (1-3).

This study investigates whether PST is an independent risk factor for LE, and identifies other potential predictors by comparing patients who did and did not receive PST.

MATERIAL and METHODS

Study Population and Design

Patients diagnosed with breast cancer are evaluated in the breast council and their treatments are planned. Among these patients, those who agreed to participate in the study, accepted the necessary follow-up and measurements to be made at the required time intervals and were included in the study. After Ethics Committee approval from the University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital (decision no.: 69/21, date: 10 May 2022), 80 patients were prospectively enrolled. Participants were grouped based on PST status. According to the treatment plan, LE follow-up, examination, and measurements were recorded at 1, 6, 12, 18, and

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24 months before and after PST (n=40) and/or surgery (n=40) (Figure 1). All patients came for follow-up for at least 2 years.

Measurements

Arm volume of the operated side was calculated using circumferential tape measurements at 7 cm intervals and the truncated cone formula.

Circumferential measurements were initiated at the ulnar styloid process, with subsequent measurements taken at 7-cm intervals. The volume of each conical segment was calculated using the following formula, and the differences in volume between the arms were analyzed:

* $V = \frac{h(C2 + Cc + c2)}{2\pi}$

• V: upper extremity volume

• C: circumference of the lower segment

• c: circumference of the upper segment

• π: 3.14

• h: distance between the measurements (set as 7 cm in this study).

LE was defined by a volume difference of ≥200 mL or a circumference difference ≥2 cm. Arm volume differences over time were also analyzed.

Statistical Analysis

Data were analyzed using SPSS v25. Descriptive statistics, t-tests, Mann-Whitney U, chi-square, and repeated measures ANOVA were employed. P<0.05 was considered significant

All statistical analyses were performed using the Statistical Package for Social Sciences for Windows, version 25.0.

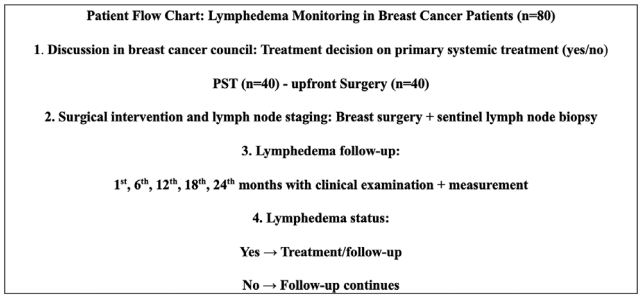

Figure 1. Patients diagnosed with breast cancer are evaluated in the breast council and their treatments are planned. Among these patients, those who agreed to participate in the study, accepted the necessary follow-up and measurements to be made at the required time intervals and were compliant were included in the study. According to the treatment plan, lymphedema follow-up, examination and measurements were recorded at the specified time intervals before and after PST and or surgery.

PST: Primary systemic therapy

RESULTS

Among 80 patients, LE was detected in 7 (8.8%), all of whom had Stage 1 LE (1,4). These patients were advised to elevate their limbs, to receive manual massage, and were followed up clinically, without any progression of their condition. The characteristics of the surgical techniques employed and the distribution of lymph nodes and tumor types are summarized in Table 1. When PST status, chemotherapy, and hormone therapy were evaluated separately, no statistically significant differences were observed between patients with and without LE. Likewise, the diagnostic and therapeutic approaches regarding LE did not differ significantly (Table 2).

Axillary RT (71.4% in LE group vs. 32.9% in non-LE group; p=0.043) and seroma (85.7% vs. 38.4%; p=0.038) were significantly associated with LE (Table 3).

When the measurements of both arms were considered during both the preoperative and postoperative periods, an increase in the left arm measurement was observed in patients with LE at 1 month postoperatively (Table 4). Moreover, when the relationship between inter-arm volume difference and LE was examined, the values at 1 and 18 months postoperatively were found to be significantly different (Table 5).

Volume differences in the operated arm were observed at 1 and 18 months in the LE group (p=0.055 and 0.044, respectively).

In all patients diagnosed with LE (whether right or left), the dominant side was the right. In the subgroup of patients with a right dominant arm, the measurements and their corresponding arm volumes for both right and left arms for patients with and without LE are illustrated in Figures 2 and 3. Although the median values did not reveal a significant difference overall, the 1- and 18-month time points were particularly notable.

At 1 month postoperatively, total arm volume was higher in patients with LE, reaching borderline statistical significance (p=0.055). At 18 months, the volume difference in patients with LE was significantly higher (p=0.044) (Figure 4).

DISCUSSION

The incidence of breast cancer is increasing, and advances in diagnosis and treatment are prolonging patient survival, while breast cancer treatment-related LE ranges from 8.4% to 21.4%, consistent with figures reported in the literature (4-6). Furthermore, its relationship with age has been examined, and age is not directly associated with the development of LE (7,8). A retrospective study by Donahue et al. (8) found that smoking did not affect the development of breast cancer-related LE over a 3-year follow-up period. These findings are consistent with our results.

Table 1. Distribution of patients according to applied surgical technique, lymph node and tumor type, PST status, presence of lymphedema, and treatment approach

Variable	n (%)
Surgical	
Mastectomy + SLNB	27 (33.7)
MKC + SLNB	53 (66.3)
Axilla	
SLNB	80 (100.0)
SLNB + AD	20 (25.0)
SLNB method	
Isosulfan blue (IB)	73 (91.3)
Radiocolloid	6 (7.4)
IB + radiocolloid	1 (1.3)
Lymph node count	
1/2/3/4/5/6/7	6/13/23/24/7/3/4
Number of positive lymph nodes	
01/2/3/4/5/6	54 (67.5)/5/10/8/1/1/1
Tumor type: DCIS/invasive	2 (2.4)/78 (97.6)
ER status	
Negative/positive	15 (18.8)/65 (81.2)
PR status	
Negative/positive	32 (40.0)/48 (60.0)
CERB2	
Negative/positive	71 (88.8)/9 (112)
Neoadjuvant endocrine therapy	
Did not received/received	71 (87.5)/8 (12.5)
Neoadjuvant chemotherapy-taxane based	
Did not receive/recived	9 (22.5)/31 (77.5)
Lymphedema no/yes	73 (91.3)/7 (8.7)
Detected lymphedema side (surgical side)	
Right/left	2 (71.4)/5 (28.6)
Axillary RT no/yes	51 (61.7)/29 (36.3)
Aspiration/seroma	
No/yes	46 (57.5)/34 (42.5)
Preop FNAB axilla	
Not done/done	46 (57.5)/34 (42.5)
Preop IIAB axilla result	
Benign/malignant	62 (65.0)/38 (35.0)

PST: Primary systemic treatment, SLNB: Sentinel lymph node biopsy, ER: Estrogen receptor, PR: Progesterone receptor, FNAB: Fine needle aspiration biopsy, DCIS: Ductal carcinoma *in situ*.

Although direct comparisons of LE rates have not been made in studies that have focused predominantly on non-invasive methods for axillary staging, there is strong evidence to support the idea that even minimal surgical interventions in the axilla may affect the planning of diagnostic and treatment strategies. However, no significant differences were detected (9,10). A study by Nakagawa et al. (11) suggested that Chemotherapy may be a causal factor for LE. Their aimed was to determine whether chemotherapy affects the lymphatic vessels and blood vessels in the skin and subcutaneous fat and to investigate how these Changes relate to the degree of edema after Chemotherapy. In contrast, several studies have shown that neoadjuvant chemotherapy, especially taxane-based agents, plays a role in

Table 2. Relationship between neoadjuvant treatment status and lymphedema

Variable	No lymphedema [n=34-(%)]	Lymphedema present [n=6-(%)]	p
NET			
Tamoxifen			
Did not receive treatment	29 (85.2)	6 (100)	0.977
Received treatment	5 (14.8)	0 (0)	
Filgrastin			
Did not receive treatment	30 (88.2)	6 (100)	0.852
Received treatment	4 (11.8)	0 (0)	
NACT			
Paclitaxel			
Did not receive treatment	7 (20.6)	2 (33.3)	0.490
Received treatment	27 (79.4)	4 (66.7)	
Cyclophosphamide			
Did not receive treatment	7 (20.6)	3 (50)	0.125
Received treatment	27 (79.4)	3 (50)	
Transtuzumab			
Did not receive treatment	28 (82.4)	5 (83.3)	0.953
Received treatment	6 (17.6)	1 (16.7)	
Doxorubicin			
Did not receive treatment	8 (23.5)	3 (50)	0.152
Received treatment	26 (76.5)	3 (50)	
Carboplatin			
Did not receive treatment	31 (91.2)	6 (100)	0.657
Received treatment	3 (8.8)	0 (0)	

NET: Neoadjuvant hormone therapy, NACT: Neoadjuvant chemotherapy.

the development of breast cancer-associated LE by increasing capillary permeability and promoting protein accumulation in the interstitial space. In a prospective study conducted by Nguyen Stringer et al. (12), only 74 out of 273 patients who underwent an axillary lymph node dissection (ALND) developed breast cancer-associated LE. Notably, all of these patients received taxane-based chemotherapy. The risk of developing LE was found to be three times higher in patients who received taxane-based chemotherapy than in those who did not (12-14). In contrast, in a prospective cohort study conducted by Montagna et al. (15), when the risk and findings were analyzed, no statistically significant difference was observed in the rates of LE according to the chemotherapy regimen. When taxane-based regimens were evaluated as a separate group (n=31), statistical analysis yielded a p-value of 0.490. In our series, no significant difference was found between the groups receiving and not receiving Taxane-based chemotherapy.

The risk of breast cancer-associated LE was strongly associated with ALND. There are different results in studies on this subject, and it is known that routine ALND increases the rate of LE when it is performed for curettage rather than for staging purposes. No relationship was observed between axillary surgery for diagnosis or staging purposes and LE in our series. A large prospective study by Warren et al. (16) showed that axillary RT significantly increased the risk of LE compared with whole breast/chest wall irradiation. Similarly, a 15-year follow-up study by Poortmans et al. (17).

Breast cancer LE as a risk factor for RT. Axillary RT was a risk factor for LE (p=0.043), while RT to the whole breast and chest wall was not associated with a risk of LE (p=1.00). Axillary management and its universal approaches have become a focus in recent years. Numerous studies, along with relevant reviews and meta-analyses, emphasize minimizing the extent of axillary surgery (18). The risk of breast cancer-associated LE was most strongly associated with ALND. There are different results in studies on this subject, it is known that routine ALND increases the rate of LE when performed for curettage rather than staging purposes (18). It is widely accepted that the origin of breast cancer LE is multifactorial (19,20) and can be modified by the city, surgical techniques, and extent of lymph node dissection after surgery.

A study published in 2019 showed that lymph node metastasis is a significant risk factor for the development of LE in breast cancer patients. In addition, the risk of LE was associated with the number and characteristics of metastatic lymph nodes. In independent lymphadenectomy (LE) with 10 or more metastatic

Table 3. Relationship between patients' treatment/procedural status and lymphedema

Variable	No lymphedema [n=73-(%)]	Lymphedema present [n=7-(%)]	p
Surgical			
Mastectomi + SLNB	24 (32.9)	3 (42.9)	
MKC + SLNB	49 (67.1)	4 (57.1)	0.594
Axilla			
SLNB	73 (100.0)	7 (57.1)	
SLNB + AD	17 (23.3)	3 (42.9)	0.253
SLNB technique			
Isosulfan blue (IB)	67 (91.8)	6 (85.7)	
Radiocolloid	5 (6.8)	1 (14.3)	
IB+ radiocollaoid	1 (1.4)	0 (0.0)	0.744
Axillary RT			
No	49 (67.1)	2 (28.6)	
Yes	24 (32.9)	5 (71.4)	**0.043**
RT			
Thoracic RT	23 (31.5)	2 (28.6)	
Whole-breast RT	50 (68.5)	5 (71.4)	1.000
Aspiration/seroma			
No	45 (61.6)	1 (14.3)	
Yes	28 (38.4)	6 (85.7)	**0.038**
Preop FNAB axilla			
Not done	44 (60.3)	2 (28.6)	
Done	29 (39.7)	5 (71.4)	0.129
Preop FNAB axilla result			
Bening	49 (67.1)	3 (42.9)	
Malignant	24 (32.9)	4 (57.1)	0.232

SLNB: Sentinel lymph node biopsy, RT: Radiotherapy, FNAB: Fine needle aspiration biopsy.

Table 4. Relationship between follow-up measurements of the right and left arms and lymphedema

Variables	No lymphedema (n=73)	Lymphedema present (n=7)	p
Pre-op right	1598.0±330.5	1660.7±240.1	0.627
Pre-op left	1587.8±317.3	1680.4±206.3	0.453
Post-op right	1578.2±320.2	1722.7±196.0	0.246
Post-op left	1570.4±306.0	1674.3±198.6	0.383
1. month right	1607.0±339.6	1740.5±219.1	0.313
1. month left	1588.9±335.5	1765.7±137.3	**0.016**
6. month right	1594.5±349.9	1686.1±160.7	0.497
6. month left	1574.2±335.8	1732.2±255.1	0.230
12. month right	1590.9±331.0	1724.2±154.5	0.297
12. month left	1570.7±325.3	1747.6±270.8	0.168
18. month right	1600.3±349.6	1740.7±200.1	0.301
18. month left	1577.9±326.9	1745.0±273.4	0.195
24. month right	1593.9±335.0	1695.5±175.7	0.433
24. month left	1569.8±321.5	1742.9±273.0	0.173

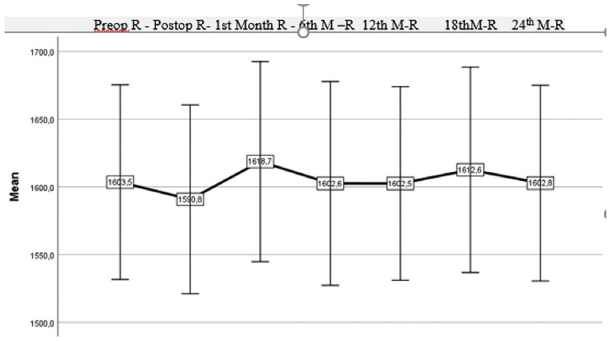

Figure 2. Changes in the mean right arm volume measurements over the follow-up period.

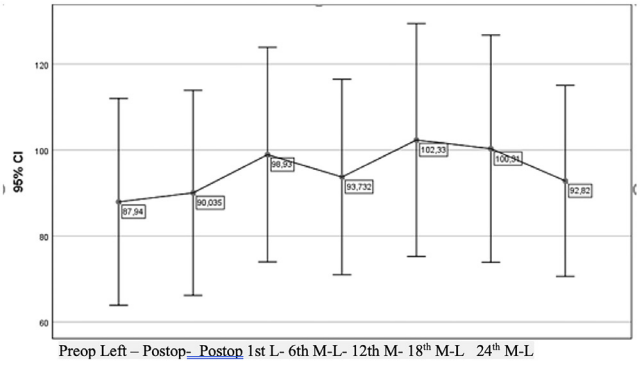

Figure 3. Changes in the mean left arm volume measurements over the follow-up.

CI: Confidence interval

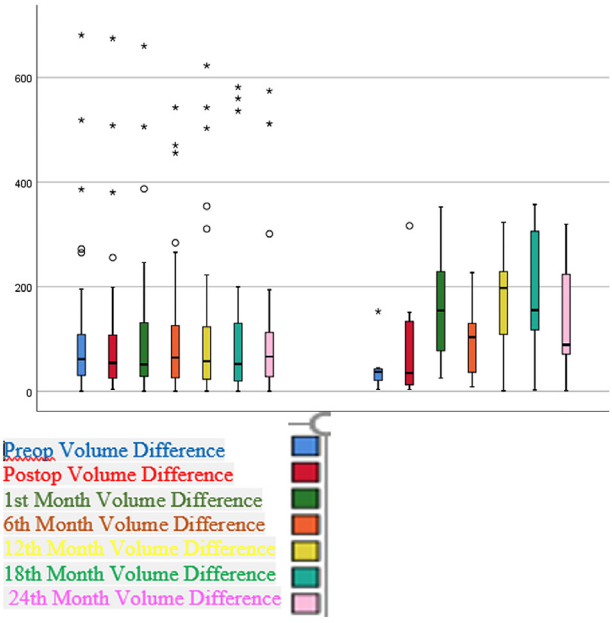

Figure 4. Relationship between the median difference in arm volume and lymphedema status.

At 1 month po. with LE, reaching borderline statistical significance (p=0.055).

At 18 months, with LE was significantly higher (p=0.044).

LE: Lymphedema.

lymph nodes, the risk was 1.78 times higher than in those with three or fewer metastatic lymph nodes and 2.17 times higher than in those without lymph node metastasis (21). Similar studies with a 5 year follow-up have shown that both axillary lymph node metastases and advanced cancer stage are associated with LE (22,23). In our series, the detection of LE was more frequent in patients who received PST, which is consistent with information about the relationship between cancer stage and LE. However, an analysis was not performed on this relationship. No relationship was observed between axillary surgery for diagnosis or staging purposes and LE. Additionally, when considered in terms of the number of LE nodes, no association with LE was detected in our patients who underwent axillary surgery for staging purposes, and the number of lymph nodes was limited.

In a retrospective cohort study conducted by Toyserkani et al. (24), involving all unilateral breast cancer patients treated between 2008 and 2014, LE was developed in 291 out of 1,822 patients, with seroma being identified as an independent risk factor. In contrast, a prospective study by Koelmeyer et al. (25) found no significant association between seroma and breast cancer-related LE. The surgeon's patient volume and experience may be effective in this regard (26). Our patients were operated on by physicians experienced in breast surgery; however, only two of the patients diagnosed with LE (25%) were operated on specifically by a breast surgeon.

Table 5. Relationship between the median difference in arm volume and lymphedema status

Variable	No lymphedema (n=73)	Lymphedema present (n=7)	p-value
Pre-op volume difference	61.3 (30,1108,5)	37.2 (20,842,6)	0.125
Post-op volume difference	54.4 (24,9107,6)	35.0 (12,4133,6)	0.621
1. month volume difference	51.2 (28,3131,1)	154.2 (77,4228,9)	**0.055**
6. month volume difference	64.4 (25,8125,7)	103.3 (36,4129,6)	0.714
12. month volume difference	57.3 (22,7123,2)	197.6 (108,6228,9)	0.104
18. month volume difference	52.1 (19,4130,0)	155.1 (117,3305,9)	**0.044**
24. month volume difference	66.3 (27,8112,4)	89.0 (71,1223,7)	0.217

To summarize, the LE incidence rate of 8.8% aligns with prior literature. Although some studies implicate PST and taxanes in LE development, our findings do not support this association. Axillary RT and postoperative seroma were the only modifiable risk factors significantly linked to LE. Dominant arm status and surgeon experience were also explored, though conclusions were limited by sample size. With close and regular follow-up, early diagnosis and a conservative approach, LE can be kept under control. In our very limited series of patients, the stage in terms of LE remained the same during follow-up.

Study Limitations

The study's prospective design and consistent measurement protocol strengthens its findings, though the small number of LE cases and limited statistical power remain limitations.

CONCLUSION

This study aimed to determine to determine whether PST (especially taxane-based neoadjuvant chemotherapy) is an independent risk factor for breast cancer-associated LE and to evaluate the impact of early diagnosis and prevention on quality of life.

Our results did not reveal a statistically significant association between PST or taxane-based chemotherapy and LE. However, postoperative seroma and axillary RT were significantly associated with the development of LE.

We conclude that early LE may be related to surgical factors and seroma, while later LE is likely related to RT. Emphasis should be placed on longer follow-up of patients and on early diagnosis and preventive strategies.

Ethics

Ethics Committee Approval: After Ethics Committee approval from the University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital (decision no.: 69/21, date: 10 May 2022), 80 patients were prospectively enrolled.

Informed Consent: Informed consent documents, obtained before treatment from each patient are available in patient files.

Acknowledgments

The Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Footnotes

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Author Contributions

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

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ORIGINAL ARTICLE
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Insight into the early postoperative improvement of the functionality of the reconstructed urethra after distal hypospadias repair treated by the Snodgrass technique

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ABSTRACT

Objective: This study aimed to evaluate the functional status of the urethra using uroflowmetry before surgery, as well as three and six months postoperatively in cases of distal hypospadias.

Material and Methods: Thirty-nine consecutive patients who underwent surgery for distal hypospadias (hypospadias group) between 2016 and 2019 were prospectively included as part of this study. The control group consisted of 40 patients with a normal urethra who underwent surgery due to conditions other than hypospadias (phimosis, undescended testis, hernia). Uroflowmetry was performed preoperatively in these patients. Postoperative uroflowmetry was performed at three and six months following hypospadias surgery. Uroflowmetric results [maximum flow rate (Q_{max}), average flow rate (Q_{ave}), voided volume, void duration, flow start time, time to maximum urine flow rate, post-void residual urine, flow curve] were compared between the groups.

Results: The mean age for the patients with distal hypospadias was 35.9±29.6 months and 40.8±26.1 months for the control group. Pre- and postoperative Qmax values (three and six months after surgery) were 6.9 mL/s (0.1-15), 6.4 (0.2-14), and 7.5 (2.5-15). Q_{ave} values were preoperatively 4.0 (0.1-12.1), 3.8 (0.3-8.1), and 4.7 (1.0-11.1) mL/s three and six months after surgery, respectively. Bell-type flow was the most frequent uroflow flow curve in the preoperative hypospadias and control groups (95% and 66.6%, respectively). Postoperatively, bell-type flow remained the most common pattern, while a significant reduction in plateau-type flow was observed. Four boys (10.3%) had symptoms of obstruction.

Conclusion: Surgery improved urination dynamics and partial urethral obstruction of hypospadias cases that were present from the baseline. The urinary flow rates improve over time as the reconstructed neourethra regains functionality six months after the tubularized incised plate procedure.

Keywords: Distal hypospadias repair, uroflowmetry, urethral obstruction, functional status

INTRODUCTION

Hypospadias are common genital birth anomalies, affecting about 1/300 boys, and the incidence may increase (1). Due to the great cosmetic and functional outcomes, tubularized incised plate (TIP) urethroplasty has gained popularity and been used extensively in distal hypopadias since Snodgrass first described it in 1994 (2). To differing degrees, complications such as fistulae and obstruction of the neourethra have been documented (2). Snodgrass stressed that in order to prevent fistulae from forming, the neourethra must be covered with well-vascularized tissue. Additionally, in order to lower the risk of meatal stenosis, the urethral plate should not be closed too far distally (3). Establishing a consistent and sufficient caliber urethra up to the meatus is essential for the functional success of hypopadias repair. Uroflowmetry, voiding cystourethrography, and direct observation of the urinary stream are the available techniques to assess the reconstructed urethra (3).

Uroflowmetry has gained importance in the postoperative follow-up of hypospadias surgery (4-7) due to its non-invasiveness, inexpensiveness, and more objective assessment than direct observation.

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Although the cosmetic effect is satisfactory after TIP urethroplasty, there are still controversies regarding the evaluation of the functional state of the neourethra.

Numerous studies have used uroflowmetry to investigate TIP functional outcomes using various nomograms and definitions of obstruction (3,4,8). Because of the increased flow rates and spontaneous normalization of the curves observed in the first year following surgery, the study by Holmdahl et al. (6) found that early uroflowmetry appears to be unnecessary. Even before surgery, Wolffenbuttel et al. (9) demonstrated that young boys with hypopadias were more likely to have an intermittent flow pattern and lower flow rates than boys in good health of the same age. While many boys with a maximum flow rate (Q_{max}), in the low, normal, or obstructive range did not report obstructive symptoms, Andersson et al. (10) observed spontaneous improvement seven years following TIP repair.

Primary goal of the follow-up is early detection of obstruction, with it being before or after hypospadias repair.

This study aimed to determine chronological changes in uroflowmetry before and after distal hypospadias repair using the Snodgrass technique and determine the earliest lower time limit for establishing neourethra functionality after TIP urethroplasty.

MATERIAL and METHODS

Forty-six consecutive patients who underwent surgery for distal hypospadias (hypospadias group) at Clinical Center University of Sarajevo, Bosnia and Herzegovina, between 2016 and 2019 were assessed for eligibility. The inclusion criteria were as follows: Patients with distal hypospadias, patients who underwent uroflowmetry investigation preoperatively, three and six months after surgery, and patients whose parents signed informed consent to participate in the study.

Patients with proximal hypospadias, megameatus intact prepuce variant, and those with a previously failed repair were excluded from the study (one boy with urethral fistula who needed reoperation was switched off, four patients refused to participate, and two patients could not be contacted in the study). The study also excluded patients with any associated neurological or urological abnormality related to the bladder, which could potentially affect flow patterns. After excluding the patients who did not meet the inclusion criteria, 39 were included in the current study. All patients received preoperative local androgen therapy (2.5% dihydrotestosterone, or DHT). Androgen therapy was applied before preoperative uroflow. The follow-up rate was 84.8%. The surgical technique was standard, and the choice of technique was driven by the physician's preference. Local dartos flaps were used to cover the urethroplasty in multiple layers. Uroflowmetry was done before surgery, three months after surgery, and six months after surgery. Within five minutes of voiding, residual urine was measured using ultrasonography.

Urological ultrasound was performed to get specific information on pre- and post-void residual volume, bladder characteristics, upper tract status and associated malformations. Uroflowmetry was performed in the outpatient office using a rotating disk sensor. The groups were compared for uroflowmetric values: Q_{max}, average flow rate (Q_{ave}), voided volume (VV), void duration, flow start time, time to maximum urine flow rate, and flow curve. After urination, the post-void residual urine amount was examined with ultrasonography. Compared with preoperative values, postoperative dilation was done only in patients with decreased urinary flow. The flow curve classification proposed by the International Child Continence Society was used to evaluate uroflowmetry results (11).

The Q_{max} and VV results were expressed as standard deviation (SD) and interpreted according to a Siroky nomogram. Q_{max} and VV were considered normal if they were >-1 SD and obstructed if they were <-2 SD (12).

Statement of Ethics

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: 0302-53945/17; date of approval: 21 November 2017). Informed consent was obtained from the parents of all patients or their guardians.

Statistical Analysis

Mean and SD with range were used to present numerical variables. Absolute numbers and percentages were used to present categorical variables. The Shapiro-Wilk test was used to test the normality of the distribution of quantitative variables. The quantitative variables compared across the follow-up using Wilcoxon's, Shapiro-Wilk, and Mann-Whitney U tests. All statistical assays were performed using the Statistical Package for the Social Sciences (SPSS) IBM Version 22.0. Statistical significance was accepted at the $p<0.05$ level.

RESULTS

The average age at the first uroflowmetry of the patients in the hypospadias group was 35.9±29.6 months and 40.8±26.1 months for the control group (p=0.43).

Uroflowmetry was performed preoperatively, three and six months postoperatively (39 boys) (Table 1). In the 39 boys with distal hypospadias at preoperative baseline, the mean max flow rate was 6.9 mL/s (range 0-15, SD 3.3), Q_{ave} 4.0 mL/s (range 0.1-12.1, SD 2.9), VV of 83.8 mL (range 10-449, SD 78.2). 22.5% of patients had Q_{max} below the -2 SD. Three months post-surgery,

Table 1. Uroflowmetry data in patients with hypospadias (preoperatively, three and six months after surgery) and controls in the study

Variable	C: Control (n=40)	H_0: Hypospadias preoperatively (n=39)	H_3: Hypospadias 3 months after surgery (n=39)	H_6: Hypospadias 6 months after surgery (n=39)	p-value C vs. H_0	p-value C vs. H_6	p-value H_0 vs. H_3	p-value H_0 vs. H_6	p-value H_3 vs. H_6
VV (mL) Mean, range (SD)	108, 16-337 (67.8)	83.8, 10-449 (78.2)	112.7, 14-297 (78.1)	100.6, 14-300 (61.9)	**0.02**	0.63	**0.02**	**0.02**	0.48
Tq (s) Mean, range (SD)	24.1, 4-72 (17.8)	52.5, 4-120 (32.7)	54.3, 3-136 (35.1)	40.1, 2-120 (32.2)	**0.000**	0.06	0.45	0.18	**0.03**
T100 (s) Mean, range (SD)	13.8, 4-38 (7.9)	25.2, 5-128 (21.4)	35.5, 5-180 (36.9)	25.9, 7-120 (21.9)	**0.000**	**0.000**	**0.03**	0.93	**0.05**
Q_{max} (mL/s) Mean, range (SD)	10.1, 4.5-17.5 (3.4)	6.9, 0.1-15 (3.3)	6.4, 0.2-14 (3.3)	7.5, 2.5-15.5 (3.4)	**0.000**	**0.002**	0.14	0.56	**0.02**
Tq_{max} (s) Mean, range (SD)	6.8, 1-17 (3.9)	11.7, 2-128 (21.2)	22.2, 1-180 (36.8)	13.3, 1-138 (22.6)	0.64	0.16	0.12	0.19	**0.04**
Q_{ave} (mL/s) Mean, range (SD)	8.0, 1.7-13.5 (2.9)	4.0, 0.1-12.1 (2.9)	3.8, 0.3-8.1 (1.9)	4.7, 1-11.1 (2.5)	**0.000**	**0.000**	0.61	0.17	**0.04**
PVR (mL) Mean, range (SD)	0.50, 0-10 (2.2)	4.7, 0-75 (13.5)	10.7, 0-130 (24.0)	2.6, 0-34 (7.6)	0.06	0.12	0.08	0.33	**0.003**

Only significant p-values are bolded. PVR: Post-void residual urine, Q_{ave}: Average flow rate, Q_{max}: Maximum flow rate, SD: Standard deviation, T100: Void duration, Tq: Flow start time, Tq_{max}: Time to maximum urine flow rate, VV: Voided volume.

the average Q_{max} was 6.4 mL/s (range 0.2-14, SD 3.3), Q_{ave} 3.8 mL/s (range 0.3-8.1, SD 1.9), with a mean VV of 112.7 mL (range 14-297, SD 78.1). Nineteen (49%) had Q_{max} below the -2 SD. Six months post-surgery, the average Q_{max} was 7.5 mL/s (range 2.5-15.5, SD 3.4), Q_{ave} 4.7 mL/s (range 1-11.1, SD 2.5), with a mean VV of 100.6 mL (range 14-300, SD 61.9). Foqur (10.3%) had Q_{max} below the -2 SD.

The Q_{max} values differed significantly between the hypospadias and the control groups preoperatively and six months following surgery, respectively (p<0.001 and 0.002). However, the Q_{max} values measurement results were not significant within the hypospadias group three and six months after surgery, respectively (p=0.14 and 0.56)

There was a significant difference in the preoperative Q_{ave} values between the hypospadias and control groups (p<0.001), as well as between the groups six months after surgery (p<0.001). No significant difference in the Q_{ave} values was observed within the hypospadias group in two tested periods (p=0.61, 0.17, respectively).

In 39 patients with distal hypospadias, there was a significant increase in maximum flow (p=0.02) and Q_{ave} (p=0.04) in patients with calibrated urethra 15 (38.5%); moreover, in 11 patients (28.2%) with plateau-shaped urination, the curves decreased six months postoperatively after urethral dilatation. The increased flow rate was not as evident in four patients with distal hypospadias as in other cases; they retained a plateau-shaped curve and were treated with dilatation.

The flow curve shapes (Figure 1) were noted in most cases and described as plateau-shaped in 15 (38.5%), bell-shaped in 21 cases (53.8%), and three cases (7.7%) with interrupted flow curves at the three-month follow-up. However, four plateau (10.3%) and 35 (89.7%) bell-shaped curves were noticed at the six months follow-up. No statistically significant difference was present in the appearance of the curve within the hypospadias group at the baseline and three months after surgery (p=1.0). However, we noticed a significant difference in the appearance of the curve within the hypospadias group at the baseline and six months after surgery (p=0.002). Similarly, a significant difference in the appearance of the curve between hypospadias and control groups was observed at the baseline (p=0.001). However, the difference was insignificant at the six months follow-up (p=0.41).

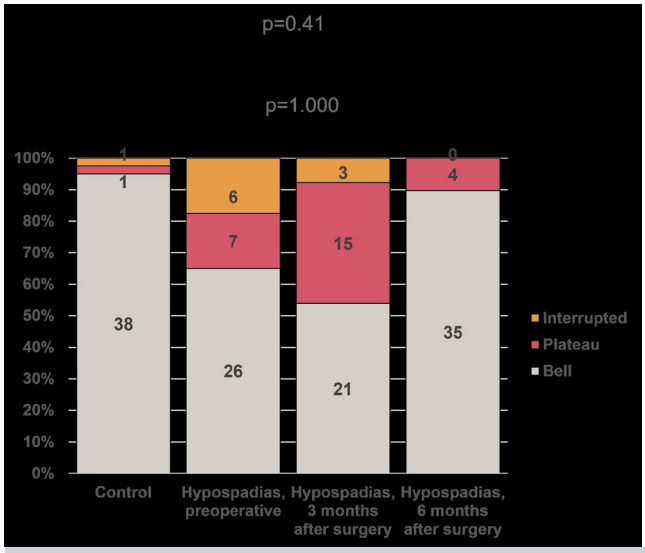

Figure 1. The flow curve shapes.

DISCUSSION

TIP urethroplasty often obstructs flow at uroflowmetry after the surgery. However, despite that, it is still the most used technique for the surgical repair of primary hypospadias (9).

The clinical information on chronological changes in uroflowmetry before and after distal hypospadias repair from Bosnia and Herzegovina is very limited, and the present analysis is the first systematic study with a follow-up.

Uroflowmetry has become an important part of mid- and long-term follow-up following hypopadias surgery because it can identify urethral strictures even when they are asymptomatic (1,13-16). While Lorenzo and Snodgrass (13) reported flow rates in the lower part of the normal range 0.5-7 years after surgery, Marte et al. (4) reported that one-third of the boys had abnormal flow curves 1.8 years after TIP repair. The obstructed pattern has been suggested to be caused by a stiff neourethra with low compliance. Six months following surgery, our study showed spontaneous normalization of the curves and increased flow rates, which lends credence to this theory.

To avoid urethral fistulas, many surgeons advise routine urethral calibration and dilatation following TIP repair (16,17). Less than half of the patients (15 out of 39 boys) who had obstructive flow three months after surgery in this prospective study had a true obstructed urethra at calibration. Even before surgery, Wolffenbuttel et al. (9) found that young boys with hypopadias had lower flow rates and an intermittent flow pattern compared to healthy boys of the same age. These authors hypothesized that the obstructed flow we even observe after surgery may be caused by the hypospadiac urethra's already reduced compliant state, which may be caused by a partially absent or structurally abnormal surrounding spongiosal body (18,19).

Over the course of these six months, we found that one-third of the boys with extremely low flows experienced spontaneous improvements in their Q_{max} to levels within the normal range. Consistent with other reports, obstruction was strongly associated with a plateau flow curve and a low Q_{max} (20). The bell-type flow was more prevalent in our study, despite the fact that studies reporting uroflowmetry results following hypopadias surgery are more likely to have a plateau-type curve (21,22). Following surgery, the most typical uroflow curve was bell-type flow, but plateau-type flow significantly decreased. This suggests that hypopadias surgery increases urine flow and decreases urine flow duration.

A comparison of the uroflowmetry results of the hypospadias cases with the control group showed lower flow rates with residual urine in the bladder before the surgery. When they were compared again postoperatively, there was a significant difference in the flow rate and residual urine amount between the postoperative hypospadias and control groups. However, there was no difference between the postoperative and preoperative evaluation results. These results indicate that urinary dynamics in patients with hypospadias and partial urethral obstruction were already impaired preoperatively but improved following surgery. However, our study has shown that a preoperative flow assessment is equally essential. 33.4% incidence of preoperative poor flow rates is probably inherent to the anomaly.

Comparing preoperative and postoperative voiding dynamics is comparatively rare, despite the fact that similar studies have been done in the literature (7,9,22,25). Interestingly, compared to earlier studies, the patient population in this one is younger. Using an ultrasound probe to measure flow, Olsen et al. (7) examined 21 infants with hypopadias and contrasted them with an age-matched control group. They came to the conclusion that, in contrast to none in the control group, 31% of infants with hypopadias void with low Q_{max} and plateau-shaped curves. Wolffenbuttel et al. (9), using the same technique on 42 patients, found that 41% of children had a plateau pattern following surgery, compared to 6% before.

In our study as well 77.5% patients (29/40) with preoperative non-obstructive flow rates had post-operative Q_{max} >-1 SD while 22.5% (9/40) with preoperative obstructive flow rates remained obstructed (Q_{max} <-2 SD) even after the repair. Tuygun et al. (25) found that 25% of older children had low preoperative flow rates that normalized after TIP repair using preoperative and post-operative uroflowmetry.

Only a few studies have been made on this topic, but they all show varying rates of poor preoperative flow characteristics (7,9,23-25). All patients in our study with poor postoperative flows but good preoperative flows had clinical obstruction requiring meatal dilatation. Therefore, we suggest that such

a finding alert the surgeon to a possible correctible cause. On the other hand, obstructive flows in the postoperative follow-up were of little significance if the preoperative flows were also poor, indicating an inherent abnormality.

We also found a significant improvement in the Q_{max} from three to 6 months postoperatively. This suggests that over time, after hypospadias surgery, the urethra improves, probably because of the resolution of edema and collagen remodeling. Several other studies have expressed a similar viewpoint (6,8,24-35).

Study Limitations

The present study had several limitations. First, the follow-up period was short so urethral strictures after six months were not recorded and analyzed; second, the number of included patients was small; and third, the study was conducted in a single institution, limiting its generalizability. The strength of this study is that it is one of the few series reporting the results of uroflowmetry performed pre- and postoperatively in patients undergoing distal hypospadias repairs.

CONCLUSION

The present study is the first to evaluate urethral function before and after the surgical treatment of distal forms of hypospadias in Bosnia and Herzegovina. Early uroflowmetry three months after the surgery for distal forms of hypospadias is an inadequate diagnostic method in assessing urethral function, except in the presence of clinical suspicion of urethral obstruction. In comparison, uroflowmetry six months after surgery is an adequate diagnostic method in assessing urethral function. The increase in the Q_{max} and Q_{ave} parameters of the uroflowmetry and the normalization of the curves during the monitoring period indicate that the urethra becomes more elastic and wider over time.

The functional outcome of the neourethra, as assessed by uroflowmetry six months postoperatively, confirmed that the reconstructed neourethra achieved functional normalization following the TIP procedure. We advocate using uroflowmetry for routine postoperative follow-up after hypospadias repair as a simple, non-invasive, objective test.

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: 0302-53945/17; date of approval: 21 November 2017).

Informed Consent: Informed consent was obtained from the parents of all patients or their guardians.

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Footnotes

Author Contributions

Concept - A.J., Z.Z., S.V.; Design - A.J., U.G.; Supervision - S.V., Z.Z.; Fundings - A.J., A.M., U.G.; Data Collection or Processing - A.J., U.G., A.M.; Analysis or Interpretation - A.J., Z.Z., B.K.; Literature Search - A.J., B.K.; Writing - A.J., Z.Z., B.K., S.V.

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ORIGINAL ARTICLE
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Preoperative CONUT score predicts postoperative complications in stage I-III gastric cancer patients undergoing curative gastric resections

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ABSTRACT

Objective: The controlling nutritional status (CONUT) score, calculated using serum albumin, total cholesterol, and lymphocyte count, is an effective predictor of post-operative complications (PC) following oncologic resections in gastrointestinal system cancers. This retrospective study aimed to investigate the impact of pre-operative CONUT scores on overall post-operative complications (OPC) in patients with stage I-III gastric cancer (GC) who underwent gastrectomy.

Material and Methods: Patients who underwent curative gastric resection for GC between January 2013 and December 2024 were retrospectively analyzed. Patients with a preoperative CONUT score of 0-1 were classified as the normal CONUT group. In contrast, those with a score of 2 or higher were classified as the high CONUT group. Preoperative, intraoperative, and postoperative data were reviewed. Risk factors for the development of OPC were evaluated using univariate and multivariate analyses.

Results: In the high CONUT group, American Society of Anesthesiologists scores, neutrophil/lymphocyte ratio, lymphatic invasion rates, TNM stages, duration of intensive care unit stay, OPC rates, and comprehensive complication index values were significantly higher ($p<0.05$). Multivariate analysis revealed that advanced TNM stage [odds ratio (OR): 5.8, 95% confidence interval (CI): 1.4-24.6, p=0.016] and a high CONUT score (OR: 4.1, 95% CI: 1.3-13.0, p=0.014) were independent risk factors for the development of PC.

Conclusion: Pre-operative CONUT score may serve as a predictor of OPC following curative GC resections.

Keywords: Gastric cancer, gastrectomy, gastrointestinal surgery

INTRODUCTION

Malnutrition has gained increasing global recognition over the years. According to the United Nations' 2030 Agenda for Sustainable Development, malnutrition is one of the main topics (1). In parallel, the volume and frequency of scientific research on malnutrition in the medical literature have also grown, enabling the generation of more reliable data. Although the specific prevalence of malnutrition may vary by country, its significance as a public health issue remains consistent across different settings. In high-income countries, the prevalence of malnutrition among hospitalized patients has been reported to be as high as 30% (2), whereas in low- and middle-income countries, this rate may reach up to 80% (3,4).

Malnutrition negatively affects both clinical outcomes and healthcare economics. Medically, it is associated with lower quality of life, increased morbidity, lower immune function, delayed wound healing, decreased muscle strength, and ultimately, increased mortality. From an economic standpoint, these complications often result in prolonged hospital stays, increased intensive care unit (ICU) admissions and duration, and higher overall healthcare costs (5,6). Given these consequences, it is evident that malnutrition, a preventable condition, may lead to substantial clinical and financial burdens if left unrecognized and adequately unmanaged. Therefore, raising awareness, improving knowledge, and clinical experience, and integrating standardized protocols for the identification and management of malnutrition into daily clinical practice are essential steps. In this regard, a multicenter survey involving 25 European countries revealed that only 52% of participating hospitals had routine

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protocols for malnutrition screening, underscoring the need for further improvements (7).

The prevalence of malnutrition in surgical patients can reach up to 20% (8). Among those undergoing surgery for gastrointestinal (GI) malignancies, malnutrition is particularly prevalent. Cancer cachexia and disease-related restrictions in oral intake often lead to malnutrition even at the time of diagnosis. Furthermore, in the post-operative period, malnutrition may adversely affect wound healing and increase both morbidity and mortality (9).

Various functional, biochemical, and radiological methods are currently used to identify and assess malnutrition. However, no universally accepted "gold standard" method has yet been established, due to limitations such as high cost, complexity, time requirements, or lack of validation of these tools. As a result, different centers continue to employ a range of screening and assessment methods (10). Practical tools that are cost-effective and easy to use are understandably preferred. One such tool is the controlling nutritional status (CONUT) score, which is derived from routinely available laboratory parameters (11). The impact of the pre-operative CONUT score on both short- and long-term outcomes following surgical resection of upper GI and colorectal cancers has been reported in various studies (12-15).

This single-center retrospective study aimed to investigate the impact of pre-operative CONUT scores on early post-operative outcomes in patients who underwent curative gastric resections for stage I-III adenocarcinoma of the stomach.

MATERIAL and METHODS

All patients who underwent gastric resections in Başkent University İstanbul Hospital between January 2013 and December 2024 were retrospectively analyzed. Only patients who underwent gastrectomy for histologically confirmed gastric adenocarcinoma (stage I-III) were included in the study. Patients who underwent gastric resections for benign conditions such as bleeding, perforation, or trauma; patients with tumors other than adenocarcinoma (e.g., neuroendocrine tumors, GI stromal tumors); patients who received neoadjuvant chemotherapy; and patients who underwent palliative resections for stage IV disease were excluded.

In addition to age, sex, and body mass index (BMI), American Society of Anesthesiologists (ASA) scores and the presence of cardiovascular disease, hyperlipidemia, and diabetes mellitus data were retrospectively recorded. Pre-operative hemoglobin, serum albumin, total protein, creatinine, and total cholesterol levels, white blood cell counts, neutrophil counts, platelet counts, lymphocyte counts, neutrophil to lymphocyte ratios, and CONUT scores were also recorded (Table 1) (11).

Histopathological findings, including T stage and N stage, pathological TNM stages, differentiation grade of tumors, presence of signet-ring cells, presence of lymphatic, perineural, and vascular invasions, the largest diameter of tumors, and total harvested lymph node counts were also evaluated. Malignant lymph node ratios were calculated as a percentage by dividing the number of malignant lymph node counts by the number of total harvested lymph node counts.

Duration of operation and post-operative outcomes: Requirements for ICU care, duration of ICU stay, length of hospital stay, and post-operative complications were recorded. Reoperation rates were noted. Post-operative complications were classified according to the well-known Clavien-Dindo scoring system (16). Comprehensive complication index (CCI) scores: (17) were used to evaluate the severity of the complications. The adjuvant chemotherapy administrations were evaluated in terms of post-operative outcomes.

The patients were classified according to their CONUT scores. The patients with a 0-1 CONUT score were evaluated in the normal CONUT group, and patients with a CONUT score ≥2 were evaluated in the High CONUT group. Pre-operative variables and 30-day early post-operative outcomes were compared.

This study was approved by the Başkent University Institutional Review Board (date: 24.07.2025, decision no: KA25/283).

Prior to inclusion in this retrospective study, informed consent was obtained either from the patients themselves or their first-degree relatives. All participants received comprehensive explanations about the surgical procedure, including potential risks, possible complications, anticipated outcomes, and estimated mortality rates. Additionally, they were informed that their anonymized clinical data might be used for scientific purposes. Written consent confirming their understanding and approval was collected before the operations took place.

Statistical Analysis

Statistical analyses were conducted using SPSS software (version 25.0; SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation when they followed a normal distribution, based on Kolmogorov-Smirnov or Shapiro-Wilk tests (with Shapiro-Wilk applied for $n<30$). In cases where normality was not observed, data were expressed as medians. Group comparisons for continuous variables were performed using either the Student's t-test or the Mann-Whitney U test, depending on whether parametric or non-parametric criteria were met. Categorical data were compared using the chi-square test or Fisher's exact test, as appropriate. To adjust for possible confounding variables and to identify factors independently associated with postoperative complications, multivariate logistic regression analysis was employed. Variables with a p-value less than 0.10 in the univariate analysis were entered into the multivariate model. Statistical significance was defined as a p-value below 0.05.

RESULTS

General Outcomes

During the study period, a total of 167 consecutive gastric resections were performed at our surgical clinic (Figure 1). A total of 27 patients were excluded because they underwent benign procedures. Twenty-one patients with non-adenocarcinoma tumors were excluded. Nineteen patients who underwent palliative procedures, seventeen patients who underwent neoadjuvant chemotherapy, and fifteen patients with missing data were also excluded. Finally, 68 patients who underwent gastrectomy for stage I-III gastric adenocarcinoma were analyzed (Figure 2). All operations were carried out via an open surgical approach by an experienced surgical team with more than a decade of academic and clinical expertise.

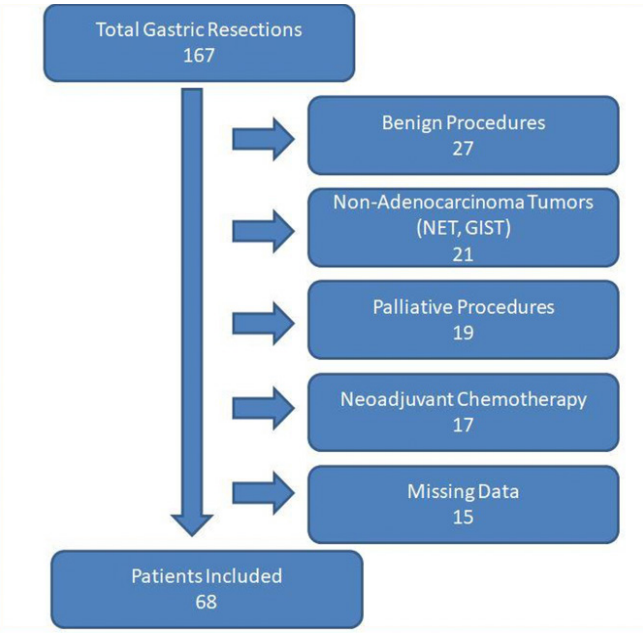

Figure 1. Flowchart diagram depicting the selection of the participants.

NET: Neuroendocrine tumors, GIST: Gastrointestinal stromal tumors

The mean age of the study population was 66.1 (±13.3). Forty patients (58.8%) were male, and the mean BMI was 24.9 (±4.9). The number of patients in both groups was the same. The pre-operative variables and distribution of the patients are shown in Table 2. A statistically significant difference was observed in ASA score distribution, as the high CONUT group included a greater number of ASA III patients (p=0.022). Lymphocyte count, serum albumin, and total cholesterol levels —the three components of the CONUT score— were significantly lower in the high CONUT group. In addition, the neutrophil-to-lymphocyte ratio also differed significantly between the groups (Table 2).

Histopathological investigations revealed that the high CONUT group had more advanced TNM-staged patients (p=0.044), and the presence of the lymphatic invasion was significantly higher in the high CONUT group (p=0.009) (Table 3).

The early post-operative outcomes are shown in Table 4. Duration of ICU stay, the presence of overall post-operative

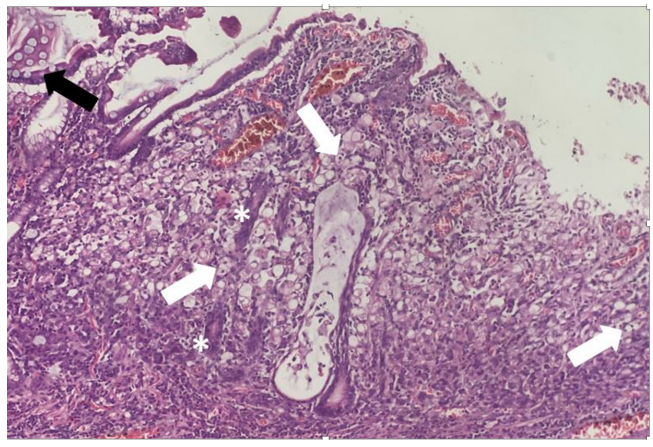

Figure 2. Histopathological examination of a 77-year-old female patient. Signet-ring cells with peripherally located hyperchromatic nuclei and intracellular mucin (white arrows). Adjacent intestinal metaplasia (black arrow) and rare normal gastric tubular structures (asterisk). H&E stain, ×100.

H&E: Hematoxylin & eosin

Table 1. CONUT scoring system

Variables	Undernutrition status			
	Normal	Light	Moderate	Severe
Albumin (g/dL)	≥3.5	3.0-3.49	2.5-2.9	<2.5
Points	0	2	4	6
Total lymphocyte count (cell/mm³)	>1600	1200-1599	800-1199	<800
Points	0	1	2	3
Total cholesterol (mg/dL)	>180	140-180	100-139	<100
Points	0	1	2	3
Total CONUT score	0-1	2-4	5-8	9-12

CONUT: Controlling nutritional status.

Table 2. Preoperative data of the patients

Parameter	Total (n=68)	Normal CONUT (0-1, n=34)	High CONUT (≥2, n=34)	p-value
Age (years, mean, SD)	66.1 (±13.3)	65.3 (±12.9)	66.8 (±13.9)	0.666
Sex (n, %) Male Female	 40 (58.8%) 28 (41.2%)	 18 (52.9%) 16 (47.1%)	 22 (64.7%) 12 (35.3%)	0.460
Body mass index (kg/m^2)	24.9 (±4.9)	24.8 (±4.5)	25.2 (±5.5)	0.911
ASA score (n, %) I II III IV	 6 (9%) 24 (35.8%) 35 (52.2%) 2 (3%)	 4 (12.1%) 17 (51.8%) 11 (33.3%) 1 (3%)	 2 (5.9%) 7 (20.6%) 24 (70.6%) 1 (3%)	0.022
Diabetes mellitus (n, %)	28 (41.2%)	12 (35.3%)	16 (47.1%)	0.460
Hyperlipidemia (n, %)	22 (32.4%)	14 (41.2%)	8 (23.5%)	0.194
Cardiovascular disease (n, %)	34 (50%)	15 (44.1%)	19 (55.9%)	0.467
Hemoglobin (g/dL)	11.7 (±2.3)	12.2 (±2.4)	11.1 (±2.2)	0.052
Platelet (cell/mm^3)	264 (71.6-573)	273 (71.6-573)	238 (77-573)	0.844
White blood cell count (cell/mm^3)	7065 (2560-14100)	7545 (2560-12000)	6775 (3100-14100)	0.462
Neutrophil count (cell/mm^3)	4300 (1700-9800)	4115 (200-8080)	4405 (1700-9800)	0.243
Lymphocyte count (cell/mm^3)	1770 (338-4000)	2005 (1246-4000)	1470 (338-400)	0.008
Neutrophil/lymphocyte ratio	2.31 (0.87-2307)	1.96 (1-2307)	3.21 (0.87-1603)	0.004
Creatinine (mg/dL)	0.83 (0.6-3)	0.8 (0.6-3)	0.9 (0.6-1.7)	0.584
Total protein (g/dL)	6.7 (±0.7)	6.9 (±0.6)	6.6 (±0.7)	0.055
Albumin (g/dL)	3.8 (±0.6)	4.1 (±0.4)	3.4 (±0.6)	0.001
Total cholesterol (mg/dL)	177.9 (±31.7)	189.9 (±27.3)	165.9 (±31.7)	0.001

SD: Standard deviation, CONUT: Controlling nutritional status, ASA: American Society of Anesthesiologists.

complications, and the CCI scores were statistically higher in the High CONUT group ($p<0.05$).

Postoperative Complications

There were 29 patients (42.7%) who developed post-operative overall complications. Nine of these patients were in the normal CONUT group and 20 were in the high CONUT group; all were classified as Clavien-Dindo grade I-V complications.

The univariate analysis revealed that the ASA score, TNM stage, presence of perineural invasion, the CONUT score, and malignant lymph node ratio were statistically higher in the patients who developed overall post-operative complications (Table 5). The multivariate logistic regression analysis revealed that higher TNM stage and High CONUT score were independent risk factors for developing overall post-operative complications (Figure 3, Table 5).

Normal CONUT Group

Post-operative complications occurred in 9 of the 34 patients in the normal CONUT group. In a 72-year-old male patient, evisceration developed on post-operative day (POD) 7, necessitating relaparotomy. The second surgery was uneventful, and the patient was discharged without complications on POD 9. An 81-year-old female patient was discharged on POD 8 but presented to the emergency department on POD 17 with symptoms of upper GI bleeding. Following medical stabilization, upper GI endoscopy revealed bleeding from the gastrojejunostomy anastomosis. Endoscopic clip placement was performed, and the patient was discharged in stable condition three days later. During this second hospitalization, two packages of red blood cells (RBC) and two packages of fresh frozen plasma were transfused.

Two female patients aged 42 and 77 developed respiratory distress, and pleural effusion was detected on POD 5. Both patients underwent percutaneous pleural catheter insertion, which led to clinical improvement. The catheters were removed after 48 hours, and both patients were discharged, without complications, 72 hours later. A 37-year-old male patient developed a superficial surgical site infection requiring wound care and antibiotic therapy. He also received one unit of RBCs and was discharged uneventfully on POD 11. A 52-year-old female patient developed urinary retention; requiring urinary re-catheterization, she also required one unit of RBC transfusion. A 76-year-old female patient experienced delayed gastric emptying, necessitating parenteral nutritional support and

prolonged hospitalization. The patient was discharged on POD 15 in stable condition. A 51-year-old male patient required only two units of RBC transfusion, without any additional complications.

Finally, a 74-year-old male patient developed atrial fibrillation followed by cardiopulmonary failure and subsequent multiorgan failure. Despite 15 days of intensive care support, the patient did not survive.

High CONUT Group

Post-operative complications occurred in 20 patients. A 67-year-old female patient developed respiratory distress and oxygen desaturation, requiring re-intubation. Following ICU support

Table 3. Histopathological evaluations of the patients

Parameter	Total (n=68)	Normal CONUT (0-1, n=34)	High CONUT (≥2, n=34)	p-value
pT stage (n, %)				
I	12 (17.6%)	7 (20.6%)	5 (14.7%)	0.085
II	9 (13.2%)	5 (14.7%)	4 (11.8%)	
III	12 (30.9%)	14 (41.2%)	7 (20.6%)	
IV	26 (38.2%)	28 (23.5%)	18 (52.9%)	
pN stage (n, %)				
0	26 (38.2%)	15 (44.1%)	11 (32.4%)	0.254
I	14 (20.6%)	9 (26.5%)	5 (14.7%)	
II	9 (13.2%)	3 (8.7%)	6 (17.6%)	
III	19 (27.9%)	7 (20.6%)	12 (35.3%)	
TNM stage (n, %)				
I	18 (26.5%)	10 (29.4%)	8 (23.5%)	0.044
II	8 (11.8%)	7 (20.6%)	1 (2.9%)	
III	42 (61.8%)	17 (50%)	25 (73.5%)	
Differentiation grade (n, %)				
Well	10 (14.7%)	8 (23.5%)	2 (5.9%)	0.114
Mild	10 (14.7%)	5 (14.7%)	5 (14.7%)	
Poor	48 (70.6%)	21 (61.8%)	27 (79.4%)	
Signet cell (n, %)	26 (38.2%)	12 (35.3%)	14 (41.2%)	0.803
Lymphatic invasion (n, %)	52 (76.5%)	21 (61.8%)	31 (91.2%)	0.009
Perineural invasion (n, %)	39 (57.4%)	17 (50%)	22 (64.7%)	0.327
Vascular invasion (n, %)	13 (19.1%)	5 (14.7%)	8 (23.5%)	0.539
Tumor diameter (mm)	47 (15-120)	45 (15-120)	50 (15-100)	0.853
Total harvested lymph node	23 (8-56)	22 (8-47)	24 (8-56)	0.602
Malignant lymph node	2 (0-46)	1 (0-30)	6 (0-46)	0.066
MLNR	11 (0-100)	5 (0-91)	24 (0-100)	0.084

MLNR: Malignant lymph node ratio, CONUT: Controlling nutritional status.

Table 4. Postoperative outcomes

Parameter	Total (n=68)	Normal CONUT (0-1, n=34)	High CONUT (≥2, n=34)	p-value
Operation time (min)	197 (50-600)	195 (50-360)	202 (75-600)	0.348
Length of hospital stay (days)	8 (4-24)	7 (4-23)	8 (5-24)	0.078
Intensive care unit requirement (n, %)	38 (55.9%)	15 (44.1%)	23 (67.6%)	0.087
Intensive care duration (days)	1 (0-28)	0 (0-28)	1 (1-7)	0.026
Postoperative complication (n, %)	29 (42.6%)	9 (26.5%)	20 (58.8%)	0.014
Comprehensive complication index (%)	0 (0-100)	0 (0-100)	20.9 (0-100)	0.008
Reoperation (n, %)	3 (4.4%)	1 (2.9%)	2 (5.9%)	0.746
Mortality (n, %)	5 (7.4%)	1 (2.9%)	4 (11.8%)	0.356
Adjuvant chemotherapy (n, %)	42 (61.8%)	20 (58.8%)	22 (64.7%)	0.803

Min: Minutes, CONUT: Controlling nutritional status.

Table 5. Factors related to overall complications

Variable	Univariate analysis			Multivariate analysis		
	Overall complication		p-value	Odds ratio	(95% CI)	p-value
	Yes (n=29, 42.7%)	No (n=39, 57.3%)				
Age (years, mean, SD)	67.4 (±13.7)	65.1 (±13.1)	0.486			
Sex, male (n, %)	19 (65.5%)	21 (53.8%)	0.455			
ASA score (n, %)						
I	2 (6.9%)	4 (10.3%)	0.036			
II	5 (17.2%)	19 (48.7%)				
III	21 (72.4%)	15 (38.5%)				
IV	1 (3.4%)	1 (2.6%)				
TNM stage (n, %)						
I	3 (10.3%)	15 (38.5%)	0.023	Ref.		
II	3 (10.3%)	5 (12.8%)		5.5	(0.7-43.1)	0.102
III	23 (79.3%)	19 (48.7%)		5.8	(1.4-24.6)	0.016
Perineural invasion (n, %)	22 (75.9%)	17 (43.6%)	0.013			
CONUT score (n, %)						
Normal	9 (31%)	25 (64.1%)	0.002	Ref.		
High	20 (69%)	14 (35.9%)		4.2	(1.3-130)	0.014
MLNR	30 (0-100)	5 (0-9)	0.030			

CI: Confidence interval, ASA: American Society of Anesthesiologists, CONUT: Controlling nutritional status, MLNR: Malignant lymph node ratio, SD: Standard deviation.

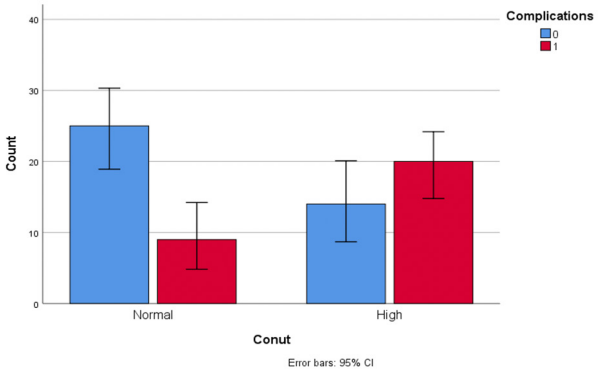

Figure 3. Multivariate logistic regression analysis revealing the relationship between the CONUT score and overall complications.

0: Cases without complications, 1: Cases with complications, CI: Confidence interval, CONUT: Controlling nutritional status

between POD 1 and POD 6, she was discharged without complications on POD 11. An 83-year-old male patient developed fever on POD 4. Imaging revealed an intra-abdominal abscess. As percutaneous drainage was unsuccessful, relaparotomy was performed. The patient was discharged in stable condition on POD 18. A 60-year-old male patient developed acute kidney injury followed by multiorgan failure. After re-intubation and initiation of hemodialysis, on POD 4, he was discharged uneventfully on POD 13.

Four male patients, aged 61, 66, 75, and 77, experienced post-operative respiratory distress due to pleural effusion and required percutaneous drainage. They were discharged uneventfully on POD 11, 15, 11, and 17, respectively. The 77-year-old patient also underwent relaparotomy on POD 6 due to evisceration.

Five patients required RBC transfusions only. Specifically, one unit was administered to a 52-year-old female and a 45-year-old male, two units to a 77-year-old female and an 85-year-old male, and three units to a 79-year-old male.

A 79-year-old male patient required percutaneous cystostomy on POD 5 due to severe urinary retention and was discharged on POD 12. A 75-year-old male patient with no prior history of epilepsy experienced a seizure. Radiological and neurological evaluations revealed no evidence of metastasis, bleeding, or ischemia. The seizure was medically managed, and the patient was discharged uneventfully following adjustment of antiepileptic treatment. A 73-year-old female patient developed a superficial surgical site infection, which was managed successfully with bedside drainage and antibiotic therapy. The patient was discharged on POD 12. A 47-year-old female patient developed an esophagojejunostomy leak requiring endoscopic covered stent placement. Additionally, bilateral pleural effusions necessitated percutaneous catheter insertion. The patient was discharged on POD 24.

In the high CONUT group, four patients died due to post-operative complications. A 55-year-old male patient developed an esophagojejunostomy anastomotic leak, which required endoscopic covered stent placement and bilateral pleural drainage catheter insertion. The patient had underlying interstitial lung disease and developed severe pneumosepsis. Following re-

intubation on POD 11, he eventually died on POD 29 despite intensive supportive care. A 79-year-old male patient died on POD 21 due to septic shock secondary to a retroperitoneal abscess that developed as a result of a duodenal stump leak. A 76-year-old female patient developed an esophagojejunostomy anastomotic leak and underwent endoscopic stent placement. However, she succumbed to septic shock on POD 8. Lastly, a 77-year-old male patient developed severe pneumosepsis, which progressed to multi-organ failure. Despite aggressive management, the patient died on POD 21.

Statistical analysis demonstrated that the mortality rates were statistically similar in the two groups (p>0.05).

DISCUSSION

Multivariate analysis in this single-center retrospective study demonstrated that a pre-operative CONUT score of ≥2 was an independent risk factor for the development of post-operative overall complications in patients undergoing curative gastrectomy for stage I-III gastric adenocarcinoma [odds ratio (OR): 4.2] (Table 5). Another independent risk factor identified was advanced TNM stage (OR: 5.8) (Table 5).

Several recent studies have reported that a high pre-operative CONUT score is a significant risk factor for post-operative complications in patients undergoing gastric resection for gastric cancer (18-21). In a 2021 study by Sun et al. (18) involving 1,479 patients, the overall post-operative complication rate was 29.3%. Multivariate analysis demonstrated that a CONUT score ≥2 was an independent risk factor for post-operative complications (OR: 1.15, 95% CI 1.07-1.24, p<0.001) (18). In subgroup analysis, Sun et al. (18) also showed that a high CONUT score conferred a similar risk in both early and advanced-stage gastric cancer patients. In a 2021 study by Qian et al. (19), which evaluated 309 patients with gastric cancer, the post-operative complication rate was 29.4%. Multivariate analysis identified a CONUT score ≥2.5 as an independent predictor of post-operative complications (OR: 2.43, 95% CI 1.21-4.86, p=0.012). In a large-scale database analysis by Ryo et al. (20), including 3.484 patients, a CONUT score ≥2 was significantly associated with an increased risk of post-operative pulmonary complications. Similarly, in a 2022 study by Xiao et al. (21), which evaluated 106 patients with gastric cancer, a high CONUT score was shown to be an independent risk factor for the development of overall post-operative complications.

Some studies in the literature have focused exclusively on geriatric populations. In a study conducted by Suzuki et al. (22), from Kobe in 2018, which included 211 patients over the age of 75 who underwent gastrectomy for gastric cancer, a high pre-operative CONUT score was identified as an independent risk factor for post-operative infectious complications unrelated to surgery. Furthermore, when overall morbidity rates were analyzed, patients classified in the moderate-to-severe malnutrition group had higher rates of overall morbidity, although the difference approached but did not reach statistical significance (p=0.09). In 2019, a study by Huang et al. (23) from China investigated 357 patients over the age of 65 who underwent gastrectomy for gastric cancer. The authors found that a high CONUT score was an independent risk factor for the development of post-operative complications (OR: 2.69, 95% CI 1.63-4.45, p<0.0001). More recently, Lin et al. (24) published a study in 2023 focusing on patients over the age of 60 who underwent gastrectomy for gastric cancer. This study, which included 203 patients, similarly demonstrated that a high pre-operative CONUT score was an independent predictor of post-operative complications. In these three studies, the reported rates of overall post-operative complications ranged from 31.6% to 39%. Our overall complication rate was 42%.

In the literature, there are three meta-analyses that have investigated the association between pre-operative CONUT scores and postoperative complications following gastrectomy. In the meta-analysis published by Takagi et al. (25) in 2019, which included five studies and a total of 2.482 patients, a high pre-operative CONUT score was found to be significantly associated with an increased risk of overall post-operative complications (OR 1.39, 95% CI 1.12-1.72, p=0.003). Liu et al. (26) in their 2023 publication, presented a comprehensive analysis of 19 studies involving a total of 9,746 patients. A more recent meta-analysis, conducted by Yin et al. (27) in 2023, similarly demonstrated that a high CONUT score was associated with a higher incidence of post-operative complications (OR 1.64, 95% CI 1.31-2.06). Consistent with the previous two meta-analyses, their results showed that a high pre-operative CONUT score was significantly associated with increased post-operative morbidity (OR 1.96, 95% CI 1.5-2.57, p<0.0001). Another notable common finding across all three analyses was the association between higher CONUT scores and more advanced TNM stages. Despite the relatively small sample size in our study, our findings are in line with these recent meta-analyses in terms of both post-operative morbidity and the relationship with advanced disease stage.

Although numerous retrospective studies and meta-analyses have demonstrated an association between high CONUT scores and increased post-operative complications, some studies have reported no such relationship. In a study conducted by Liu et al. (28) in 2018, which included 697 consecutive patients who underwent gastrectomy for stage II and III gastric cancer, complication rates were similar between patients with low and high CONUT scores. Similarly, in a 2021 study by Jin et al. (29), which involved 272 patients who received neoadjuvant chemotherapy followed by gastrectomy, the preoperative CONUT score was not found to be a significant predictor of either overall or severe postoperative complications. These discrepancies may be attributed to differences in patient

demographics, country-specific healthcare settings, institutional management protocols, or the threshold values used to define high CONUT scores across studies.

Study Limitations

The present study has several considerable limitations. The retrospective analysis and the single-center setting represent major constraints that may affect the generalizability of the outcomes. Additionally, the considerably small sample size may have limited the robustness of the statistical analysis. Nonetheless, evaluating long-term oncological outcomes in future studies may provide a more comprehensive understanding of the prognostic value of the CONUT score in patients with gastric adenocarcinoma, particularly when considered alongside short-term post-operative complications. We aim to address this aspect in future research. Furthermore, collecting detailed pre-operative data regarding weight loss and oral intake status could contribute to a more multidimensional assessment of nutritional status and potentially enhance the reliability of the findings.

CONCLUSION

This study provides valuable preliminary evidence supporting the potential role of the CONUT score as a practical tool for perioperative risk stratification in patients undergoing gastrectomy for gastric cancer. The identification of high CONUT scores and advanced TNM stage as independent risk factors for post-operative complications suggests that nutritional and tumor-related parameters both contribute significantly to short-term surgical outcomes. Although limited data exist in the literature, our findings are in line with recent studies that have also reported an association between higher CONUT scores and increased risk of post-operative morbidity. Further multicenter prospective studies with larger patient cohorts and long-term follow-up are needed to validate these results and to define the clinical utility of the CONUT score in the management of gastric cancer patients.

Ethics

Ethics Committee Approval: This study was approved by the Başkent University Institutional Review Board (date: 24.07.2025, decision no: KA25/283).

Informed Consent: Prior to inclusion in this retrospective study, informed consent was obtained either from the patients themselves or their first-degree relatives. All participants received comprehensive explanations about the surgical procedure, including potential risks, possible complications, anticipated outcomes, and estimated mortality rates. Additionally, they were informed that their anonymized clinical data might be used for scientific purposes. Written consent confirming their understanding and approval was collected before the operations took place.

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Footnotes

Author Contributions

Concept - İ.T., A.S.K.; Design - İ.T., A.S.K.; Data Collection or Processing - İ.T.; Analysis or Interpretation - İ.T., A.S.K.; Literature Search - İ.T.; Writing - İ.T., A.S.K.

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ORIGINAL ARTICLE
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Anticipating critical view of safety challenges in laparoscopic cholecystectomy for symptomatic cholelithiasis patients: Can we predict them earlier?

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ABSTRACT

Objective: Laparoscopic cholecystectomy (LC) is the gold standard treatment for symptomatic cholelithiasis. Identifying the critical view of safety (CVS) is crucial in this procedure to prevent complications, but achieving CVS can be challenging, necessitating bailout procedures. This study analyzes factors influencing CVS identification and describes bailout procedures used when CVS identification fails.

Material and Methods: We collected data from symptomatic cholelithiasis patients undergoing LC at Cipto Mangunkusumo Hospital from January to October 2023. Factors contributing to CVS identification failure were analyzed, and bailout procedures were described.

Results: Among 107 symptomatic cholelithiasis patients, the mean age was 50.38 years, with the majority being female (55.14% of whom were female). CVS was identified in 88 patients (82.24%). Univariate analysis showed that history of endoscopic retrograde cholangiopancreatography (ERCP) [odds ratio (OR) 5.46], Bile duct (BD) stent (OR 16.53), and diagnosis of cholecystitis (acute, OR 6.17; chronic; OR 4.00) significantly increased CVS identification failure risk. Multivariate analysis identified BD stent as the only significant risk factor (OR 7.41). Higher failure rates were associated with Parkland scores of 4-5, Nassar scores of 4, and G10 scores of 4-5. Among those with CVS identification failure, 5 completed cholecystectomy via top-down approach, 6 underwent subtotal fenestrating cholecystectomy, 6 underwent subtotal reconstituting cholecystectomy, and 2 converted to open cholecystectomy.

Conclusion: Predicting CVS identification failure using preoperative parameters and intraoperative scoring systems is crucial for anticipating surgical complexity and ensuring timely intervention. History of ERCP, BD stent presence, and cholecystitis diagnosis were significant predictors of CVS identification failure. Intraoperative scoring systems reliably predicted CVS identification failure.

Keywords: Bailout procedures, cholelithiasis, critical view of safety, laparoscopic cholecystectomy, risk factors

INTRODUCTION

Cholelithiasis is a common condition encountered in digestive surgery. While the majority of patients with cholelithiasis remain asymptomatic, approximately 1-2% develop symptoms in a year and 20% experience symptoms over a 15-year period. Symptoms of cholelithiasis manifest as a consequence of stone migration to either the cystic duct or common bile duct (CBD), thereby inciting biliary colic pain. Left untreated, this condition can escalate to cholecystitis, perpetuating discomfort and complications (1).

Presently, the gold standard intervention for symptomatic cholelithiasis patients entails laparoscopic cholecystectomy (LC) (2). However, to circumvent potential procedural complications, notably injury to the CBD and major blood vessels, meticulous identification of critical anatomical structures is paramount (3). The concept of the critical view of safety (CVS), pioneered by Strasberg, encompasses three defining criteria: (1) Visualization of only two structures unequivocally connected to the gallbladder, (2) separation of the lower one-third of the gallbladder from the liver to expose the cystic plate, and (3) absolute clarity of the hepatocystic triangle, ensuring unobstructed visualization of all cystic structures (4).

However, identifying the CVS is not always straightforward. Several factors can make visualization challenging, including inflammation, bleeding, and adhesions, which obscure critical anatomical structures and increase the risk of misidentification.

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Given these challenges, predicting the likelihood of CVS failure is crucial in laparoscopic cholecystectomy. Early recognition of potential difficulties allows for timely expert consultation, better anticipation of complications, and adequate preparation for alternative bailout strategies.

This study aims to identify the risk factors associated with failure to achieve CVS during LC in symptomatic cholelithiasis patients. We also describe the bailout strategies used in these cases, such as fundic (top-down) approach, subtotal cholecystectomy, and conversion to open surgery. Early recognition of CVS failure is essential to minimize complications and improve patient safety.

MATERIAL and METHODS

Data Collection

This study was an observational case-control study conducted at Cipto Mangunkusumo Hospital, the main referral hospital in Indonesia. We applied total sampling by including all symptomatic cholelithiasis patients who underwent LC from January to October 2023.

Data were collected from medical records, which included basic characteristics such as gender and age, as well as medical history, including prior endoscopic retrograde cholangiopancreatography (ERCP), BD stent placement, diagnosis of cholecystitis, and other comorbidities. Intraoperative scoring was also documented, including the Parkland grading scale, Nassar scale, and G10 scoring system. In cases of CVS identification failure, we documented the bailout strategies used, such as the fundibular approach (top-down), subtotal cholecystectomy, and conversion to open cholecystectomy.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 24. Patients were divided into two groups based on whether CVS identification was achieved or not. Variables were categorized into preoperative findings and intraoperative scoring, and comparisons were made between the two groups. For preoperative findings, we analyzed gender, age, ERCP history, BD stent placement, and cholecystitis diagnosis to assess any significant differences between the groups, while categorical variables were further analyzed to calculate their respective odds ratios (OR). Variables that demonstrated significant differences, including history of ERCP, BD stent placement, and cholecystitis diagnosis, were then subjected to multivariate analysis to obtain adjusted ORs. Comorbid variables were presented descriptively.

Intraoperative scoring comparisons were conducted between the CVS-identified and CVS-unidentified groups. The Parkland, Nassar, and G10 scoring systems were categorized into two groups: Low scores (1-3) and high scores (4-5). Multivariate analysis was then performed to obtain adjusted ORs for these intraoperative variables. Among the 19 cases with CVS identification failure, the bailout strategies used were shown descriptively. Lastly, surgical outcomes, including surgery duration and intraoperative bleeding volume, were compared between the CVS-identified and CVS-unidentified groups.

Surgical Technique

The patient was placed in a supine position under general anesthesia. Following asepsis and antisepsis procedures, a 10-mm trocar was inserted at the subumbilical site using the Hasson technique. Carbon dioxide insufflation was then initiated to establish pneumoperitoneum. The patient was subsequently repositioned into a reverse Trendelenburg position with a left tilt to optimize exposure of the gallbladder and hepatobiliary structures. A second 10-mm trocar was introduced at the subxiphoid region, followed by the placement of a 5-mm trocar approximately 4 cm below the right costal margin, parallel to the midclavicular line.

The gallbladder was identified, and dissection was initiated at its lower one-third to separate it from the liver, thereby exposing the cystic plate. The CVS was then achieved by ensuring the identification of only two structures leading to the gallbladder: The cystic artery and the cystic duct. Additionally, the hepatocystic triangle was clearly delineated, bordered superiorly by the inferior edge of the liver, medially by the common hepatic duct, and laterally by the cystic duct. All fat and fibrous tissue surrounding the cystic duct and artery was carefully cleared before proceeding with ligation. Once CVS was confirmed, the cystic artery and cystic duct were securely clipped and then transected.

Following ductal and arterial division, the gallbladder was carefully freed from the liver bed using electrocautery and retrieved using an endobag to prevent bile spillage. Hemostasis was ensured before desufflation of CO_2 and removal of trocars. Finally, the surgical site was closed appropriately.

LC was performed by at least two surgeons specializing in hepato-pancreato-biliary surgery, each with experience in over 300 laparoscopic cholecystectomies.

Intraoperative Scoring

The Parkland grading system categorizes the difficulty of LC based on intraoperative findings. Grade 1 represents a normal gallbladder with no adhesions, while Grade 2 involves minor adhesions at the gallbladder neck. Grade 3 includes signs of inflammation, such as hyperemia, peri-cholecystic fluid, body adhesions, or gallbladder distension. Grade 4 involves extensive adhesions obscuring most of the gallbladder or cases with abnormal liver anatomy, intrahepatic gallbladder, or impacted stones (Mirizzi syndrome). Grade 5 represents the most severe

cases, including perforation, necrosis, or complete inability to visualize the gallbladder due to dense adhesions (5).

The G10 scoring system evaluates LC complexity using a maximum score of 10, based on eight parameters: Gallbladder adhesion, distended or contracted gallbladder, inability to grasp without decompression, stone >1 cm impacted in Hartmann's pouch, body mass index >30, adhesions from previous surgery, presence of free bile or pus outside the gallbladder, and presence of a fistula. A higher score indicates a more challenging surgical procedure (6).

The Nassar grading system assesses surgical difficulty based on three criteria: Gallbladder characteristics, cystic pedicle condition, and adhesions. Grade 1 represents an easily dissectible gallbladder with a thin, clear cystic pedicle and minimal adhesions. Grade 2 involves a packed gallbladder or mucocele, a fat-laden cystic pedicle, and simple adhesions. Grade 3 indicates a contracted or fibrotic gallbladder with acute cholecystitis, an abnormal cystic pedicle, and dense adhesions. Grade 4 represents the most complex cases, characterized by a completely obscured gallbladder, empyema, gangrene, or a mass along with dense adhesions, making dissection significantly challenging (7).

Intraoperative scoring was determined by consensus between the operator and assistant.

Ethics Statement

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, with approval number DP.04.03/D.IX.1.23/222/2025, dated April 14th, 2025.

RESULTS

There were 107 symptomatic cholelithiasis patients who underwent LC. The mean age of the patients was 50.38 [95% confidence interval (CI) 47.60-53.15], and the majority were female (55.14%). In 88 patients (82.24%), the CVS was successfully identified, while in 19 patients (17.76%), it was not. There was no significant difference in gender and age between the identified and unidentified CVS groups (Table 1).

Forty-eight patients (44.86%) had a history of previous ERCP, and 10 patients (9.43%) had a BD stent. The history of ERCP and BD stent placement has a significant association with the successful identification of CVS. Fifty-nine patients (55.14%) did not have cholecystitis, 11 (10.28%) had acute cholecystitis, and 37 (34.58%) had chronic cholecystitis. There was a significant association between the diagnosis of cholecystitis and the success of CVS identification (Table 1). Post hoc analysis showed significant differences in proportions between those with acute or chronic cholecystitis and those without cholecystitis, with p-values of 0.027 and 0.021, respectively. Multivariate analysis showed that only BD stent placement was a significant independent risk factor for the failure to identify CVS (p=0.018; OR 7.41, 95% CI 1.40-40.00; Table 2).

Other pathological findings were observed in both the gallbladder and surrounding structures, as shown in Table 3. Patients with Mirizzi syndrome and gallbladder empyema had a higher proportion of CVS identification failure. In addition, cystic duct was successfully identified in all patients with other pathologies, such as gallbladder carcinoma, gallbladder polyp, pancreatitis, and hepatic cirrhosis.

Table 1. Univariate analysis of preoperative parameters

Variables	CVS identified (n=88)	CVS unidentified (n=19)	p-value	OR (CI 95%)
Gender				
Male	37	11	0.315	1.90 (0.69-5.17)
Female	51	8		
Age (years)	50.00±14.88	52.11±12.76	0.568	-
History of ERCP				
No	63	6	0.002*	5.46 (1.87-15.96)
Yes	25	13		
BD stent				
No	85	12	<0.001*	16.53 (3.76-72.71)
Yes	3	7		
Cholecystitis diagnosis on admission				
No	54	5	0.016*	-
Acute	7	4		6.17 (1.33-28.57)
Chronic	27	10		4.00 (1.24-12.87)

*: p<0.05 is considered significant, CVS: Critical view of safety, BD: Bile duct, OR: Odds ratio, CI: Confidence interval, ERCP: Endoscopic retrograde cholangiopancreatography.

Table 2. Multivariate analysis of preoperative parameters

Variables	p-value	OR (CI 95%)
History of ERCP	0.176	2.41 (0.67-8.62)
BD stent	0.018*	7.41 (1.40-40.00)
Cholecystitis diagnosis on admission		
Acute	0.090	4.35 (0.80-23.81)
Chronic	0.167	2.49 (0.68-9.01)

*: p<0.05 is considered significant, BD: Bile duct, OR: Odds ratio, CI: Confidence interval, ERCP: Endoscopic retrograde cholangiopancreatography.

Table 3. Patient's comorbid

Comorbid	CVS identified	CVS unidentified
Mirizzi syndrome type I (n=1)	0	1
Mirizzi syndrome type II (n=1)	0	1
Mirizzi syndrome type III (n=1)	0	1
Gallbladder empyema (n=3)	1	2
Gallbladder carcinoma (n=2)	2	0
Gallbladder polyp, cholesterolosis (n=1)	1	0
Pancreatitis (n=3)	3	0
Hepatic cirrhosis (n=2)	2	0

CVS: Critical view of safety.

Table 4. Intraoperative scoring of cholecystectomy complexity

Intraoperative scoring	CVS identified (n=88)	CVS unidentified (n=19)
Parkland		
1	48	0
2	10	0
3	21	4
4	8	9
5	1	6
Nassar		
1	54	0
2	17	0
3	14	10
4	3	9
G10		
1	59	0
2	19	0
3	6	4
4	4	14
5	0	1

CVS: Critical view of safety.

Table 4 presents the intraoperative scoring results of Parkland, Nassar, and G10, along with the proportion of successful CVS identification for each score. All patients with Parkland scores of 1-2 (58 subjects), Nassar scores of 1-2 (71 subjects), and G10 scores of 1-2 (78 subjects) had successful CVS identification. However, patients with a Parkland score of 4-5, a Nassar score of 4, and a G10 score of 4-5 had a higher proportion of identification failure compared to other scoring ranges. Multivariate analysis showed that Parkland scores of 4-5 and G10 scores of 4-5 significantly increased the risk of CVS identification failure with ORs of 18.92 and 48.11, respectively, while a Nassar score of 4 was not significant (Table 5).

Patients with CVS identification failure (19 subjects) underwent bailout procedures. Initially, all patients underwent the top-down procedure. If cholecystectomy was still not feasible, patients underwent subtotal cholecystectomy. There are two types of subtotal cholecystectomy: Fenestrating type, where the remnant gallbladder is left open, and reconstituting type, where the remnant gallbladder is sutured closed. Five subjects successfully underwent cholecystectomy with the top-down approach. Among the 14 subjects in whom the top-down approach to cholecystectomy failed, 6 underwent subtotal fenestrating cholecystectomy, 6 underwent subtotal reconstituting cholecystectomy, and 2 underwent conversion to OC (Table 6). Conversion to OC was performed due to uncontrolled bleeding during surgery.

There were significant differences in the duration of surgery and intraoperative bleeding between patients with successful CVS identification and those with CVS identification failure (Table 7).

DISCUSSION

Symptomatic gallstones are one of the indications for LC. The CVS serves as a crucial intraoperative marker in LC procedures. Successful identification of the cystic duct, CBD, and common hepatic artery (CVS) is imperative for reducing iatrogenic complications, such as injury to the CBD and large blood vessels, which are associated with high mortality and morbidity rates (4). To date, there have been few studies addressing the failure to identify the CVS in LC among patients with symptomatic gallstones.

In this study, the success rate of identifying the CVS was 82.24%. Out of 48 male patients, 11 (22.92%) experienced CVS identification failure, whereas 8 out of 59 female patients (13.56%) experienced failure. There was no significant difference in the success rate of CVS identification between the two groups. The majority of previous studies have reported a higher incidence of CVS identification failure in male patients, while some have found no significant difference between genders, as observed in this study (8-13). Male patients have a higher risk of failing CVS identification primarily due to the increased

Table 5. Univariate and multivariate analysis of intraoperative scoring

Intraoperative scoring	Univariate		Multivariate	
	p-value	OR (CI 95%)	p-value	OR (CI 95%)
Parkland 4-5	<0.001*	32.92 (8.96-120.87)	0.004*	18.92 (2.58-138.68)
Nassar 4	<0.001*	25.50 (5.91-110.00)	0.474	0.38 (0.03-5.35)
G10 4-5	<0.001*	78.75 (17.73-349.72)	<0.001*	48.11 (7.06-328.00)

*: p<0.05 is considered significant, CI: Confidence interval, OR: Odds ratio.

Table 6. Bailout procedure

Bailout procedures	Frequency (n=19)
Completed top-down	5 (26.31%)
Subtotal fenestrating	6 (31.58%)
Subtotal reconstituting	6 (31.58%)
Conversion to open cholecystectomy	2 (10.53%)

Table 7. Comparison of surgery duration and intraoperative bleeding

Variables	CVS identified	CVS unidentified	p-value
Duration (minutes)	130 (120-180)	180 (120-240)	0.019*
Bleeding (cc)	5 (3-10)	20 (10-50)	0.001*

*: p<0.05 is considered significant, CVS: Critical view of safety.

incidence of acute cholecystitis and its sequelae, which lead to intense inflammation and firm adhesions that obscure anatomical details. Additionally, males tend to have a higher pain threshold, leading to delayed medical consultation and subsequent anatomical changes in the gallbladder that further complicate dissection and identification. However, it is the underlying cholecystitis rather than male sex itself that serves as the main contributing factor (13,14). The mean age of patients who experienced CVS identification failure was 52.11, while the mean age of those who succeeded was 50.00. There was no significant difference between the two groups.

Previous bile duct interventions, including ERCP and bile duct stent placement, were found to significantly increase the risk of CVS identification failure (p=0.002 and p<0.001, respectively). Multivariate analysis identified bile duct stent placement as an independent risk factor, with an OR of 7.41 (95% CI 1.40-40.00). These findings are consistent with previous studies, such as that of Nassar et al. (15) which reported that a history of gallbladder intervention was associated with an increased risk of CVS identification failure (OR 11.11), with ERCP specifically contributing an OR of 9.08. Similarly, Nagata et al. (11) demonstrated that prior biliary drainage significantly increased the likelihood of CVS identification failure. The increased risk is due to anatomical changes from these interventions, such as fibrosis, scarring, and adhesions, which hide key landmarks. Additionally, ERCP-related changes may promote bacterial colonization, leading to chronic inflammation and further complicating dissection. These factors collectively contribute to the difficulty in achieving a clear CVS (11,15,16).

The diagnosis of cholecystitis also significantly affects the failure of CVS identification (p=0.016), although multivariate analysis yielded non-significant results with an OR of 4.35 (95% CI 0.80-23.81) for acute cholecystitis and OR of 2.49 (95% CI 0.68-9.01) for chronic cholecystitis. Acute cholecystitis increases the risk of failure in achieving the CVS due to the presence of significant inflammation, edema, and increased vascularity, which lead to tissue adhesions between the gallbladder and surrounding structures. These factors obscure anatomical landmarks, making dissection more difficult and increasing the likelihood of CVS identification failure. Similarly, chronic cholecystitis contributes to CVS failure through long-standing inflammation that results in fibrosis, scarring, and gallbladder contraction (16,17).

Three patients experienced Mirizzi syndrome, classified as type I, II, and III, with one patient in each type. All three patients failed in CVS identification. Similarly, two out of three patients with gallbladder empyema failed to identify the CVS. A study by Nassar et al. (15) showed comparable results where Mirizzi syndrome and gallbladder empyema increased the risk with ORs of 20.00 and 33.33, respectively. Both conditions are associated with significant anatomical defects in biliary structures, thereby increasing the risk of CVS identification failure (17,18). Patients with other comorbid conditions, such as gallbladder carcinoma, cholesterolosis, pancreatitis, and hepatic cirrhosis, were able to identify CVS successfully.

Based on our intraoperative gallbladder complexity scoring, patients with Parkland scores of 1-2, Nassar scores of 1-2, and G10 scores of 1-2 did not experience CVS identification failure. However, patients with Parkland scores of 4-5, Nassar scores of 4, and G10 scores of 4-5 were at increased risk of CVS identification failure, although only Parkland scores of 4-5 and G10 scores of 4-5 showed significance in multivariate analysis. Studies by Gupta et al. (9) and Nassar et al. (15) also observed a significant decrease in success rates with increasing gallbladder complexity scores.

According to a study by Nassar et al. (15), early identification of the likelihood of CVS identification failure is necessary, comprising preoperative prediction and intraoperative grading

(15). This is to expedite operation time, considering studies by Mischinger HJ that show a fourfold increase in perioperative complications in patients with operation durations exceeding 2 hours, compared to those with durations of 30-60 minutes (19-22).

Patients with identified CVS had significantly shorter operation durations and less bleeding. Similar results were also found in studies by Gupta et al. (9), Nassar et al. (15), Onoe et al. (12), and Stoica et al. (22). This emphasizes the importance of the operator's skills and underscores the need for early identification of the likelihood of CVS identification failure in surgeries.

Patients who experience CVS identification failure will undergo alternate strategies. The fundus-down, also called fundus-first or top-down approach, is the first choice in the bailout strategy, involving dissection from the fundus towards the cystic duct and cystic artery (19-22). A variation of the fundus-down approach, called the lateral dorsal infundibular approach, starts with fenestration between the cystic plate and the gallbladder wall, followed by dissection cephalically and then caudally towards the cystic duct (19). This approach is performed when there is strong adhesion of the gallbladder to the liver, making traction impossible. Among the 19 patients undergoing the top-down procedure, five successfully underwent cholecystectomy, with one of them utilizing the lateral dorsal infundibular approach.

If with both techniques the cystic duct and cystic artery cannot be isolated, rendering total cholecystectomy unfeasible, subtotal cholecystectomy may be considered (5). Subtotal cholecystectomy has been proven to reduce bile duct injury rates (19). There are two subtypes of subtotal cholecystectomy: Reconstructive, where the remaining part of the gallbladder is closed, and fenestrated, where the remaining part is left open, while the inner mouth of the cystic duct is sutured closed. Among the 14 patients who failed cholecystectomy with the top-down approach, 12 underwent subtotal cholecystectomy, with 6 using the fenestrating type, and 6 using the reconstituting type.

Conversion to open surgery is employed to prevent iatrogenic injury or to rectify existing injuries. In situations where the Calot triangle cannot be visualized, anatomical conditions remain unclear, and operation duration exceeds 30-60 minutes with no significant progress, conversion to open surgery may be considered. Likewise, if injuries have already occurred, such as bile duct injury or massive bleeding, conversion to open surgery may also be contemplated (5,23-25). In this study, 2 patients underwent conversion to open surgery due to uncontrolled bleeding. One patient experienced bleeding during the top-down approach, resulting in bleeding in the liver bed, which could not be controlled. The bleeding originated from variations in the anatomy of the hepatic artery branches or the right portal vein. This patient had Mirizzi syndrome type 2 with Parkland, Nassar, and G10 scores of 4. Another patient underwent the top-down approach and then underwent subtotal cholecystectomy. However, during the dissection of the omentum to identify the Hartmann pouch, an injury occurred to a branch of the right portal vein, leading to uncontrollable bleeding. This patient had Parkland, Nassar, and G10 scores of 5, 4, and 4, respectively.

Study Limitations

This study has several limitations. Because this is a single-center study conducted at a tertiary referral hospital, the findings may not be generalizable to other institutions with different case complexity, surgical expertise, and healthcare settings, such as community or secondary hospitals. Multicenter studies are needed to validate these findings across diverse clinical environments. Additionally, this study focused on preoperative and intraoperative factors and immediate postoperative outcomes; it did not assess long-term complications such as bile duct injury, strictures, or symptom recurrence, which are important to understand the full impact on patient outcomes and quality of life. Lastly, the relatively small sample size may limit the statistical power of the multivariate analysis, potentially overlooking significant associations, thus, larger studies are needed to confirm the identified risk factors.

CONCLUSION

A history of biliary interventions—particularly ERCP and BD stent placement—and a diagnosis of cholecystitis on admission were identified as significant preoperative predictors of CVS identification failure, with BD stent placement being an independent risk factor. Intraoperative findings such as Mirizzi syndrome and gallbladder empyema were also associated with a higher likelihood of failure. Additionally, high scores (≥4) in intraoperative scoring systems like Parkland, Nassar, and G10 reliably predicted CVS identification difficulty.

These findings highlight the importance of thorough preoperative assessment to anticipate challenging cases. Surgeons should be especially cautious in patients with these risk factors, and be prepared to implement appropriate bailout strategies or seek expert assistance when necessary. High intraoperative scores should prompt early intraoperative decision-making to avoid complications and improve patient safety.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, with approval number DP.04.03/D.IX.1.23/222/2025, dated April 14th, 2025.

Informed Consent: Written informed consent was obtained from all patients prior to their inclusion in the study, including consent for the use of anonymized data for publication.

Footnotes

Author Contributions

Concept - A.N.L.L.; Design - A.N.L.L., V.M.G.M., I.J.; Data Collection or Processing - F.I., L.S., A.S.P.; Materials - W.S.J., T.J.M.L., V.M.G.M.; Analysis or Interpretation - A.N.L.L., Y.M., V.M.G.M.; Literature Search - D.N.W., I.J., V.M.G.M.; Critical Review - W.S.K., T.J.M.L., Y.M.; Writing - A.N.L.L., I.J., D.N.W.

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ORIGINAL ARTICLE
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Long-term outcomes of surgery for chronic pancreatitis: A single-center experience

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ABSTRACT

Objective: There are limited data on the long-term outcomes after surgery for chronic pancreatitis. The aim of the current study was to assess the long-term pain relief and survival outcomes following surgical intervention for chronic pancreatitis.

Material and Methods: This was a single-center retrospective cohort study that included 36 patients who underwent surgery for chronic pancreatitis. The study analyzed 30-day morbidity and mortality rates, long-term pain relief, and endocrine and exocrine insufficiency. Additionally, 10-year overall survival rates were assessed.

Results: The 30-day morbidity rate was 12/36 (33.4%), with no reported mortality. The median preoperative and postoperative visual analog scale scores were 9 (8-9) and 1 (1-2), respectively (p<0.001). Among 34 patients with severe pain, 33 (97%) reported substantial improvement. Long-term mortality was 6/36 (16.7%), and the 1-year, 5-year, and 10-year overall survival rates were 97%, 90%, and 85%, respectively. Factors associated with inferior survival included preoperative diabetes mellitus (p<0.001), hospital admissions after surgery (p=0.002), failure to gain weight after surgery (p=0.001), postoperative body mass index <18.5 kg/m^2 (p=0.029), and poor pain control after surgery (p=0.004). Conversely, preoperative endoscopic stent placement (p=0.031) was linked to improved 10-year overall survival.

Conclusion: Surgery offers long-term pain relief for chronic pancreatitis, and outcomes can be optimized through early identification and management of high-risk factors.

Keywords: Chronic pancreatitis, endoscopic retrograde cholangiopancreatography, Frey's procedure, long-term survival

INTRODUCTION

Chronic pancreatitis (CP) is a progressive inflammatory disorder that leads to irreversible destruction of the pancreatic parenchyma. This condition significantly impacts a patient's quality of life due to persistent pain, pain-related disability, and concurrent co-morbidities that often result in hospital admissions and the use of opioids (1-3). Diagnostic delays are common due to the non-specific symptoms and limited value of radiological investigations in the early stages of CP (4).

The more advanced stages of CP are characterized by uncontrolled pain, exocrine and endocrine insufficiency, and in rare cases, pancreatic cancer (5,6). Treatment typically follows a step-up approach, beginning with conservative measures, then proceeding to endoscopic interventions, with surgery considered as a last resort (7).

Approximately 40-75% of CP patients eventually require surgery, which aims to provide pain relief, manage complications, and improve quality of life (8). Despite the positive outcomes of surgery for CP, the optimal timing for intervention is still debated (9-11). Various surgical procedures can be performed, including drainage, resectional, and combined resection and drainage procedures, depending on the anatomical features of the pancreas and surrounding structures (8,12-15).

Although there has been progress in understanding the pathophysiology of CP, there are still gaps in its management. Many CP patients experience delays in receiving medical care, and not all are suitable candidates for surgery. Long-term data on these patients are limited, but it is known that infections, cardiovascular issues, and diabetes-related complications are major factors contributing to long-term mortality (6).

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As a specialized unit for hepato-pancreatico-biliary conditions, our team treats both adult and pediatric patients with advanced CP requiring surgery. The purpose of this study is to present the short-term and long-term outcomes of surgery for CP from a single center.

MATERIAL and METHODS

This single-center retrospective cohort study examined patients who underwent surgery for CP between March 2012 and October 2022, with a minimum follow-up of six months (n=36). The study was approved by the Shifa International Hospital Ethics Review Committee (date: 06.09.2023) and Institutional Review Board (IRB #0313-23) and was conducted in accordance with the Declaration of Helsinki and STROBE guidelines.

Patient Details

The diagnosis of CP was based on a typical history of recurrent episodes of abdominal pain, nausea or vomiting, and any concurrent symptoms of exocrine or endocrine insufficiency (steatorrhea, or diabetes mellitus), combined with radiological evidence of CP such as pancreatic atrophy, pancreatic duct dilation or disruption, pancreaticolithiasis, and parenchymal calcifications on abdominal ultrasound and computed tomography (CT). In patients with atypical features, magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography (ERCP) were performed to establish the diagnosis (4). Idiopathic CP was a diagnosis of exclusion, while other etiologies were confirmed on radiological investigations, such as the presence of gallstones on ultrasound pancreatic divisum on CT.

Pain was assessed using the visual analogue scale [(VAS), range: 0-10], frequency and duration of pain attacks, and the need for painkillers. Good pain control was defined as a post-operative VAS score ≤3. We assessed long-term pain relief and patients were contacted in 2023 to extract information regarding pain control. Post-operative complications were categorized according to the Clavien-Dindo classification (16). Patients were considered to have endocrine insufficiency if there was a known history of diabetes mellitus, confirmed by fasting blood glucose levels >125 mg/dL, or when patients were on diabetic medications. Exocrine insufficiency was considered if there was steatorrhea or if patients required enzyme replacement therapy for better control of bowel movements. Body mass index (BMI) was categorized as underweight (<18.5 kg/m^2), normal (18.5 kg/m^2-25 kg/m^2), overweight (25 kg/m^2-30 kg/m^2), and obese (>30 kg/m^2). All patients were discussed in a multidisciplinary team meeting, and Frey's procedure was performed for patients with diffuse and multifocal involvement of the pancreas (12).

Statistical Analysis

Clinicopathological data were extracted from electronic medical records and patient files, and all patients were followed until June 2023. Patient demographics, clinical presentation, details of diagnostic workup and endoscopic intervention, operative details, and post-operative outcomes were analyzed. The primary objective of the study was to determine long-term overall survival (OS) and pain relief after surgery. Additionally, endocrine and exocrine insufficiency, postoperative hospitalizations, change in weight, and BMI after surgery were examined. Continuous data were presented as median with interquartile range and were compared using the Mann-Whitney U test. Kaplan-Meier survival analysis was used to determine OS, and the log-rank test was used to determine significance. Survival was calculated by subtracting the date of death from the date of surgery. All statistical tests were two-tailed, and a p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, v26).

RESULTS

Patient Details

The median age was 24.5 years (range 12.2-45.0), with 12 (33.3%) patients under 16 years old. The median preoperative BMI was 20.8 (range 16.7-23.9) kg/m^2, and the median time from symptoms to diagnosis was 30 (range 19.5-55) months (Table 1). All patients required painkillers, and 13 (36.1%) had 10 or more hospitalizations before surgery. The median pancreatic duct diameter on imaging was 5.7, (range 4-8.4) mm, with 20 (55.6%) patients having a duct diameter >5 mm. Out of 36 patients, 33 (91.7%) underwent ERCP before surgery, and 14 (38.9%) had ERCP with pancreatic duct stenting. Preoperative biopsy was performed on 4 (11.1%) patients due to suspicion of malignancy, but all cases were negative.

30-day Outcomes

Out of 36 patients, 31 (86.1%) underwent Frey's procedure, and five (13.9%) had Whipple's procedure (Table 2). The 30-day morbidity rate was 12/36 (33.4%), with no mortality. Two patients had grade 4 complications, including pneumonia (n=1) and sepsis (n=1).

Long-term Outcomes

The median follow-up was 71.1 months (range 16.1-90.3). The 1,5, and 10-year OS rates were 97%, 90%, and 85% (Figure 1). During follow-up, there were 6 (16.7%) mortalities, attributed to exocrine insufficiency (n=3), diabetes and its complications (n=2), and pneumonia (n=1). Preoperative diabetes mellitus (p<0.001), multiple hospital admissions after surgery (p=0.002), failure to gain weight after surgery (p=0.001), post-operative BMI <18.5 kg/m^2 (p=0.029), and poor pain control after surgery (p=0.004) were associated with inferior long-term survival (Table 3). Preoperative endoscopic stent placement (p=0.031) was associated with improved 10-year OS.

Table 1. Patient characteristics, radiological and endoscopic details	
Variables	**Number (n=36)**
Age in years, median (IQR)	24.5 (12.25-45)
Sex, n (%)	
Male	19 (52.8)
Female	17 (47.2)
Etiology, n (%)	
Idiopathic	21 (58.3)
Gallstones	11 (30.6)
Pancreatic divisum	2 (5.6)
Autoimmune	2 (5.6)
Duration of symptoms, median (IQR), months	30 (19.5-55)
Number of preoperative hospitalizations, n (%)	6.5 (2.3-14.8)
Patients with ≥10 hospitalizations, n (%)	13 (36.1)
Visual analog scale score, median (IQR)	9 (8-9)
Severity of abdominal pain, n (%)	
Severe	34 (94.4)
Moderate	2 (5.6)
Patients on analgesics, n (%)	36 (100)
Patients with comorbidities, n (%)	6 (16.7)
Preoperative BMI, median (IQR), kg/m^2	20.8 (16.7-23.9)
BMI categories, n (%)	
<18.5 kg/m^2	12 (33.3)
18.5-24.9 kg/m^2	19 (52.8)
25-29.9 kg/m^2	4 (11.1)
>30 kg/m^2	1 (2.8)
Preoperative exocrine insufficiency, n (%)	9 (25)
Preoperative endocrine insufficiency, n (%)	5 (13.9)
Preoperative insulin dependence, n (%)	3 (8.3)
Preoperative jaundice, n (%)	5 (13.9)
Pancreatic duct diameter, median (IQR), mm	5.7 (4-8.4)
Pancreatic duct diameter, n (%)	
<3 mm	4 (11.1)
3-5 mm	12 (33.3)
>5 mm	20 (55.6)
Parenchymal calcifications, n (%)	26 (72.2)
Pancreatic strictures, n (%)	
Diffuse/generalized	3 (8.3)
Head	9 (25)
Neck	2 (5.6)
Body	2 (5.6)
Distal bile duct and pancreatic duct	9 (25)
Pancreatolithiasis, n (%)	14 (38.9)
Preoperative ERCP, n (%)	33 (91.7)
Preoperative ERCP stenting, n (%)	14 (38.9)
Number of ERCPs, n (%)	
One	23 (63.9)
Two	6 (16.7)
Three or more	4 (11.1)
Preoperative biopsy, n (%)	4 (11.1)

IQR: Interquartile range, ERCP: Endoscopic retrograde cholangiopancreatography, BMI: Body mass index.

Table 2. Operative details and short-term outcomes	
Variables	**Number (n=36)**
Surgical procedure, n (%)	
Frey's procedure	31 (86.1)
Whipple's procedure	5 (13.9)
Cholecystectomy	36 (100)
Hepaticojejunostomy	7 (19.4)
Operative time, median (IQR), minutes	300 (240-420)
Intraoperative blood loss, median (IQR), mL	400 (200-600)
30-day post-operative morbidity, n (%)	12 (33.4)
Grade 1	2 (5.6)
Wound infection	2 (5.6)
Grade 2	8 (22.3)
Chyle leak	2 (5.6)
Wound infection	6 (16.7)
Grade 3	**0 (0)**
Grade 4	2 (5.6)
Pneumonia	1 (2.8)
Sepsis	1 (2.8)
Grade 5	0 (0)
Intensive care unit stay, median (IQR), days	1 (1-2)
Hospital stay, median (IQR), days	5 (5-6)

IQR: Interquartile range.

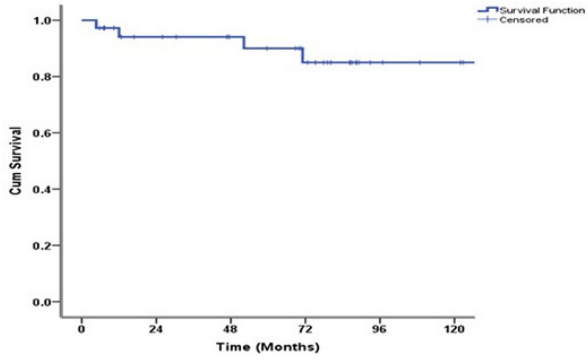

Figure 1. Estimated 1, 5 and 10-year overall survival in patients who underwent surgery for chronic pancreatitis.

Pain Control, Pancreatic Function, BMI

The VAS score improved for all patients after surgery, with a median preoperative and postoperative VAS score of 9 (8-9) and 1 (1-2) ($p<0.001$). Complete pain control was achieved in 19 (52.8%) patients, and 14 (38.9%) reported substantial improvement with occasional episodes of mild pain. Notably, out of 34 patients with severe pain before surgery, 33 (97%) experienced substantial improvement. Overall, good pain control was achieved in 28/36 (77.8%) patients (VAS ≤3).

Table 3. Factors associated with 10-year overall survival after surgery for chronic pancreatitis

Variables	10-year OS (%)	p-value
Sex		0.229
Male	90	
Female	79	
Etiology		0.584
Idiopathic	71	
Gallstones	91	
Preoperative exocrine dysfunction		0.688
Present	74	
Absent	83	
Preoperative diabetes mellitus		<0.001
Present	40	
Absent	86.5	
Preoperative BMI		0.230
<18.5 kg/m^2	64.2	
≥18.5 kg/m^2	91.7	
Preoperative hospitalizations		0.054
≤2	66.7	
>2	90.7	
Preoperative ERCP and stenting		0.031
Yes	100	
No	72	
Pancreatic duct diameter		0.590
<3 mm	100	
3-5 mm	83.3	
>5 mm	81.6	
Pancreatic stricture		0.330
Yes	92	
No	69.3	
Pancreatolithiasis		0.867
Yes	79.6	
No	85.9	
Pancreatic calcifications		0.737
Yes	86.2	
No	77.1	
Preoperative jaundice		0.118
Yes	60	
No	88	
Post-operative pain relief		0.004
Yes	92.6	
No	60	
Post-operative weight gain		0.001
Yes	94.4	
No	60	
Post-operative BMI		0.029
<18.5 kg/m^2	65.6	
≥18.5 kg/m^2	88	
New onset exocrine insufficiency		0.073
Yes	75	
No	85.5	
Post-operative hospitalizations		0.002
≤2	93.1	
>2	52.5	

BMI: Body mass index, ERCP: Endoscopic retrograde cholangiopancreatography, OS: Overall survival.

DISCUSSION

In this study, we report long-term outcomes with surgical management of CP. Due to no cases of alcohol-related CP, a relatively young age at the time of surgery, and zero short-term mortality, a 10-year OS rate of 85% was achieved. To the best of our knowledge, this is the first study from Pakistan examining long-term outcomes after surgery for CP. A number of preoperative and postoperative factors were associated with long-term survival and can serve as useful markers to establish nutritional goals, devise follow-up plans, and evaluate pancreatic endocrine and exocrine function.

Overall, we found surgical intervention to be safe and effective, with excellent long-term survival after surgery, comparable to contemporary reports on surgical outcomes in CP (6,17). Factors such as smoking, alcohol and opioid use, concomitant diabetes mellitus, poor pain control despite surgery, and low BMI have been associated with mortality in CP (18-20). Inferior long-term survival was also significantly associated with preoperative diabetes mellitus and more than two hospital admissions after surgery. More importantly, preoperative endoscopic stent placement, weight gain, and pain relief with surgery were associated with improved survival. These factors can be used to devise follow-up plans in patients with CP. More intensive post-operative surveillance strategies and clearly defined nutritional goals are needed when these factors are present.

Surgery is performed in CP for unrelenting and troublesome pain (21). Complete pain control is achieved in 37% compared to 17% (p=0.008), of patients undergoing surgical versus endoscopic therapy (22). The role of surgery versus endoscopy in patients with early CP remains debatable. In the ESCAPE trial, early surgery was associated with lower pain scores compared with endoscopic management (11). In a recent systematic review and meta-analysis, surgery was associated with better overall pain control [odds ratio (OR) 0.33, 95% confidence interval (CI) 0.23-0.47, p<0.001, I^2=4%]. However, considering that surgical intervention is a significant undertaking, the authors concluded that surgery should be considered when endoscopy fails (23). Out of 36 patients in the current study, 33 (91.7%) underwent ERCP and 14 (38.9%) had pancreatic stent placement. Due to ineffective pain control by endoscopy, surgical intervention was performed. On the last follow-up, 19 out of 36 (52.8%) patients were completely pain-free, and 33 out of 36 (91.7%) patients with severe pain reported substantial pain relief after surgery. Therefore, the step-up approach starting with medical management, endoscopy, and finally surgery appears to be a reasonable option in CP.

The impact of surgery on long-term endocrine and exocrine function in CP remains less clearly understood. Two recently concluded systematic reviews reported conflicting results. Hughes and colleagues have shown that there is no difference in endocrine failures following surgical therapy [48 out of 135 (36%)], or endoscopic therapy [49 out of 124 (40%)], [OR (95% CI) 0.71 (0.30-1.69), p=0.44]. Similarly, no significant difference in exocrine failure rate following surgery [39 out of 55 (71%)] and endoscopy [43 out of 57 (75%)] [OR (95% CI) 0.62 (0.12-3.12), p=0.56] was reported (22). On the other hand, Ma et al. (23) reported less endocrine insufficiency after surgery compared to endoscopy [OR 2.10, 95% CI 1.20-3.67, p=0.01, I^2=0%]. Steatorrhea and diabetes mellitus are reported in 13-19% and 14.7-43.8% of patients, respectively (24). Hence, the progressive deterioration of pancreatic function after surgery might represent one of the biggest challenges in managing these patients in the long term and is a major cause of morbidity, and incurred treatment costs. With regard to the choice of surgical procedure, Frey's procedure is commonly used in CP (25,26). Whipple's procedure is reserved for patients with a suspicious mass in the head of the pancreas and head-dominant pathology. We also preferred Frey's procedure as it was indicated in the majority of our patients with CP, was relatively easy to perform, and was associated with low morbidity.

Study Limitations

Our study had the limitations typical of a retrospective, non-randomized study. As a referral center and quaternary care hospital, we see very few patients with early CP. Nevertheless, we report the impact of surgery on long-term pain relief, pancreatic function, and OS in patients with advanced CP. We have reported 10-year OS based on Kaplan-Meier curves, and five patients had an actual follow-up longer than ten years. We did not compare outcomes of surgery with endoscopy because, in a non-randomized setting and with a unique referral pattern, we couldn't carry out such a study. In 21 (58.3%) patients, the etiology of CP could not be determined. This is much higher than reports from the West, but similar results have been reported from India (27).

CONCLUSION

The current study shows that the majority of patients with CP achieve pain relief through surgery. More importantly, Frey's procedure in these patients is associated with excellent short-term and long-term outcomes. Not all patients benefit from surgery, and we need to refine patient selection in CP. Moreover, risk factors for inferior long-term survival should be identified, permitting tailored follow-up protocols.

Ethics

Ethics Committee Approval: The study was approved by the Shifa International Hospital Ethics Review Committee (date: 06.09.2023) and Institutional Review Board (IRB #0313-23) and was conducted in accordance with the Declaration of Helsinki and STROBE guidelines.

Informed Consent: A verbal informed consent was provided by the participants of the study.

Footnotes

Author Contributions

Concept - A.A., A.B.H.B.; Design - A.A., A.B.H.B.; Supervision - N.Y.K., A.B.H.B.; Data Collection or Processing - S.T.A., A.A.; Analysis or Interpretation - S.T.A., A.A., A.B.H.B.; Literature Search - S.T.A., A.A., A.B.H.B.; Critical Review - N.Y.K., A.B.H.B.; Writing - A.A., A.B.H.B.

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

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ORIGINAL ARTICLE
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Diagnostic utility of inflammatory ratios and nutritional scores in acute mesenteric ischemia: A retrospective single-center study

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ABSTRACT

Objective: Acute mesenteric ischemia (AMI) is a rare but highly fatal vascular emergency. Due to its non-specific clinical presentation, early diagnosis remains a major challenge. This study aimed to evaluate the diagnostic utility of selected inflammatory ratios and nutritional scores in differentiating AMI from other causes of acute abdominal pain.

Material and Methods: This retrospective, single-center study included 40 patients diagnosed with AMI and 40 control patients who presented with non-specific abdominal pain and had no definitive diagnosis. Preoperative laboratory parameters obtained upon emergency admission were analyzed. Calculated indices included neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), prognostic nutritional index (PNI), C-reactive protein (CRP)-to-albumin ratio (CAR), and CRP-to-LDH ratio (CLDR), among others. Group comparisons, Pearson correlation analyses, and receiver operating characteristic (ROC) curve analyses were performed.

Results: Compared to controls, AMI patients showed significantly elevated levels of NLR, PLR, SII, CAR, and CLDR, and significantly lower levels of PNI ($p<0.05$). ROC analysis revealed that SII [area under the curve (AUC) =0.89], NLR (AUC =0.86), and PNI (AUC =0.81) demonstrated the strongest diagnostic performance. Several indices were found to be strongly correlated, Including NLR with SII and CAR with CLDR. The observed mortality rate in the AMI group was 52.5%.

Conclusion: Inflammatory and nutritional markers, particularly SII, NLR, and PNI, appear to offer valuable diagnostic support in identifying AMI. These indices may help prioritize patients for advanced imaging and early intervention, especially in resource-limited emergency settings. Further prospective multicenter studies are needed to confirm their clinical utility.

Keywords: Acute mesenteric ischemia, systemic inflammation index, prognostic nutritional index, CRP to albumin ratio, diagnostic biomarker

INTRODUCTION

Acute mesenteric ischemia (AMI) is a life-threatening vascular emergency that occurs due to the sudden interruption of blood supply to the intestines. If not diagnosed and treated promptly, it can progress rapidly to transmural infarction, multi-organ failure and death (1). Although rare—accounting for approximately 0.09-0.2% of all acute abdominal presentations— AMI carries an alarmingly high mortality rate, often exceeding 50% in delayed cases (2,3). The disease is commonly caused by arterial embolism or thrombosis; mesenteric venous thrombosis; or non-occlusive mesenteric ischemia (NOMI) (4).

Despite its potentially devastating outcome, AMI frequently presents with vague and non-specific symptoms such as abdominal pain, nausea, vomiting, and diarrhea, which overlap significantly with more benign causes of abdominal pain (5). The classical triad of abdominal pain, fever, and leukocytosis is seen in only about one-third of patients, contributing to delayed diagnosis and intervention (6). As a result, many cases are identified at advanced stages when irreversible intestinal damage has already occurred (3,6).

Contrast-enhanced computed tomography angiography (CTA) remains the gold standard for AMI diagnosis, offering high sensitivity and specificity in detecting mesenteric occlusion and ischemia (7,8). However, delays in image acquisition or interpretation, limited access to scanners, and contraindications to contrast in certain patients may hinder its timely use. These limitations have prompted investigations

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into alternative, easily obtainable and non-invasive diagnostic strategies (9,10).

Recent research has focused on inflammatory and nutritional biomarkers as adjunctive tools for early recognition of AMI. Markers, such as the neutrophil to lymphocyte ratio (NLR), the platelet to lymphocyte ratio (PLR), and scores like the prognostic nutritional index (PNI), have shown promise in identifying systemic inflammatory response and nutritional depletion associated with bowel ischemia (11,12).

This study aims to assess and compare the diagnostic utility of selected inflammatory ratios and nutritional scores in distinguishing patients with AMI from those presenting with other causes of acute abdominal pain. By elucidating the potential role of these non-invasive laboratory markers, we aim to enhance early diagnostic accuracy and contribute to improved clinical decision-making and patient outcomes. Although these parameters alone may not provide a definitive diagnosis, they may offer valuable supportive evidence and help prioritize patients for advanced imaging studies such as CTA, thus contributing to more timely diagnosis and treatment.

MATERIAL and METHODS

Research Design, Setting and Study Period

This retrospective study was conducted at Bolu Abant İzzet Baysal University İzzet Baysal Training and Research Hospital. The study included adult patients (≥18 years), diagnosed with AMI between January 2014 and January 2024. The study received ethical approval from the Bolu Abant İzzet Baysal University Faculty of Medicine Hospital Ethics Committee (approval number: 2024/298, date: 19/11/2024).

Patient Selection and Data Collection

Among 172 patients initially diagnosed with mesenteric ischemia, 40 patients who met the diagnostic criteria for AMI and were treated with medical therapy, endovascular intervention, or surgery were included in the study group. Patients with chronic mesenteric ischemia, NOMI or veno-occlusive mesenteric ischemia were excluded. The control group consisted of 40 patients who presented with non-specific abdominal pain and were discharged without a definitive diagnosis after clinical evaluation.

Demographic characteristics, comorbidities, imaging findings, treatment methods, and laboratory values were retrospectively obtained through the hospital's electronic medical records system (KARMED®). Only preoperative laboratory data -obtained at the time of emergency department admission and prior to any intervention- were included in the analysis. Postoperative values were intentionally excluded to preserve the diagnostic relevance of the findings.

Laboratory Parameters and Calculated Indices

All laboratory tests were performed in the central laboratory of our institution using standardized procedures. Hematological parameters including platelets (PLT), lymphocytes (LYM), monocytes (MONO), neutrophils (NEU), platelet distribution width (PDW), and mean platelet volume (MPV) were measured using an automated hematology analyzer (Mindray BC-6800, Shenzhen, China). Biochemical parameters such as albumin (ALB), C-reactive protein (CRP), urea, sodium (Na), potassium (K), calcium (Ca), and lactate dehydrogenase (LDH) were analyzed using a Beckman Coulter AU5800 chemistry analyzer (Brea, CA, USA). Prothrombin time (PT) was measured using a Sysmex CS-2100i coagulation analyzer (Kobe, Japan).

The Following Derived Ratios and Indices Were Calculated

Inflammatory ratios: NLR, PLR, lymphocyte to monocyte ratio (LMR), platelet to PDW ratio (PPR), MPV to platelet ratio (MPR), CRP to albumin ratio (CAR), CRP to LDH ratio (CLDR), LDH to albumin ratio (LDAR), urea to albumin ratio (UAR), albumin to prothrombin time ratio (APR), sodium to potassium ratio (NaKR) and sodium to calcium ratio (NaCaR).

Composite indices: High-sensitivity modified glasgow prognostic score (HSmGPS), systemic immune-inflammation index (SII) and PNI.

Rationale for Parameter Selection

The laboratory parameters and derived indices included in this study were selected based on their clinical relevance, accessibility during emergency admission, and prior evidence of their association with systemic inflammation, tissue ischemia, and nutritional status. Neutrophils, lymphocytes, CRP, albumin, urea, and LDH were included due to their well-established roles in the inflammatory and metabolic responses characteristic of AMI.

Derived ratios such as NLR, PLR, CAR, SII, and PNI were chosen based on existing literature supporting their diagnostic and prognostic utility in various acute and critical conditions, including gastrointestinal ischemia.

Commonly performed laboratory tests such as arterial blood gases, D-dimer, troponin, and fibrinogen were not included due to inconsistent availability or substantial missing data in the retrospective records. To ensure data quality and consistency, we prioritized parameters with high completeness across the 10 year study period. Only preoperative laboratory values obtained at the time of emergency admission were analyzed to maintain temporal relevance to the diagnostic process. We acknowledge this limitation and suggest that future prospective studies include a broader spectrum of biomarkers to improve early diagnostic accuracy in AMI.

Statistical Analysis

All statistical procedures were carried out using IBM SPSS Statistics version 27. The Kolmogorov-Smirnov test was utilized to determine whether the data followed a normal distribution. For variables with normal distribution, comparisons between groups were made using the Independent Samples t-test, while the Mann-Whitney U test was employed for non-normally distributed variables. Pearson's correlation was used to assess linear relationships among significant variables. The diagnostic accuracy of the parameters and their optimal thresholds was evaluated using receiver operating characteristic (ROC) curve analysis. Statistical significance was defined as a p-value less than 0.05.

RESULTS

A total of 40 patients diagnosed with AMI from January 2014 to January 2024 were included in the study group. Additionally, 40 patients who presented to the hospital with abdominal pain but were not diagnosed with any specific pathology after clinical evaluation were assigned to the control group.

The mean age of the AMI group was 69.2±14.2 years, with 22 males (55%) and 18 females (45%). In the control group, the mean age was 67.47±13.1 years, consisting of 21 females (52.5%) and 19 males (47.5%). Among the AMI patients, 34 had chronic comorbidities and 14 were receiving anticoagulant therapy. Nineteen patients underwent emergency surgery, six received endovascular interventions, and fifteen were managed conservatively with medical treatment. Despite these interventions, 21 patients died, corresponding to a mortality rate of 52.5%. The average length of hospital stay was 8 days.

A normality test was conducted on all laboratory parameters. For variables with a normal distribution (LYM, MONO, NEU, PDW, MPV, ALB, Na, and K), the Independent Samples t-test was used; for those not normally distributed (PLT, PT, CRP, urea, Ca and LDH), the Mann-Whitney U Test was applied. The comprehensive comparison results are presented in Table 1.

To assess correlations among parameters found to be statistically significant in group comparisons, the Pearson correlation test was performed. While most parameters (LYM, MONO, NEU, PDW, MPV, ALB, Na, K, PLT, PT, CRP, urea, Ca and LDH) exhibited weak to moderate correlations with one another, a strong positive correlation was observed between monocyte and neutrophil counts (R=0.662).

In addition to basic laboratory values, derived ratios and scores —including NLR, PLR, LMR, PPR, APR, NaKR, NaCaR, PNI, and SII— demonstrated a normal distribution, whereas HSmGPS, MPR, CAR, CLDR, LDAR, and UAR did not. Accordingly, the Independent Samples t-test was used for normally distributed variables, and the Mann-Whitney U test for non-normally distributed ones. The results of these analyses are summarized in Table 2.

Further correlation analysis was conducted among significant ratios and scores. Strong positive correlations were found among NLR, PLR, and SII; between PLR and SII; APR and PNI; CAR and CLDR; UAR and HSmGPS; and CLDR and HSmGPS.

ROC curve analysis was performed for each variable to evaluate diagnostic performance. For each parameter, the area under the curve, standard error, p-value, cut-off point, sensitivity, specificity, and 95% confidence intervals were calculated. Although these findings are detailed in Table 3 and visualized in Figures 1 and 2, it was determined that each statistically significant parameter exhibited strong discriminative power in distinguishing between the AMI and control groups.

Table 1. Comparison of laboratory parameters between two groups

	p-value
Lymphocytes	<0.001
Monocytes	0.001
Neutrophils	<0.001
Platelet distribution width	<0.001
Mean platelet volume	<0.001
Albumin	<0.001
Sodium	0.001
Potassium	0.741
Platelet	0.969
Prothrombin time	<0.001
C-reactive protein	<0.001
Urea	<0.001
Calcium	0.002
Lactate dehydrogenase	<0.001

Table 2. Comparison of biochemical ratios and scoring systems between two groups

	p-value
Prognostic nutritional index	<0.001
Neutrophil to lymphocyte ratio	<0.001
Platelet to lymphocyte ratio	<0.001
Lymphocyte to monocyte ratio	<0.001
Platelet to platelet distribution width ratio	0.521
Albumin to prothrombin time ratio	<0.001
Sodium to potassium ratio	0.457
Sodium to calcium ratio	0.156
Systemic inflammation index	<0.001
High sensitivity modified glasgow prognostic score	<0.001
Mean platelet volume to platelet ratio	0.031
C-reactive protein to albumin ratio	<0.001
C-reactive protein to lactate dehydrogenase ratio	<0.001
Lactate dehydrogenase to albumin ratio	<0.001
Urea to albumin ratio	<0.001

DISCUSSION

AMI, though rare, continues to present significant diagnostic challenges due to its non-specific clinical findings and its rapid progression to intestinal necrosis. The necessity of early diagnosis and timely intervention has intensified interest in the clinical use of rapid, easily accessible and cost-effective biomarkers, particularly in situations where time and resources are limited (1,2,10).

In this retrospective study, we compared the diagnostic performance of conventional laboratory tests and novel derived ratios and scores in AMI patients against a control group presenting with non-specific abdominal pain. Our findings suggest that certain inflammatory and nutritional parameters can provide meaningful support in the early diagnosis and clinical management of AMI.

Recent studies have particularly focused on systemic inflammation and nutrition-based indices such as NLR, PLR, and SII. These ratios, which integrate basic hematological parameters, have demonstrated prognostic value in various critical conditions (3,6,11). In our study, SII emerged as the most diagnostically powerful marker, showing high sensitivity and specificity, consistent with findings reported in the literature on ischemic stroke and myocardial infarction (11,13,14). This

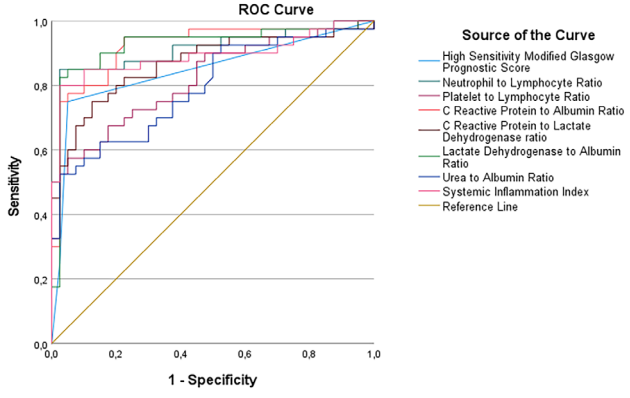

Figure 1. ROC curve of biochemical ratios and scoring systems in predicting AMI.

ROC: Receiver operating characteristic, AMI: Acute mesenteric ischemia

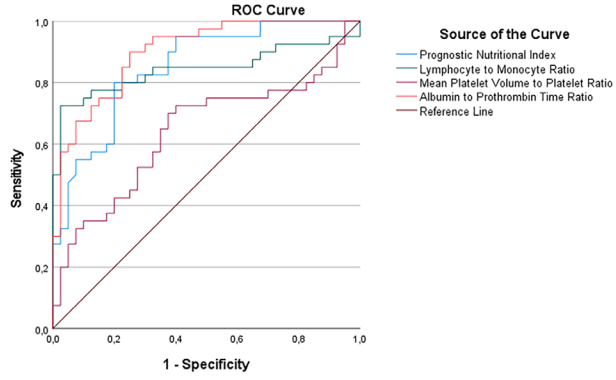

Figure 2. ROC curve of biochemical ratios and scoring systems in predicting AMI.

ROC: Receiver operating characteristic, AMI: Acute mesenteric ischemia

Table 3. ROC analysis of laboratory parameters, biochemical ratios and scoring systems

Test	AUC (95%)	SE	p-value	Asymtotic 95% confidence interval		Cut-off	Sensitivity (%)	Specificity (%)
				Lower bound	Upper bound			
High sensitivity modified Glasgow prognostic score	0.847	0.047	<0.001	0.755	0.939	0.50	75.0	95.0
Neutrophil to lymphocyte ratio	0.914	0.035	<0.001	0.846	0.982	3.71	85.0	85.0
Platelet to lymphocyte ratio	0.816	0.048	<0.001	0.722	0.909	169.89	72.5	72.5
C-reactive protein to albumin ratio	0.920	0.033	<0.001	0.854	0.985	0.26	82.5	82.5
C-reactive protein to lactate dehydrogenase ratio	0.868	0.042	<0.001	0.786	0.949	0.035	80.0	80.0
Lactate dehydrogenase to albumin ratio	0.924	0.035	<0.001	0.856	0.992	5.94	85.0	85.0
Urea to albumin ratio	0.792	0.050	<0.001	0.694	0.891	0.93	67.5	67.5
Systemic inflammation index	0.892	0.040	<0.001	0.813	0.971	956.24	85.0	85.0
Prognostic nutritional index	0.850	0.042	<0.001	0.767	0.932	410.00	80.0	80.0
Lymphocyte to monocyte ratio	0.844	0.049	<0.001	0.748	0.940	2.61	77.5	77.5
Mean platelet volume to platelet ratio	0.640	0.064	0.031	0.515	0.765	0.03	65.0	65.0
Albumin to prothrombin time ratio	0.900	0.033	<0.001	0.835	0.965	3.16	77.5	77.5

AUC: Area under the curve, SE: Standard error, ROC: Receiver operating characteristic.

supports the use of SII as a surrogate indicator of systemic vascular stress.

NLR and PLR levels, were significantly elevated in patients with AMI, consistent with prior studies emphasizing their diagnostic and prognostic relevance in ischemic abdominal pathology (6,14). Khan et al. (6) reported that an NLR >9.9 is effective in differentiating AMI from other acute abdominal conditions. Augène et al. (15) also identified PLR as an independent predictor of short-term mortality.

The PNI was significantly lower in the AMI group in our study. This finding is in line with earlier studies showing that low PNI is associated with worse clinical outcomes and increased surgical risk in ischemic intestinal conditions (16,17). As such, PNI reflects both nutritional status and immune suppression.

Inflammation-nutrition composite ratios such as the CAR and the CRP to LDH ratio (CLDR) were also significantly elevated in AMI patients. CAR, in particular, has been reported to outperform CRP alone in mortality prediction across various acute diseases including AMI (14,16). While CLDR has been less frequently studied, our results suggest that it may hold additional prognostic value.

In addition to these more commonly assessed indices, our study also evaluated less frequently explored parameters such as the HSmGPS, LDAR, UAR, LMR, MPR, and APR. Although these parameters did not demonstrate diagnostic power comparable to SII or NLR, they provide new avenues for clinical interpretation.

HSmGPS, which combines CRP and albumin levels, has shown prognostic value in oncology and sepsis literature, though it has been rarely studied in AMI. In our study, HSmGPS levels were higher in the AMI group, consistent with trends reported in inflammatory conditions (16,18), although the difference did not reach statistical significance.

LDAR and UAR, which reflect metabolic stress and catabolic burden, were also elevated in AMI patients. These ratios may indicate tissue damage and renal dysfunction, though their diagnostic validity in AMI remains to be established (14,18). APR, which reflects hepatic synthetic capacity under inflammatory stress, showed potential discriminatory power but did not achieve statistical significance in our study. MPR, though conceptually promising as an index of platelet activation, and LMR, widely used in cancer prognosis, demonstrated inconsistent results in our cohort, possibly due to sample size limitations or biological variability (3,19-21).

Alternative parameters have also been evaluated in the literature. For instance, whole blood viscosity has been proposed as a marker for mesenteric arterial thrombosis, although it was not assessed in our study (22). Likewise, several meta-analyses have emphasized the role of traditional markers such as D-dimer and lactate in the early detection of AMI and proposed composite laboratory models for improved diagnostic accuracy (23).

The mortality rate observed in our study was 52.5%, which aligns with previously reported ranges of 50-70% for AMI (1,2,24). This persistently high fatality rate underscores the need for rapid diagnostic methods that can aid in earlier recognition and intervention, particularly when access to imaging is limited or delayed.

Strengths of our study include both conventional and novel laboratory parameters, providing a more comprehensive assessment of systemic response to mesenteric ischemia. However, limitations include its retrospective and single-center design, relatively small sample size, and single-time-point laboratory data collection, which may not reflect dynamic changes over the disease course.

CONCLUSION

According to this study, some nutritional and inflammatory biomarkers, including SII, NLR, PLR, PNI, CAR and CLDR, may be useful in the early diagnosis of AMI. These markers are inexpensive, simple to acquire and could help clinicians make decisions when imaging is not easily accessible, especially in emergency rooms. Newer markers like LDAR, UAR and HSmGPS may also provide insightful information, but further study is required to fully understand their diagnostic utility. Given the high death rate linked to AMI, using these biomarkers in early diagnostic processes could facilitate quicker triage and improved results. To validate these results, larger prospective investigations are required.

Ethics

Ethics Committee Approval: study received ethical approval from the Bolu Abant İzzet Baysal University Faculty of Medicine Hospital Ethics Committee (approval number: 2024/298, date: 19/11/2024).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Concept - F.B.; Supervision - M.Ş., S.P.Ö.; Design - F.B., M.F.K.; Data Collection or Processing - F.B., M.F.K.; Analysis or Interpretation - F.B., M.F.K., O.Ç.; Literature Search - F.B., B.Ö.; Critical Review - M.Ş., B.Ö., O.Ç., S.P.Ö.; Writing - F.B.

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

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ORIGINAL ARTICLE
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Non-standardized surgery lateral internal sphincterotomy: Is there a consensus?

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ABSTRACT

Objective: Lateral internal sphincterotomy (LIS) is considered the gold standard surgical treatment for chronic anal fissures. However, substantial variation exists in the surgical techniques applied. This study aims to evaluate practice differences among surgeons performing LIS and to assess whether a consensus has been established.

Material and Methods: An anonymous online survey was conducted to assess surgeons' technical approaches to LIS. Data were collected using a 24-question survey targeting surgeons from various countries.

Results: A total of 207 surgeons (131 from Türkiye, 76 from other countries) responded. The majority were male (73.3%) and between 40 and 64 years of age (64.7%). Most participants (70%) had more than 10 years of surgical experience, and 55% were affiliated with academic centers. The open technique was preferred by 73.6% of respondents, while 21.4% opted for the closed method. Partial sphincterotomy was favored by 66%, followed by complete (21%) and tailored (12%) approaches. Substantial heterogeneity was noted in bowel preparation, patient positioning, incision type, and management of skin tags or hypertrophied papillae. Only 6% reported routine use of anorectal manometry. Variations were more prominent across countries than between demographic groups. The principal finding of the study is the lack of a standardized approach to LIS across international surgical communities.

Conclusion: There is no standardized approach to LIS among surgeons. Surgical technique preferences vary significantly and appear to be influenced more by geographic practice location than by individual surgeon characteristics such as age, gender, or experience.

Keywords: Chronic anal fissure, lateral internal sphincterotomy, international survey

INTRODUCTION

A chronic anal fissure is a common proctological disease that significantly impairs quality of life (1). The treatment expectation for this benign pathology is a permanent and effective solution with minimal side effects. Treatment options range from non-operative medical therapies to surgical interventions. While medical treatment is often used as the initial approach, surgery is usually reserved as a last resort. The most commonly currently used surgical treatment methods are lateral internal sphincterotomy (LIS), fissurectomy, and advancement flaps.

According to many societal guidelines, LIS is the surgical treatment of choice for chronic anal fissures (2,3). Furthermore, many studies show that surgical treatment of chronic fissures with LIS has a higher healing rate and improves quality of life compared to conservative and medical treatments (4,5).

Despite its widespread use and acceptance as the gold standard surgical treatment, significant variations in LIS technique persist. These include differences in incision type, extent of sphincterotomy, preoperative preparation, and adjunctive procedures. This study aimed to identify such variations in practice among surgeons and evaluate the potential for standardization and consensus.

MATERIAL and METHODS

Study Design and Survey Distribution

Ethics committee approval was obtained for the study (Ankara University- application number: 2022000546/i09-575-22, date: 13:10.2022). The study was an open survey

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dedicated to general and colorectal surgeons with varying levels of experience and from different types of hospitals and countries. The questionnaire was developed based on current literature and was available in both Turkish and English. It was distributed via SurveyMonkey (San Mateo, CA) through social media platforms (Twitter, WhatsApp), e-mail, and personal invitations.

Survey Content

The survey comprised 24 questions evaluating surgical preferences regarding LIS. Topics included anorectal manometry use, bowel preparation, patient positioning, retractor type, incision method, sphincterotomy technique and extent, fissurectomy, and management of hypertrophied anal papillae or skin tags. Demographic data were also collected, including country, gender, years of experience, institutional setting, and procedure volume.

Statistical Analysis

Survey responses were collected anonymously over a two-month period. Participants were divided into two groups based on their country of practice (Türkiye or other countries) for comparative analysis. Responses were analyzed using SPSS v20.0. All survey questions yielded categorical data, which were presented as frequencies and percentages. Stasistical comparisons between groups were conducted using the chi-square test. A p-value of <0.05 was considered statistically significant.

RESULTS

Responses were obtained from 207 surgeons: 131 from Türkiye and 76 from other countries (Argentina, Azerbaijan, Belgium, Brazil, Colombia, El Salvador, France, Honduras, India, Italy, Kenya, Mexico, Netherlands, Panama, Paraguay, Portugal, Spain, USA, UK, Canada, Venezuela). The majority of participants (73.33%) were male, and 64.7% were aged between 40 and 64 years (Table 1).

Surgeons in the Turkish group were older, on average, than those in the international group. Most participants (70%) had over 10 years of surgical experience, 55% worked in academic institutions, and 61% performed more than 10 procedures for CAF per year.

The open LIS technique was the predominant approach (73.6%), with Turkish surgeons significantly more likely to prefer the open technique compared to their international counterparts (Table 2). Preferences for sphincterotomy size were 66% partial, 21% complete, and 12% tailored. There was a notable difference between groups regarding fissure length preferences.

Substantial variability was observed in preoperative bowel preparation, patient positioning, retractor selection, incision methods, and additional procedures, such as fissurectomy and skin tag excision. The use of preoperative anorectal manometry was reported by only 6% of surgeons, with most respondents deeming it unnecessary. Variations in technique were evident between countries but were not significantly associated with demographic factors such as age, gender, or surgical experience.

Table 1. Surgeon demographics

	n=131 Türkiye	n=76 World	p-value
Age year, n (%)			
25-39	27 (20.6)	38 (50)	**0.000***
40-64	100 (76.3)	34 (44.7)	
65 and over	4 (3)	4 (5.3)	
Gender, n (%)			
Male	91 (69.5)	61 (80.3)	0.091
Female	40 (30.5)	15 (19.7)	
Surgical experience year, n (%)			
1-10	22 (16.8)	42 (45.3)	**0.000***
11-20	58 (44.3)	19 (25)	
21 and over	51 (38.9)	15 (19.7)	
LIS per year, n (%)			
0-5	34 (26)	57 (75)	**0.000***
6-10	22 (16.8)	16 (2.1)	
11-20	31 (23.7)	2 (2.6)	
21 and over	44 (33.6)	1 (1.3)	
Type of hospital, n (%)			
Academic	74 (56.5)	41 (56.2)	**0.000***
Community	24 (18.3)	28 (38.4)	
Private	33 (25.2)	4 (5.5)	

*: Statistically significant differences in bold, LIS: Lateral internal sphincterotomy.

Table 2. Surgeon preferences			
	n=131 Türkiye	**n=76 World**	**p-value**
Preoperative			
Preoperative manometry, n (%)			
Yes	2 (1.5)	10 (13.2)	0.001*
No	129 (98.5)	66 (86.8)	
Preoperative bowel preperation, n (%)			
Yes oral & enema	2 (1.0)	0	
Yes enema	77 (37.2)	26 (12.6)	**0.00***
No	52 (25.1	50 (24.2)	
Operative			
Open vs. closed LIS, n (%)			
Open	117 (89.3)	45 (59.2)	0.000*
Closed	13 (9.9)	31 (40.8)	
Sphincterotomy size, n (%)			
Complete	34 (26)	10 (13.2)	
Partial	86 (65.6)	51 (67.1)	0.009*
Tailored	10 (7.6)	15 (19.7)	
Anacutaneous incision, n (%)			
Transverse	63 (48)	43 (57)	0.240
Vertical	68 (52)	33 (43)	
Hypertrophied papillae-skin tag excision, n (%)			
Yes	70 (33.8)	38 (18.4)	
No	30 (14.5)	19 (9.2)	0.00*
Sometimes	31 (15.0)	19 (9.2)	
Fissurectomy, n (%)			
Yes	19 (14.5)	17 (22.4)	
No	95 (72.5)	44 (57.9)	0.894
Sometimes	17 (13)	15 (19.7)	
Dividing internal sphincter with, n (%)			
Scalpel	16 (12.2)	16 (21.1)	
Scissors	9 (6.9)	13 (17.1)	0.008*
Electric diathermy	106 (80.9)	46 (60)	
Cauterize/curretage the fissure floor, n (%)			
Yes	49 (37.7)	31 (41.9)	
No	64 (49.2)	31 (41.9)	0.581
Sometimes	17 (13.1)	12 (16.2)	
Position, n (%)			
Lithotomy	103 (78.6)	50 (65.8)	0.043*
Jacknife	28 (21.4)	26 (34.2)	
Anesthesia, n (%)			
Local	15 (11.5)	19 (25)	
Spinal	68 (51.9)	40 (52.6)	
Laryngeal mask	43 (32.8)	12 (15.8)	0.021*
General anesthesia	5 (3.8)	5 (6.6)	
Retractor, n (%)			
None	41 (31.3)	7 (9.2)	
Anal speculum	75 (57.3)	31 (40.8)	
Park	3 (2.3)	13 (17.1)	0.000*
Hill ferguson	8 (6.1)	15 (19.7)	
Other	4 (3.1%)	9 (11.8)	
Postoperative			
Anal tampon, n (%)			
Yes	67 (51.1)	32 (42.1)	0.192
No	63 (48.1)	44 (57.9)	
Sitz bath, n (%)			
Yes	78 (59.5)	54 (71.1)	0.097
No	53 (40.5)	22 (28.9)	

*: Statistically significant differences in bold, LIS: Lateral internal sphincterotomy.

DISCUSSION

The results of this international survey highlight the lack of a standardized surgical technique for LIS. Despite this heterogeneity, LIS continues to yield high success rates, raising questions about which aspects of the procedure are truly critical for outcomes. There is no general agreement on many subjects regarding the LIS technique. It appears that there are no established standards in certain aspects, and a variety of techniques are implemented in clinical practice. The high success of a technique with such different applications is an interesting phenomenon. Isn't the devil in the details? Or, regardless of the details, is adequate cutting of the internal sphincter the most important factor determining success, and do the surgeons have the freedom they desire when performing their surgeries?

One of the controversial issues regarding LIS is the incision technique. The procedure can be performed in either an open or a closed manner. In the open approach, the anoderm is incised to visualize and divide the internal sphincter muscle directly. In contrast, the closed technique involves inserting a blade beneath the anoderm or into the intersphincteric space, allowing the sphincter to be divided without extensive incision of the anal mucosa. Based on high-quality evidence, there is no significant difference between the two techniques in terms of the rate of healing or incontinence. Open sphincterotomy has been associated with higher postoperative pain and a delayed healing rate of the surgical site (6).

The current ASCRS guideline states that both techniques can be used at the surgeon's discretion (2). While this suggestion has been adopted by the international group, participants in the Turkish group mainly preferred the open technique. There was no relationship between the choice of technique outside the country and the surgeon's age, gender, or experience.

The extent of the sphincterotomy also remains controversial. Complete or longer sphincterotomy divides the internal anal sphincter muscle to the level of or just proximal to the dentate line. The tailored, or partial sphincterotomy, divides the internal anal sphincter only to the level of the apex of the fissure.

Based on the evidence, tailored sphincterotomy yields similar healing rates but lower FI rates compared with complete LIS (7,8). Many guidelines state recommendations in favor of partial sphincterotomy, which is safer in terms of fecal incontinence (2,3,9,10). According to survey results, while complete sphincterotomy still accounts for 25% of procedures among surgeons in Türkiye, all surgeons focus on limited sphincterotomy in partial or tailored forms due to the risk of fecal incontinence.

There is a complete disagreement in approach on some details. Although circumferential or transverse incisions have been found to be advantageous in studies (11), when comparing the skin incisions used for lateral internal sphincterotomies, half of the surgeons prefer the vertical incision, and the other half prefer the transverse incision.

According to some studies, hypertrophied anal papillae, fibrous anal polyps, and skin tag excision increase patient satisfaction after anal fissure surgery (12). The issue of excision of skin tags and hypertrophied anal papillae or additional fissurectomy performed during the procedure, as well as the surgeons' tendencies, are unclear based on survey results.

Although anal manometry could detect anal tone more accurately than digital rectal examination, the impact of preoperative manometry on the outcome of anal fissure surgery is still unclear and a subject of debate. There is little guidance on how anal manometry can be used before LIS or in anal fissure management. The Italian guideline recommends that in patients with chronic anal fissures who are poorly responsive to medical therapy, an anorectal manometric evaluation may be considered to select patients without internal sphincter hypertonia (10) accurately. In the last published survey (13), almost half of the surgeons believed that manometry should be included in anal fissure management, while in our survey, more than 90% of surgeons did not use anal manometry before LIS in clinical practice.

In recent years, many studies have been published evaluating surgeons' attitudes toward the management and treatment of anal fissures (14-17). The main focus of our study is on identifying differences among LIS surgical techniques. Naturally, when comparing the results of our study with those of a recent survey that included limited questions about surgical technique, differences emerged regarding sphincterotomy technique and size.

Study Limitations

This study has several limitations. Primarily, being a questionnaire-based design, its findings may lack the robustness of data obtained through prospective or randomized controlled trials. Additionally, the sample size is relatively limited. Although the research aims to explore global practices and preferences regarding LIS, the inclusion of surgeons from 22 countries—some represented by only a small number of participants—restricts the possibility of conducting detailed subgroup analyses based on country. Nonetheless, the fact that participating surgeons have substantial experience in managing anal fissures adds credibility to the findings.

One limitation is the inability to report a response rate. Due to the open and anonymous distribution of the survey through professional networks and social media platforms, the total number of recipients could not be determined, and therefore, the response rate could not be calculated.

Furthermore, there is a potential for selection bias introduced by the method of survey dissemination. The questionnaire was distributed via open channels, including WhatsApp groups and professional mailing lists, which may have disproportionately reached surgeons with a specific interest in colorectal surgery. As a result, the responses may not fully represent the broader surgical community. To ensure transparency, both the English and Turkish versions of the survey have been provided as supplementary material.

CONCLUSION

According to ASCRS recommendations, LIS may be offered to selected pharmacologically naïve patients with chronic anal fissures. However, in real-world settings, 4.0% of anal fissures undergo surgical intervention. If the most effective treatment for anal fissure is still LIS, shouldn't we standardize the most appropriate version of the technique and pass it on to younger generations?

Ethics

Ethics Committee Approval: Approval for conducting the study was obtained from the Clinical Ethics Committee of Ankara University Medical Faculty (date: 13/10/2022, number: 2022000546/i09-575-22).

Informed Consent: N/A.

Acknowledgement

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Footnotes

Author Contributions

Concept – N.Ş., C.A.; Design – N.Ş., C.A., B.B.; Materials – N.Ş., C.A., B.B., H.M.; Data Collection or Processing – N.Ş., C.A., B.B., H.M.; Analysis or Interpretation – N.Ş., C.A., B.B., H.M.; Literature Search – N.Ş., C.A., B.B., H.M.; Critical Review – N.Ş., C.A., B.B.; Writing – N.Ş., C.A.

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

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ORIGINAL ARTICLE
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Unveiling the secrets of the profunda femoris artery: A cadaveric journey with morphometric insights

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ABSTRACT

Objective: Profunda femoris artery (PFA), a branch of femoral artery primarily supplies blood to skin, muscles of the inner thigh and proximal femur and plays a significant role in collateral blood supply. This study aimed to investigate the origin, branching pattern and morphometries of PFA in cadavers.

Material and Methods: Lower limbs of male and female cadavers (n=41) were analyzed for origin of PFA, lateral circumflex artery (LCFA) and medial circumflex artery (MCFA), distance from mid-inguinal point, course, branching pattern and their external calibers. Data were tabulated and analyzed using SPSS.

Results: The PFA showed origins that are posterolateral, posteromedial, and posterior. The distance between PFA and the midpoint of the inguinal ligament was (L=3.7-6.2; mean =5.19±0.7 cm; R=3.2-6.2 cm, mean =4.74±0.9 cm). The origin of MCFA was medial (R=61%, L=52%) and posteromedial (R=39%, L=48%); LCFA was lateral (R=100%, L=78%) and posterolateral (R=0%, L=22%). The average diameter of PFA, MCFA, & LCFA was (L=5.04, 2.9, 2.8 cm and R=5.4, 3.09, 3.71 cm). The paired t-test with a significant p-value (95% confidence) demonstrated that differences in the diameters of the arteries at the specified levels between the left and right limbs could have clinical implications, such as differences in blood flow or susceptibility to vascular conditions.

Conclusion: To reduce intra-operative and post-operative complications in the femoral region branches during diagnostic and surgical procedures, it is essential to comprehend the normal and variant positions and distances of the PFA's origin and its circumflex branches.

Keywords: Profunda femoris artery, circumflex artery, variations, vascular

INTRODUCTION

Profunda femoris artery (PFA) is the first and largest branch of femoral artery (FA). It is also known as the deep femoral artery (DFA), which arises mostly postero-laterally from the FA, 3.5 cm distal to the inguinal ligament. It spirals posterior to the superficial FA and femoral vein to reach the medial side of the femur. Near the distal third of the thigh, it perforates the adductor magnus muscle, providing the principal supply to the adductor and flexor muscles of the thigh.

PFA branches from the FA. The branching may be on the lateral, medial, or dorsal aspect of FA. The branches of PFA include circumflex arteries, both lateral and medial [lateral circumflex artery (LCFA) and medial circumflex artery (MCFA)], and three to four perforating muscular arteries, namely, perforans prima, perforans secunda, and perforans tertia (Figure 1). LCFA arises near the root of Profunda femoris and traverses the anterior and posterior branches of the femoral nerve, subsequently branching into its ascending branch, transverse, and descending branches. The lateral circumflex femoral artery (LCFA) measures 5 mm in diameter and is more prominently developed compared to the MCFA and hence is robust (1,2). MCFA arises from the posteromedial side of the PFA. It rarely arises from FA. The diameter of MCFA is around 4 mm. When the artery reaches the upper edge of the adductor magnus muscle, it splits into two branches: Transverse and ascending. These branches then connect with other arteries: The lateral LCFA, the inferior gluteal artery, and the first perforating branch of the PFA. These connections (anastomoses) help ensure a continuous blood supply to the surrounding muscles and tissues, even if one pathway is blocked or damaged.

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The head and neck of the femur are supplied by the LCFA and the Medial circumflex FA, MCFA. The important anastomoses, such as trochanteric, spinous, cruciate, and chain anastomoses, are formed by the branches of PFA (3).

PFA acts as the crucial collateral channel between the common iliac artery and the FA, extending to the distal end. The role of PFA in atherosclerotic occlusive disease, i.e., in the occlusion of the FA, is well documented in the formation of collateral arteries. These collaterals are formed among the artery of the knee joint, popliteal, its branches, and iliofemoral artery (4).

The PFA is traditionally used for other surgical purposes, while its branches are used in anterolateral perforator thigh flaps as a long vascular pedicle, during breast reconstruction after mastectomy. Knowledge on any deviation from the typical arterial pattern or structure is helpful during heart catheterization, diagnostic angiography (5), and surgeries for embolism.

Understanding the origin of the LCFA is crucial for administering anesthesia to the femoral nerve, performing orthopedic hip and femur surgeries, harvesting the anterolateral thigh flap for reconstructive surgery, and conducting bypass procedures (aorto-popliteal, intra and extra cranial, and coronary artery).

It is imperative to have a thorough understanding of the course of the MCFA during femoral osteotomies to avoid iatrogenic vascular necrosis of the head of the femur, flap reconstruction surgery, intervention radiology, and other procedures.

The study aimed in identifying the source and point of origin of PFA, measuring the distance of origin from bony landmarks, origins of MCFA and LCFA in addition to measuring the external calibers of PFA, LCFA and MCFA, analyses the statistical significance of the data.

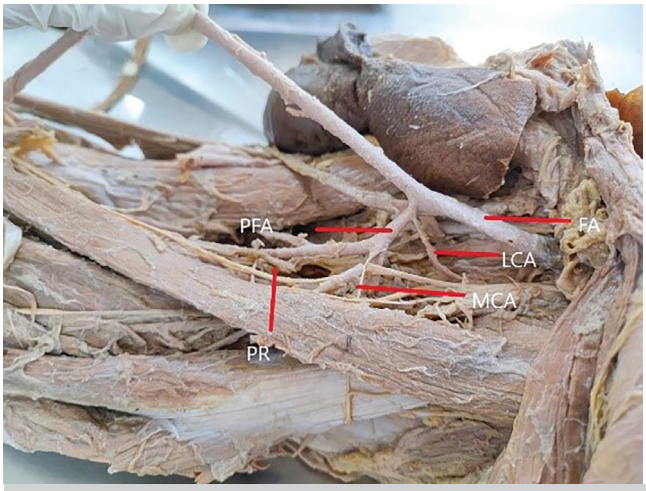


Figure 1. PFA-normal course.

FA: Femoral artery, PFA: Profunda femoris artery, LCFA: Lateral circumflex artery, MCFA: Medial circumflex artery, PR: Perforator

MATERIAL and METHODS

Meticulous dissection of 41 formalin fixed lower limb preserved specimens was carried out. An incision was made on the front of the thigh. The skin was lifted. Following this, the superficial fascia was reflected. After the identification of the long saphenous vein, the lymph nodes of the inguinal region were identified and an incision of the fascia lata was carried out to expose the femoral triangle. FA and its branches were uncovered. The PFA, along with its medial and lateral circumflex branches, was meticulously dissected. The distance from the mid-inguinal point to the origin of the PFA was precisely measured with calipers. The distance from the origin of the PFA to the pubic tubercle and the anterior superior iliac spine was measured. The diameter of the PFA, MCFA, and LCFA was measured.

All the measurements were taken in triplicate to avoid errors. Mapping of variations in branching pattern and their relation to adjacent muscles was recorded, i.e., topographic analysis.

The study design was approved by the Ethics Review Board of the Institutional Human Ethics Committee (CARE IHEC-II) (number: IHEC-I/1163/22, date: 08.08.2022). Informed consent is not applicable for this study as it was conducted on cadavers used for study purpose.

Statistical Analysis

The data obtained were entered in an Excel sheet and tabulated. SPSS software was used for tabulated data analysis. The mean, standard deviation, and standard error of the mean was calculated. Student's t-test was used to compare the means among the groups. A p-value of less than 0.05 was deemed statistically significant.

RESULTS

PFA and Its Branches

The PFA emerges from the FA posterolateral side. Originating from the lateral side of PFA is the LCFA. The medial circumflex FA emerges from the medial side PFA.

Site of Origin of PFA

The origin of PFA was from the FA (100%); no case arose from the external iliac artery. In the current investigation, three distinct PFA originating sites were identified.

On the right side, 12 cases were found to arise from the posterolateral aspect (67%) and 6 cases from the posteromedial aspect (33%). On the left side, 17 cases were found to arise from the posterolateral aspect (74%), 4 from the posteromedial aspect (17%), and 2 (9%) from the posterior aspect. We could not find any cases arising from the anterolateral aspect (Table 1).

Table 1. Origin of PFA			
S. no	**Posterior aspect (%)**	**Posterolateral aspect (%)**	**Posteromedial aspect (%)**
Right limb	-	67 (n=12)	33 (n=6)
Left limb	9 (n=2)	74 (n=17)	17 (n=4)
PFA: Profunda femoris artery.			

Pattern of Origin of PFA

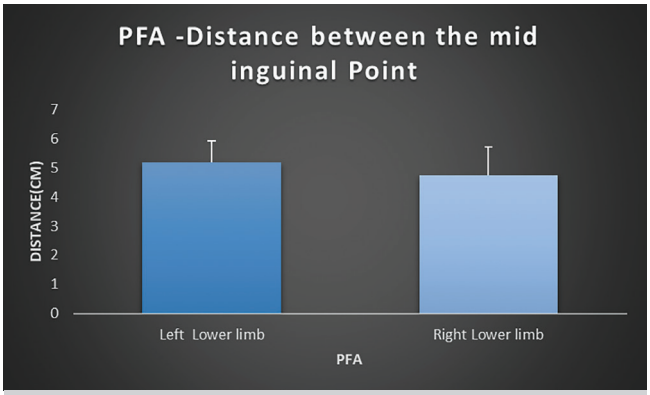
Diverse PFA origination patterns were observed in the study. In 11% of cases, the PFA on the right side originated from a common trunk with the medial circumflex femoral artery (MCFA), and in another 11%, it originated from a common trunk with the LCFA. In 26% of the cases on the left side, PFA originated as a common trunk with MCFA, and in 8.7% as a common trunk with LCFA. No instances of trifurcation were observed in either the right or left lower limb.

Origin of PFA-distance Between Mid Inguinal Point

The intervening space between PFA origin and mid-inguinal point (halfway distance between pubic symphysis and anterior superior iliac spine) was 3.7-6.2 cm in left limbs and 3.2-6.2 cm in right limbs, with mean measurements of 5.19±0.7 cm for the left limbs and 4.74±0.9 cm for the right limbs (Table 2, Graphic 1).

Site of Origin of MCFA

The origin of MCFA is 61% medial and 39% posteromedial (in the case of the right limb) and 52% medial and 48% posteromedial (in the case of the left limb). 11% in the case of the right limb arose directly from the femoral artery, and 26% in the case of the left limb arose directly from the femoral artery.



Graphic 1. Mean distance and SD from mid inguinal point with error bars.

SD: Standard deviation, PFA: Profunda femoris artery

Site of Origin of LCFA

The origin of LCFA is 100% lateral in the case of the right limb, and 78% lateral, and 22% posterolateral in the case of the left limb. 11% in case of right limb arose directly from FA and 26% in case of left limb arose directly from Femoral artery. 77% of LCFA arose distal to MCFA in the right limb, and 78% arose distal to MCFA in the left limb.

Double MCFA/LCFA

2MCFA were identified in one of the left lower limbs whereas a total of 2 duplicate LCFA were identified in another lower limb (Figure 2).

Comparative Analysis of Diameter of PFA, MCFA and LCFA

The average diameters of PFA at origin; diameter of MCFA; and diameter of LCFA were 5.04, 2.9, and 2.8, respectively, for the left limb and 5.4, 3.09, and 3.71, respectively, for the right limb (Table 3, Graphic 2). The paired t-test conducted for the diameters of PFA at the level of P1, P2, and P3 (perforator arteries) at the 95% confidence value revealed the p-value to be significant for Pairs P1, P2, and P3 for the left and right legs.

DISCUSSION

Variations were observed at the site of origin of PFA. The site of origin of PFA on the right limb was 63% in the posterolateral aspect and 37% from the posterior aspect, whereas for the left limb, it was 75% in the posterolateral aspect, 17% in the posteriormedial aspect, and 8% from the posterior aspect (Table 1). These findings are similar to the study by Rajani et al. (6). One possible explanation for variations in the PFA genesis site is variations in the rete femorale's regression pattern as an influencing factor during embryogenesis (7).

PFA's position with respect to FA is crucial because its postero-lateral orientation facilitates access, keeping FA and other structures out of the way. The medial proximity of the femoral vein to the FA poses a threat because an injury to this vein is probable, making the lateral zone of the FA more secure than the medial or posteromedial regions.

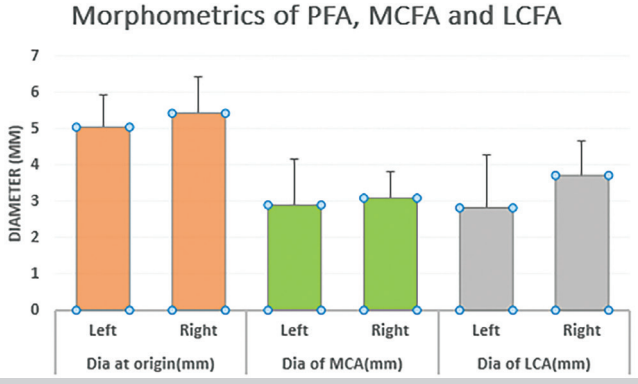
Table 2. Mean distance and SD from mid inguinal point				
S. no	**Distance from mid inguinal point (cm)**	**Range (upper and lower limit)**	**Standard deviation**	**Standard error of mean**
Left (n=23)	5.1913	3.70-6.20	±0.7321	0.18761
Right (n=18)	4.7406	3.20-6.20	±0.969	0.23455

Table 3. External caliber of PFA, MCFA and LCFA			
S. no	**Diameter at origin (mm) with SD**	**Diameter of MCFA (mm) with SD**	**Diameter of LCFA (mm) with SD**
Left (n=23)	5.0443±0.899	2.9±1.249	2.82±1.45
Right (n=18)	5.4261±0.99513	3.09±0.473	3.71±0.944

SD: Standard deviation, PFA: Profunda femoris artery, LCFA: Lateral circumflex artery, MCFA: Medial circumflex artery.

Figure 2. Variation-LCFA-right limb showing double lateral circumflex artery.

FA: Femoral artery, PFA: Profunda femoris artery, LCFA: Lateral circumflex artery, MCFA: Medial circumflex artery, PR: Perforator



Graphic 2. External caliber of PFA, MCFA and LCFA.

PFA: Profunda femoris artery, LCFA: Lateral circumflex artery, MCFA: Medial circumflex artery

PFA, with its most important branch, the lateral circumflex, facilitating collateral development, often preserves limbs in cases of atherosclerotic illness and major artery diseases involving the aorto-ileofemoral segments because of its rich collateralization (8).

The length of separation between the origin of PFA and the mid-inguinal point was 3.7-6.2 cm in left limbs and 3.2-6.2 cm in right limbs. The average measurements were 5.19±0.7 cm on the left limbs and 4.74±0.9 cm on the right limbs. This varies with the study by Nasr et al. (1), where a mean of 5.15±0.19 cm on the right side and 4.97±0.19 cm on the left side was recorded, and also with the study by Chauhan et al. (9), where 3.1-4.0 cm on the right and 2.1-3.0 cm on the left with a mean of 3.01 cm was recorded. The FA is frequently used for catheterization and angiography procedures. Thus, it is crucial to be aware of the original location and relative height of the PFA, especially its high origin, in order to prevent the potential for iatrogenic damage that could occur during therapeutic or diagnostic operations.

This study showed PFA branching pattern of type-1, type-2, but did not record any type-3 pattern as per the classification of Vazquez et al. (10). A study by Kumar and Murlimanju (11) recorded three types or patterns 1, 2, and 3 having 56%, 40%, and 4% cases, respectively.

There exist six distinct variations of the MCFA and LCFA as described by Łabętowicz (12). Haemorrhagic shock and catastrophic bleeding are examples of intraoperative problems that can be avoided by being aware of the anatomical changes in the arterial system, particularly the MCFA and LCFA. One of the PFA's branches, the MCFA is crucial for vascularizing the femur head and neck, fatty tissue in the acetabular notch, and the medial (adductor) compartment of the thigh.

The origin of the MCFA is more proximal when it emerges from the FA than when it emerges from the PFA or LCFA. This study showed that 11% of the right limbs and 26% of the left limbs had MCFA origin directly from FA.

The origin of MCFA from FA has also been documented by Appaji and Desai (13) with an incidence of 3.3%. Studying the level of MCFA is important in orthopedic surgery as its damage may induce osteonecrosis due to avascularization of the head of the femur.

LCFA, a branch of PFA, divides into three branches, namely the ascending, transverse, and descending branches. It is helpful in anastomosis at the anterior superior iliac spine. The tensor fascia lata (a versatile muscle of the anterolateral aspect of the thigh), utilized in reparative and aesthetic procedures or surgeries, receives its robust blood supply from the LCFA. In our study, 11% of the right limbs and 8.7% of left limbs showed the origin of the MCFA directly from the FA. Also, the planning of flap dissection requires thorough pre-evaluation of the origin of the LCFA (14).

The average diameter of PFA at origin, diameter of MCFA, and diameter of LCFA is 5.04, 2.9, and 2.8, respectively for the left limb, and 5.4, 3.09, and 3.71, respectively for the right limb. This correlates with a study (15) where the DFA, the MCFA, and the LCFA had respective average sizes of 5.62 mm, 3.01 mm, and 3.44 mm. Chauhan et al. (9) compared the diameters of the PFA between the right and left lower limbs and male and female limbs but did not find any significant variation between them.

The paired t-test conducted for the diameters of PFA at the level of P1, P2, and P3 (perforator arteries) at the 95% confidence level (Table 4) revealed the p-value to be significant for Pair P1, P2, and P3 for the left and right legs. This implies that variations in the diameter of the arteries of the left and right limbs at the designated levels may have clinical consequences, such as altered blood flow or an increased risk of vascular diseases.

There were variations in the numbers of MCFAs and LCFAs. 2MCFA were identified in one of the left lower limbs, and 2 duplicate LCFA were identified in the other left lower limb. This correlates with the study of Claassen et al. (2). Vascular muscle grafts and ALT flaps are significantly impacted by the course and structural diversity of LCFA. Furthermore, it is important to consider the MCFA deviations for both artery bypass treatments and hip joint surgery techniques.

CONCLUSION

Knowledge of the origin and branches of the PFA is clinically significant in diagnostic and interventional procedures. They also aid in lowering the incidence of intraoperative and postoperative complications in the femoral area.

Continued investigations into the variations in the course of the PFA and its branches can provide deeper insights. This ongoing research can enhance the current understanding and lead to improved surgical techniques and outcomes.

By focusing on these aspects, healthcare professionals can improve both the safety and efficacy of procedures involving the femoral region, ultimately leading to better patient care and outcomes.

Table 4. Statistical analysis of the morphometric by t-test at 95% confidence level

Group			Paired differences					t	df	Sig. (2-tailed)
			Mean	95% CI						
				SD	SEM	Lower	Upper			
Left	Pair 1	Dia at origin (mm) Above P1	0.92273	0.72680	0.21914	0.43445	1.41100	4.211	10	0.002
	Pair 2	Dia at origin (mm) Above P2	1.83333	0.27289	1.11141	1.54696	2.11971	16.456	5	0.000
	Pair 3	Above P1 (mm)- Above P2	1.138	0.683	0.279	0.422	1.855	4.083	5	0.010
Right	Pair 1	Dia at origin (mm) Above P1	1.06900	1.26865	0.40118	0.16146	1.97654	2.665	9	0.026
	Pair 2	Dia at origin (mm) Above P2	1.97500	0.03536	0.02500	1.65734	2.29266	79.00	1	0.008
	Pair 3	Above P1 (mm)- Above P2	1.405	0.191	0.135	-0.310	3.120	10.407	1	0.061

SD: Standard deviation, CI: Confidence interval, SEM: Standard error of mean.

Ethics

Ethics Committee Approval: The study design was approved by the Ethics Review Board of the Institutional Human Ethics Committee (CARE IHEC-II) (number: IHEC-I/1163/22, date: 08.08.2022).

Informed Consent: Informed consent is not applicable for this study as it was conducted on cadavers used for study purpose.

Footnotes

Author Contributions

Concept - H.R.; Supervision - H.R.; Data Collection or Processing - A.G.D.; Analysis or Interpretation - P.I.; Literature Search - G.K.; Critical Review- A.G.D.; Writing - A.G.D.

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ORIGINAL ARTICLE
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Are respiratory risks after cardiac surgery universal? A case study from Tuzla, Bosnia and Herzegovina

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ABSTRACT

Objective: Postoperative respiratory complications (PRCs) are a significant concern after cardiac surgery, contributing to increased morbidity and mortality. This study aimed to analyze the incidence and risk factors for PRCs in a tertiary center in Bosnia and Herzegovina and compare findings with data from developed countries.

Material and Methods: This prospective cohort study included 300 adult patients who underwent open-heart surgery with cardiopulmonary bypass at the Clinic for Cardiovascular Surgery, University Clinical Center Tuzla, between January 2020 and October 2023. Preoperative, intraoperative, and postoperative variables were analyzed, including comorbidities, surgical procedures, mechanical ventilation duration, and intensive care unit stay. PRCs were defined based on standardized clinical and radiological criteria. Multivariate logistic regression identified independent risk factors.

Results: The most common PRCs were pneumonia (37.3%), atelectasis (29.3%), pleural effusion (22.0%), and respiratory failure (10.7%). Key independent risk factors included oxygen saturation <94%, ejection fraction <45%, diabetes mellitus, anemia, and red blood cell transfusion >500 mL. In contrast to studies from developed countries, intraoperative variables were not significant predictors.

Conclusion: Our findings suggest that preoperative comorbidities play a more dominant role in PRC development in our setting compared to developed nations. The high incidence of pneumonia may reflect delayed postoperative mobilization and limited access to respiratory therapy. These results underscore the need for optimized preoperative patient management and improved postoperative respiratory care protocols in resource-limited healthcare settings.

Keywords: Postoperative respiratory complications, pneumonia, cardiac surgery, risk factors, developing countries

INTRODUCTION

Postoperative respiratory complications (PRCs) remain a leading cause of morbidity and mortality following cardiac surgery, significantly impacting patient outcomes and healthcare resource utilization. The incidence of PRCs varies widely across studies, with reported rates ranging from 2.1% to 21.6% in developed countries, while some studies from resource-limited settings suggest even higher rates (1,2). PRCs are associated with prolonged mechanical ventilation, increased intensive care unit (ICU) stay, and higher in-hospital mortality (15-45%), making their prevention and management a priority in perioperative care (3). The European Perioperative Clinical Outcome guidelines define PRCs as a spectrum of conditions, including pneumonia, atelectasis, pleural effusion, pneumothorax, bronchospasm, aspiration pneumonitis, acute respiratory distress syndrome, and pulmonary embolism (4). These complications are particularly prevalent in elderly patients and those with significant preexisting comorbidities, further complicating postoperative recovery (5,6). The development of PRCs is multifactorial, influenced by a combination of preoperative, intraoperative, and postoperative factors. Preoperative risk factors such as smoking, chronic obstructive pulmonary disease (COPD), diabetes mellitus, low ejection fraction (EF), and anemia have been widely recognized (7,8). Intraoperative factors, including prolonged cardiopulmonary bypass (CPB) time, anesthesia, blood transfusions, and fluid overload, also contribute to postoperative pulmonary dysfunction (9-11). Postoperatively, factors such as mechanical ventilation duration,

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delayed extubation, and ICU-acquired infections further increase the risk of PRCs (12). Despite advancements in perioperative management, PRCs continue to pose a challenge in both developed and developing countries. However, differences in healthcare infrastructure, patient populations, and perioperative protocols may result in variability in risk factors and outcomes. While studies from high-resource settings emphasize intraoperative and postoperative factors, emerging evidence suggests that preoperative comorbidities may play a more dominant role in developing countries (13,14). This study aims to analyze the incidence and risk factors for PRCs in patients undergoing cardiac surgery at a tertiary center in a developing country and compare the findings with studies from developed nations. Identifying modifiable risk factors specific to our patient population may help guide preventive strategies and optimize perioperative management to improve outcomes.

MATERIAL and METHODS

This prospective cohort study included 300 consecutive adult patients who underwent open-heart surgery with CPB at the Clinic for Cardiovascular Surgery, University Clinical Center Tuzla, between November 2020 and October 2023. The study was conducted in accordance with ethical principles and was approved by the Ethics Committee of the University Clinical Center Tuzla (approval no: 02-09/2-65/20, date: November 4, 2020).

Inclusion criteria: Adult patients (≥18 years) undergoing elective or urgent coronary artery bypass grafting (CABG), aortic valve replacement (AVR), mitral valve replacement (MVR), or the Bentall procedure.

Exclusion criteria: Patients witha history of previous thoracic surgery, AMI within 30 days before surgery, or pre-existing severe respiratory failure requiring prolonged ventilation (>48 h) before surgery (Figure 1).

Data collection: Clinical and demographic data were collected from the hospital's electronic medical record system. The following variables were analyzed:

Preoperative variables: [Age, sex, smoking history, body mass index (BMI), diabetes mellitus, hypertension, COPD, left ventricular EF, hemoglobin levels (anemia), and preoperative oxygen saturation (SpO_2)]. COPD was defined according to the GOLD guidelines as FEV_1/FVC <0.7 post-bronchodilator (15).

Anemia was defined according to World Health Organization criteria as hemoglobin <13 g/dL for men and <12 g/dL for women (16). Intraoperative variables: Duration of CPB and aortic cross-clamp time, type of cardiac surgery performed, red blood cell (RBC) transfusions (>500 mL/24 h). Postoperative variables: Length of mechanical ventilation and ICU stay (≥48 h vs.<48 h). Respiratory complications including pneumonia, atelectasis, pleural effusion, pneumothorax were assessed according to the ERS/ESICM/ESCMID/ALAT guidelines (17). Pneumonia was defined based on radiographic evidence of new infiltrates and at least two of the following criteria: Fever >38°C, leukocytosis (>12×10^9/L), purulent respiratory secretions, and positive microbiological cultures from endotracheal aspiration. Atelectasis, pleural effusion, pneumothorax, and pulmonary edema were diagnosed using chest radiography and clinical criteria.

Statistical Analysis

Descriptive statistics: Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as percentages. Comparative analysis: Student's t-test was used for continuous variables, and the chi-square test was used for categorical variables. Multivariate logistic regression: Variables with p<0.1 in univariate analysis were included in a multivariate model to identify independent predictors of PRCs. A p-value <0.05 was considered statistically significant. Software used: All statistical analyses were performed using IBM SPSS statistics version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Among the 300 patients included in the study, 211 (70.5%) were male and 89 (29.5%) were female. The mean age of male patients was 61.35±15.2 years, while the mean age of female patients was 55.43±12.9 years. The distribution of surgical procedures was as follows: CABGfor 98 patients (32.7%), AVR for 69 patients

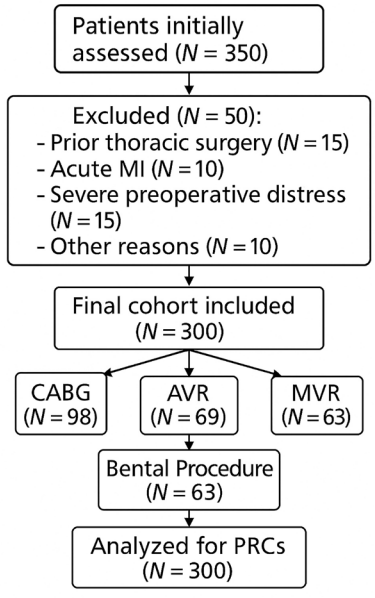

Figure 1. Flowchart of patients selection and data collection.

CABG: Coronary artery bypass grafting, AVR: Aortic valve replacement, MVR: Mitral valve replacement, PRCs: Postoperative respiratory complications

(23.0%), MVRfor 34 patients (11.3%), and Bentall procedure for 63 patients (21.0%).

Table 1. Distribution of postoperative respiratory complication in the study population

Complications	Patients (no)	Percentage (%)
Pneumonia	112	37.3
Atelectasis	88	29.33
Pleural effusion	66	22.00
Respiratory failure	32	10.66
Pulmonary edema	17	5.66
Pneumothorax	9	3.00

PRCs were observed in a significant proportion of patients (Table 1). The most common were pneumonia (37.3%), atelectasis (29.3%), pleural effusion (22.0%), followed by respiratory failure (10.7%), pulmonary edema (5.7%), and pneumothorax (3.0%). The incidence of pneumonia in our study was considerably higher than reports from developed countries.

Univariate analysis identified several preoperative risk factors significantly associated with the development of PRCs, including smoking, diabetes mellitus, COPD, elevated BMI, reduced EF, anemia, and low oxygen saturation. Conversely, age and urgency of surgery were not found to be significant predictors (Table 2).

Table 2. Univariate analysis of preoperative risk factors for postoperative respiratory complications

Variable		Patients (no)	30-day morbidity	OR (CI-95%)	p-value
Sex					
	Men	211	114	2.40	0.05
	Women	89	60		
Smoking					
	Yes	157	147	3.97	0.001
	No	143	25		
Age					
	<65 yr	159	100	1.49	0.05
	>65 yr	141	74		
Diabetes mellitus					
	Yes	151	135	5.00	0.001
	No	149	41		
Hypertension					
	Yes	244	148	3.75	0.01
	No	56	26		
COPD					
	Yes	82	56	2.00	0.049
	No	218	118		
BMI					
	<25 kg/m^2	199	134	3.33	0.029
	>25 kg/m^2	101	40		
EF <45%					
	Yes	18	11	5.32	0.001
	No	282	7		
[b]Anemia					
	Yes	31	25	4.54	0.01
	No	269	149		
Oxygen saturation					
	<94%	58	50	6.48	0.015
	>94%	242	124		
Urgent procedure					
	Yes	24	15	0.81	0.05
	No	276	159		

EF: Ejection fraction, [b]: Definition of anemia has been updates accorfing to the WHO recommendations (Hb <13 g/dL for men and <12 g/dL for non-pregnant women, Htc <38% for men and <36% for women), OR: Odds ratio, Hb: Hemoglobin, WHO: World Health Organization, CI: Confidence interval, Htc: Hydrochlorothiazide, BMI: Body mas index, COPD: Chronic obstructive pulmonary disease.

Univariate analysis identified, several intraoperative and postoperative factors significantly associated with PRCs, including prolonged operation duration, increased RBC transfusion volume, extended mechanical ventilation, and longer ICU stay. Conversely, CPB duration and pleural cavity opening did not demonstrate statistical significance (Table 3).

Multivariate logistic regression analysis identified preoperative hypoxia SpO_2 <94% (p=0.015), reduced EF <45% (p=0.001), diabetes mellitus (p=0.001), anemia (p<0.01), transfusion>500 mL (p<0.002), smoking (0.001), and hypertension (<0.01) as independent risk factors for postoperative respiratory complication (Table 4).

Table 5 presents the most common PRCs following cardiac surgery and identifies independent risk factors associated with these complications based on multivariate analysis. The data include multiple studies analyzing respiratory outcomes in different cohorts of cardiac surgery patients. The key finding from the table is that Pneumonia was the most frequently reported PRC, with incidence rates ranging from 3.0% to 37.3% across studies. Other common complications included atelectasis (10-29.3%), pleural effusion (22%), respiratory failure (10.7-21%), and pneumothorax (3-4%). Independent risk factors for PRCs included preoperative hypoxia (SpO_2 <94%), low EF, anemia, diabetes mellitus, prolonged mechanical ventilation, transfusion of RBCs (>500 mL), and reintubation.Multivariate analysis indicated that factors such as age, COPD, EuroSCORE II, and prolonged CPB time were significantly associated with higher PRC rates (p<0.05). The study reported the highest pneumonia rate (37.3%) and identified SpO_2, diabetes, and hypertension as major contributors.

Table 3. Univariate analysis of intraoperative and postoperative risk factors for postoperative respiratory complications

Variable	PRCs (%)	OR (95% CI)	p-value
Operation duration >180	34.3	2.23	<0.05
CPB >180 min	21.33	0.35	>0.05
Circulatory arrest >30 min	3.66	0.27	>0.05
Opening of the pleural cavity	19.0	0.28	>0.05
Mechanical ventilation >24 h	18.0	3.69	0.026
Transfusion>500 mL	13.0	4.35	0.022
ICU stay >48 h	30.3	2.18	<0.05

CPB: Cardiopulmonary bypass, ICU: Intensive care unite, OR: Odds ratio, CI: Confidence interval, PRCs: Postoperative respiratory complications.

Table 4. Multivariate analysis of independent risk factors for postoperative respiratory complications

Variable	OR (95% CI)	p-value
Preoperative SpO_2<94%	6.48	0.015
Ejection fraction <45%	5.32	0.01
Diabetes mellitus	5.00	0.01
Anemia	4.54	<0.01
Transfusion >500 mL	4.35	<0.02
Smoking	3.79	0.01
Hypertension	3.75	<0.01

OR: Odds ratio, CI: Confidence interval.

DISSCUSION

Our study reported a 37.3% incidence of pneumonia, which is significantly higher than rates observed in developed countries [6.26% in Piotto et al. (18), 3.1% in Allou et al. (19), and 0.58% in Naveed et al. (20)] (Table 5). Several factors may explain this discrepancy:

1. While delayed postoperative mobilization can have adverse effects, early ambulation is a key strategy for preventing pneumonia. In our setting, limitations in postoperative physiotherapy resources may have contributed to prolonged immobilization.

2. Limited respiratory therapy activation: In developed countries, standardized pulmonary rehabilitation protocols are initiated early, whereas in our center, the availability of respiratory therapists is limited.

3. Higher burden of preoperative comorbidities: Many of our patients had poorly controlled diabetes, hypertension, and pre-existing COPD, which increased their susceptibility to PRCs.

4. Variability in diagnostic criteria: While some studies required microbiological confirmation, our study relied on radiographic and clinical criteria, which may have resulted in a higher detection rate.

Preoperative vs. Intraoperative Risk Factors

A key finding in our study is that preoperative comorbidities are the dominant risk factors for PRCs, unlike studies in developed countries where intraoperative factors (CPB time, pleural cavity opening, reintubation) play a more significant role (21). Oxygen saturation <94%, EF <45%, diabetes, and anemia were the most significant independent predictors of PRCs (Table 4). Smoking, hypertension, and RBC transfusions (>500 mL/24 h) were also associated with PRCs. Intraoperative factors such as CPB duration and pleural cavity opening were not significant predictors, suggesting that our surgical techniques are comparable to those in developed countries. These findings highlight the need for improving preoperative management, including better screening for high-risk patients, early interventions for comorbidities, and optimized perioperative strategies.

Age as a risk factor: Why was it not significant? Contrary to most studies, age was not a significant predictor of PRCs in our cohort. Possible explanations include: Selection bias - younger patients with multiple comorbidities may have been included

in the surgical group, while older patients with poor prognosis may have been excluded from surgery. Differences in risk stratification - Some studies included redo surgeries, which are more common in elderly populations, whereas our study primarily analyzed first-time cardiac surgeries (22). Despite these findings, age remains an important clinical consideration and should not be disregarded in perioperative risk assessment.

Comparison with Developed Countries

Table 5 compares our findings with major studies from high-resource settings. The key takeaways include: PRC rates (especially pneumonia) were significantly higher, likely due to resource limitations, slower patient mobilization, and differences in healthcare infrastructure. Preoperative factors dominated in our study, whereas intraoperative and postoperative factors were found to be more significant in developed countries (23,24). Smoking and anemia were stronger predictors in our cohort, possibly due to higher baseline prevalence and inadequate preoperative correction (25).

Clinical Implications for Developing Countries

Based on our findings, the following strategies may help reduce PRCs in resource-limited settings: Improvement of preoperative disease control, such as better glycemic control, hypertension management, and anemia correction before surgery. Optimizing respiratory therapy - increasing the number of trained respiratory therapists and implementing standardized pulmonary care protocols (26,27).

Study Limitations

Several limitations should be considered when interpreting our findings. First, this study was conducted at a single center, which may limit the generalizability of the results to other

Table 5. Most common postoperative respiratory complications after cardiac surgery and multivariate analysis of risk factors

Author	n	Type of study	Procedure	Respiratory complications, n (%)	Independent risk factors, OR, p-value
Our study	300	Prospective	Cardiac surgery	Pneumonia, 112 (37.3) Atelectasis, 88 (29.33) Pleural effusion, 66 (22) Respiratory failure, 32 (10.66) Pulmonary edema, 17 (5.66) Pneumothorax, 9 (3)	Preoperative [c]SO_2, OR: 6.48, p<0.015 Ejection fraction, OR: 5.32, p=0.001 Diabetes mellitus, OR: 5.00, p=0.001 Anemia, OR: 4.54, p<0.01 Transfusion of [d]RBC >500 mL, OR: 4.35, p<0.002 Smoking, OR: 3.97, p=0.001 Hypertension, OR: 3.75, p<0.01
Piotto et al. (18)	2952	Prospective	[a]CABG	[b]ARDS, 11 (0.37) Pulmonary embolism, 7 (0.2) Pneumonia, 185 (6.26) Other pulmonary, 15 (0.50)	Age, OR: 1.06, p<0.001 [e]CRF, OR: 3.52, p<0.001 [f]COPD, OR: 2.65, p=0.004 CABG associated with other procedures, OR: 3.33, p<0.001 Clamping time, OR: 1.01, p=0.018
Allou et al. (19)	5582	Cohort	Cardiac surgery	Pneumonia, 174 (3.1)	Age, OR: 1.02, p=0.013 COPD, OR: 3.08, p<0.0001 Ejection fraction, OR: 0.98; p=0.009 Duration of [g]CPB, OR: 1.01, p<0.0001 Transfusion of RBC, OR: 1.67, p=0.03
Naveed et al. (20)	517	Prospective observational	Cardiac surgery	Pneumonia, 3 (0.58) Atelectasis, 20 (3.86) Respiratory failure, 8 (1.54) ARDS, 1 (0.19)	Age, OR: 4.16, p<0.001 Pre-op pulmonary hypertension, OR: 2.60, p=0.014 CPB time >120 minutes, OR: 3.62, p=0.003 Phrenic nerve injury, OR: 7.06; p=0.002
Fischer et al. (7)	676	Cohort	Cardiac surgery	Atelectasis, 111 (16) Pleural effusion, 220 (32) Respiratory failure, 141 (21%) Respiratory infection, 63 (9) Pneumothorax, 30 (4) Bronchospasm, 10 (1) Aspiration pneumonitis, 7 (1)	Age, OR: 1.09, p=0.044 EuroSCORE II, OR:1.09, p=0.010 COPD, OR: 3.14, p<0.001 CABG, OR: 0.62, p=0.016 Pressure support ventilation with PEEP, OR: 0.53, p=0.070
Urquiza et al. (3)	211	Prospective	Cardiac surgery	Pneumonia, 31 (14.6)	Hypertension, OR: 3.94, p=0.01 CRF, OR: 13.67, p=0.02 Reintubation, OR: 22.29, p=0.001 Extubation after 6 h, OR: 15.81, p=0.005

[a]CABG: Coronary artery bypass grafting, [b]ARDS: Acute respiratory distress syndrome, [c]SO_2: Oxygen saturation, [d]RBC: Red blood cells, [e]CRF: Chronic renal failure (creatinine >2 mg/dL), [f]COPD: Chronic obstructive pulmonary disease, [g]CPB: Cardiopulmonary bypass, OR: Odds ratio, CI: Confidence interval.

healthcare settings. Additionally, the diagnosis of pneumonia relied on clinical and radiographic criteria, potentially leading to an overestimation of cases. Another limitation is the lack of long-term follow-up, preventing an assessment of prolonged pulmonary outcomes. Lastly, as this was an observational cohort study, the absence of prospective trial registration highlights the need for future randomized trials to confirm these findings.

Our study identified preoperative comorbidities as the dominant risk factors for PRCs. Among them, oxygen saturation <94%, EF <45%, and diabetes mellitus were the most significant predictors. In contrast, intraoperative factors (CPB duration, pleural cavity opening) were not significant, suggesting that surgical techniques in our setting are comparable to those in developed countries. The incidence of pneumonia (37.3%) in our cohort was significantly higher than in developed countries [6.26% in Piotto et al. (18), 3.1% in Allou et al. (19), and 0.58% in Naveed et al. (20)] (Table 5). This discrepancy can be explained by delayed postoperative mobilization due to limited physiotherapy resources. There is limited access to respiratory therapy compared to standardized pulmonary rehabilitation programs in developed countries. Higher burden of preoperative comorbidities (diabetes, hypertension, COPD). Differences in pneumonia diagnostic criteria were observed, as our study relied on radiographic and clinical findings rather than microbiological confirmation (28,29). These findings emphasize the importance of optimizing preoperative risk assessment and perioperative management to minimize respiratory complications in cardiac surgery patients, particularly in resource-limited settings.

CONCLUSION

This study challenges the assumption that postoperative respiratory risks after cardiac surgery are universal. Our findings from Tuzla, Bosnia and Herzegovina, demonstrate a higher incidence of PRCs, particularly pneumonia (37.3%), compared to that in developed countries. This discrepancy suggests that risk factors and management strategies from high-resource settings may not be directly applicable to developing healthcare systems.

Unlike studies from developed nations, where intraoperative and postoperative factors play a dominant role, our results highlight preoperative comorbidities -low oxygen saturation, reduced EF, diabetes, and anemia- as the primary risk factors. These findings underscore the urgent need for tailored perioperative strategies that account for regional differences in healthcare resources, patient populations, and postoperative care protocols. Simply adopting risk models and treatment protocols from developed countries may not effectively address the unique challenges faced in resource-limited settings. To improve outcomes, a context-specific approach is essential, with emphasis on early risk assessment, preoperative optimization, structured pulmonary care, and early mobilization. Future research should focus on adapting and validating evidence-based strategies to bridge the gap between different healthcare environments and ensure more equitable surgical outcomes worldwide.

Ethics

Ethics Committee Approval: The study was conducted in accordance with ethical principles and was approved by the Ethics Committee of the University Clinical Center Tuzla (approval no: 02-09/2-65/20, date: November 4, 2020).

Informed Consent: Prospective study.

Footnotes

Author Contributions

Concept -A.K.; Design - A.K., A.S., O.K.; Fundings - A.K., A.S., I.I.; Materials - A.K., A.S.; Data Collection or Processing - A.K., A.S., O.K.; Critical Review-O.K.; Literature Search -A.S., I.I.; Writing -A.K.

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

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ORIGINAL ARTICLE
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Has the COVID-19 pandemic affected the incidence of *Helicobacter pylori* infection? Evaluation of endoscopic results in patients with dyspeptic complaints

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ABSTRACT

Objective: The coronavirus disease-2019 (COVID-19) pandemic led to widespread public health measures that reduced human-to-human contact. This study investigates the pandemic's effect on the clinical and pathological outcomes of *Helicobacter pylori* (*HP*) infection in patients with dyspeptic complaints.

Material and Methods: We retrospectively analyzed data from patients presenting with dyspepsia before the pandemic (January-December 2019) and during the pandemic (April-December 2020). Gastric biopsies were evaluated for *HP* infection and inflammation severity according to the Sydney classification. Statistical analyses compared the incidence and clinical characteristics of *HP* infection between the two periods.

Results: Among 788 patients, there was no significant difference in *HP* infection incidence or severity between the pre-pandemic and pandemic periods (p=0.51). However, more symptomatic patients presented during the pandemic, including increased cases of epigastric pain (p<0.01) and gastroesophageal reflux (p<0.001).

Conclusion: Despite social distancing measures, the incidence of *HP* infection remained unchanged. Our findings suggest that COVID-19 restrictions did not significantly impact *HP* transmission but may have influenced symptom presentation and patient healthcare-seeking behavior.

Keywords: COVID-19, gastritis, dyspepsia, *Helicobacter pylori*, hiatal hernia

INTRODUCTION

The coronavirus disease-2019 (COVID-19), identified in December 2019 in Wuhan, China, rapidly became a global pandemic, causing significant morbidity and mortality (1,2). Transmission occurs primarily in crowded areas, leading to widespread quarantine measures. *Helicobacter pylori* (*HP*), an infectious pathogen associated with gastritis, is transmitted through fecal-oral or oro-oral routes, often in public settings such as cafes and restaurants. Studies suggest its transmission is mainly interhuman and intrafamilial. The course of gastrointestinal (GI) diseases caused by *HP* is associated with many virulent factors, such as outer membrane porin proteins, flagella, and different adherence factors. They enable colonization and escape from the immune response. *HP* increases the expression of angiotensin-converting enzyme-2 (ACE-2) receptors in the GI tract, which is directly associated with the duration and severity of infection (3-7). The pandemic's restrictions on social interactions and dining out, in turn, raised questions about the restrictions' impact on *HP* transmission.

According to a cross-sectional analysis based on the population in Türkiye, more than 4600 people were tested, and a prevalence of 82.5% of the tested condition was found. In addition, the prevalence was lowest among individuals living in the southern part of the country, which has a citrus-rich diet and is the main citrus-growing area (8).

With the quarantine measures, human-to-human contact and food consumption in restaurants have decreased. Public spots have been prepared to encourage hand washing to increase personal hygiene. This strategy is based on the thought that it may restrict *HP* transmission routes.

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This study aimed to reveal whether there was a difference in HP incidence detected in gastroscopies performed on patients with dyspeptic complaints between the pandemic and pre-pandemic periods.

MATERIAL and METHODS

For the study, the date of March 2020, when the COVID-19 pandemic was announced in our country, was determined as a cut-off in determining the two groups to be compared. All patients with dyspeptic complaints who underwent gastroscopy in the endoscopy unit of Marmara University Pendik Training and Research Hospital General Surgery Department, İstanbul, Türkiye between January-December 2019 and April-December 2020 were included in the study. The patients' data in two groups were obtained retrospectively from the hospital management system electronically. Along with the patients' general demographic data, endoscopic diagnosis, pathological diagnosis, and *HP* infection severity were examined separately. The study was approved by the Marmara University Scientific Research Ethics Committee (number: 09.2024.802, date: 19.02.2024). During the study, all procedures were carried out according to the principles of the Declaration of Helsinki.

All patients were evaluated for manifestations of *HP* infection, severity of the course according to Sydney pathological criteria, and outcome of the disease process.

Patients aged 18 and older who were admitted to the endoscopy unit with dyspepsia were included in the study. Endoscopy was not performed in elective patients who were actively COVID-19-positive due to the risk of transmission. Clinical characteristics and pathological results before the pandemic (BP) were compared with patients admitted during the COVID-19 pandemic. Patients were also examined for age and gender. Endoscopic biopsy samples were transferred to the pathology laboratory under appropriate conditions. The results were evaluated according to the Sydney classification and grading system of gastritis for diagnosis (9). Criteria such as *HP* inclusion according to the Sydney system, chronic inflammation, neutrophil activity, glandular atrophy, and intestinal metaplasia were included in the pathological examination. All patients in the study, before and during the COVID-19 pandemic, were examined clinically for dyspeptic complaints (epigastric pain, gastric burn, reflux symptoms) and pathologically for the presence of gastric inflammation caused by *HP* infection, and the results were recorded. The severity of the disease in patients was graded as +, ++, +++ if *HP* inclusion was detected in biopsy materials.

Assuming 80% sensitivity/specificity, the required sample size was 264 to keep the 95% confidence interval within ±5%. Assuming the prevalence of *HP* as 50% (estimated at 55.8% in China), the total sample size was calculated to be 528.

Statistical Analysis

Parametric tests were used without the normality test due to the sample size, as justified by the Central Limit Theorem. In the analysis of the data, the mean and standard deviation, minimum and maximum values of the features, the frequency, and the percentage values were used to define categorical variables. Student's t-test was used to compare the means of two independent groups. Chi-square test statistics were used to evaluate the relationship between categorical variables. The Mann-Whitney U test statistic was used to compare the ordinal variable of the histopathological examination. The statistical significance level of the data was set at $p<0.05$. In the data evaluation, www.e-picos.com, New York software and MedCalc statistical package program were used.

RESULTS

Pathological examination confirmed that gastric inflammation and infection severity were strongly associated with *HP* presence, aligning with established literature on *HP*-related gastritis. A total of 788 patients, 434 BP (January-December 2019) and 354 during the pandemic period (P) (April-December), were included in the study. The age range was 18-85 in the BP group and 18-86 in the P group. The median age was 48 years ($p=0.37$). There were 265 women (61.1%) and 169 men (39.9%) in the BP group, and 195 women (55.1%) and 159 men (44.9%) in the P group ($p=0.09$). In the upper GI endoscopic examination, 71 patients (16.4%) were diagnosed with active gastritis, 212 patients (48.8%) with chronic gastritis, and 152 patients (35.1%) with chronic-active gastritis in the BP group. In the P group, 67 patients (18.9%) were diagnosed with active gastritis, 151 patients (42.7%) were diagnosed with chronic gastritis, and 136 patients (38.4%) were diagnosed with chronic-active gastritis. It is observed that the number of patients with chronic gastritis has decreased, and some of them have experienced an increase in symptoms or complications during the pandemic period. A significant difference was found between the groups ($p<0.01$) (Table 1).

In the endoscopic examination, 35 patients in the BP group and 36 patients in the P group were diagnosed with alkaline reflux gastritis ($p=0.25$). Hiatal hernias were detected in 143 patients in the BP group and 143 in the P group ($p=0.03$). In addition, when the hiatal hernia grade was considered, four patients in the BP group were evaluated as grade 1, 53 patients, as grade 2, 51 patients, as grade 3, and 35 patients as grade 4. In the P group, 21, 72, 35, and 15 patients were evaluated as grades grades 1, 2, 3 and 4, respectively ($p<0.001$). However, there was no significant difference between groups. More symptomatic patients were admitted during the pandemic, and endoscopies were performed on them. Despite this, the frequency of *HP* was found to be similar between groups. Although more symptomatic patients were treated, the number of patients diagnosed with

hiatal insufficiency was higher during the pandemic period. However, when the hiatal hernias were evaluated according to the grading system, a significant difference was observed, especially in grade 1 patients.

Considering the symptoms, the number of patients presenting with epigastric pain was 186 (42.9%) in the BP group and 181 (51.1%) in the P group (p<0.01). In the BP group, 131 individuals (30.2%) presented with gastroesophageal reflux, and in the P group, 149 individuals (42.1%) presented with gastroesophageal reflux (p<0.001). The number of applicants with gastric burning complaints was 82 (18.9%) in the BP group and 111 (31.4%) in the P group (p<0.001). In terms of dyspepsia, there were 193 (44.5%) patients in the BP group and 209 (59.1%) patients in the P group (p<0.001) (Table 1).

We observed that 131 patients were admitted to our hospital with complaints of gastroesophageal reflux, 82 patients with complaints of gastric burn, and 193 patients with complaints of dyspepsia. The P group determined these numbers as 181, 149, 111, and 209, respectively. There was a statistically significant difference between the groups (p<0.001). When the histopathological examination results were analysed, chronic inflammation was found in 423 patients in the BP group and 345 patients in the P group (p=0.99). Neutrophil activity was detected among 216 and 212 patients (p=0.007); glandular atrophy among 14 and 11 patients (p=0.92); and intestinal metaplasia among 28 and 24 patients (p=0.84) in the BP and P groups, respectively. *HP* was observed in 225 patients in the BP group and 191 in the P group (p=0.51) (Table 2).

The incidence of *HP* was 52.9%. In the histopathological evaluation according to the Sydney system, no significant difference was observed between the groups in the degree of chronic inflammation, neutrophil activity, glandular atrophy, intestinal atrophy, and *HP*. We observed 141 low, 175 medium,

Table 1. The effect of the pandemic process on the patient's socio-demographic and clinical status

N=788	**Total**	**Pre-pandemic (n=434)**	**Pandemic (n=354)**	**p-value**
	$\bar{x}$ ± SD	**$\bar{x}$ ± SD**	**$\bar{x}$ ± SD**	
Age	48.6±13.9	48.9±14.4	48.1±13.4	0.37
	n (%)	**n (%)**	**n (%)**	
Gender				
Male	460 (58.4)	265 (61.1)	195 (55.1)	0,09
Female	328 (41.6)	169 (39.9)	159 (44.9)	
Pathological diagnosis				
Active	147 (18.7)	71 (16.4)	67 (18.9)	**<0.01**
Chronic	330 (41.9)	212 (48.8)	151 (42.7)	
Chronic-active	311 (39.4)	152 (35.1)	136 (38.4)	
Alkalin reflux				
+	70 (8.9)	34 (7.8)	36 (10.2)	0.25
-	718 (91.1)	400 (82.2)	318 (89.8)	
Hiatal hernia				
+	286 (36.3)	143 (32.9)	143 (40.4)	**0.03**
-	502 (63.7)	291 (67.1)	211 (59.6)	
Hiatal hernia grade				
Grade I	25 (8.7)	4 (2.8)	21 (14.7)	**<0.001**
Grade II	125 (43.7)	53 (37.1)	72 (50.4)	
Grade III	86 (30.1)	51 (35.7)	35 (24.4)	
Grade IV	50 (17.5)	35 (24.4)	15 (10.5)	
Symptoms				
Epigastric pain	367 (46.6)	186 (42.9)	181 (51.1)	**<0.01**
Reflux	280 (35.5)	131 (30.2)	149 (42.1)	**<0.001**
Gastric burn	193 (24.5)	82 (18.9)	111 (31.4)	**<0.001**
Dyspepsia	402 (51.0)	193 (44.5)	209 (59.1)	**<0.001**

SD: Standard deviation.

and 101 high *HP* intensity in total. There was no significant difference between the groups we evaluated according to *HP* intensity (Table 3).

The presence of *HP* was not significantly different between patients before and during the pandemic (p=0.51). We observed that dyspeptic complaints like abdominal pain, gastric burn, and reflux were related to *HP* and its effects on gastric mucosa as reported in the literature. We know that the presence of *HP* infection in the gastric mucosa correlates with dyspeptic complaints and affects the clinical course of the disease. Our results suggest that, pandemic limitations associated with COVID-19 precautions did not significantly decrease the presence of *HP* infection.

DISCUSSION

In December 2019, a new type of COVID-19 was detected in Wuhan, China. COVID-19 infection has become a pandemic shortly after its identification in December 2019 and is responsible for the deaths of many people all over the world and in Türkiye. Patients came up with symptoms like fever, dry cough, dyspnea, pneumonia, headache, loss of taste/smell, and abdominal pain. It has been reported that the virus may enter the cell and increase intestinal permeability and intestinal inflammation. The virus was transmitted via respiratory means, especially in crowded areas.

Table 2. Evaluation of the presence of histopathological changes

N=788	Total	Pre-pandemic (n=434)	Pandemic (n=354)	p-value
	n (%)	n (%)	n (%)	
Chronic inflammation	768 (97.4)	423 (97.4)	345 (97.4)	0.99
Neutrophil activity	428 (54.3)	216 (49.8)	212 (59.9)	**0.007**
Glandular atrophy	25 (3.2)	14 (3.2)	11 (3.1)	0.92
Intestinal metaplasia	52 (6.6)	28 (6.4)	24 (6.8)	0.84
Helicobacter pylori	417 (52.9)	225 (52.1)	191 (53.9)	0.51

Table 3. Histopathological evaluation according to the Sydney system

N=788	Total	Pre-pandemic (n=434)	Pandemic (n=354)	p-value
	n (%)	n (%)	n (%)	
Chronic inflamation				
Low	345 (44.9)	179 (42.3)	166 (48.1)	0.20
Medium	290 (37.8)	171 (40.4)	119 (34.5)	
High	133 (17.3)	73 (17.3)	60 (17.4)	
Neutrophile acitivity				
<1/3	253 (57.2)	153 (58.4)	100 (55.5)	0.79
1/3-2/3	186 (42.1)	107 (40.8)	79 (43.9)	
>2/3	3 (0.7)	2 (0.8)	1 (0.6)	
Glandular atrophy				
Low	23 (92)	13 (92.9)	10 (90.9)	0.99
Medium	2 (8)	1 (7.1)	1 (9.1)	
High	-	-	-	
Intestinal metaplasia				
<1/3	47 (90.4)	24 (85.7)	23 (95.8)	0.36
1/3-2/3	5 (9.6)	4 (14.3)	1 (4.2)	
>2/3	-	-	-	
Helicobacter pylori				
Low	141 (33.8)	70 (30.9)	71 (37.2)	0.37
Medium	175 (41.9)	97 (42.9)	78 (40.8)	
High	101 (24.3)	59 (26.2)	42 (22)	

HP is a highly contagious pathogen detected in gastritis and peptic ulcer cases. It has been suggested that chronic inflammation caused by *HP* and its toxins may play a role in the pathogenesis of gastric inflammation. *HP* is transmitted in crowded areas like households, cafes, restaurants, and other similar places. Food consumption in common areas decreased with quarantine (1,2,7,10-14).

Possible transmission routes include oral-oral and fecal-oral transmission during episodes of diarrhea or vomiting. The use of contaminated municipal tap water is also suspected of being responsible for the transmission of *HP*. *HP* has been observed to be higher within families that use non-flush toilets, outdoor toilets, outdoor water taps, and river water. Gender and age do not seem to be associated with an increased risk of infection. Indeed, living in a rural area, living in crowded homes, and having contaminated drinking water sources were risk factors for *HP* infection (8,15-22).

A meta-analysis of 18 studies revealed that endoscopy is suitable for managing dyspeptic patients. Novel endoscopic techniques enable endoscopists to observe the gastric mucosa's microscopic structures and cellular morphology in real time (23-25).

The researchers reported that the virus uses ACE-2 receptors to enter the cell. We know that these receptors are widely expressed in the intestine, and *HP* increases the expression of ACE-2 receptors in the GI tract. GI symptoms such as abdominal pain and diarrhea correlated with the presence of HP in COVID-19 patients (13,14).

We examined the relationship between *HP* and the COVID-19 pandemic. All patients were evaluated for signs of *HP* infection. The pathological findings in the gastric mucosa were investigated according to the Sydney classification. We assumed there might be a decrease in *HP* rates due to the social restrictions during the COVID-19 pandemic, but there was no significant difference. Our findings contrast with some prior studies; for instance, Xu et al. (26) reported a decline in *HP* infection rates during the pandemic, whereas our study found no significant change. This discrepancy may reflect differences in population demographics, hygiene compliance, or the predominance of intrafamilial transmission in our cohort, which could be less affected by broad social restrictions. It was observed that the COVID-19 pandemic did not significantly reduce the number of patients with dyspepsia, epigastric pain, gastric burn, and gastroesophageal reflux. The pathological findings due to *HP* infection were similar between periods. The results could not clearly distinguish the clinical differences between mild, moderate, or severe *HP* infection. The detection rate of hiatal hernia (especially grade 1) was high, and more gastric burning and reflux symptoms were observed in patients who underwent endoscopy during the pandemic. The increased detection of hiatal hernias during the pandemic, particularly grade 1, may reflect heightened healthcare-seeking behavior among symptomatic patients or prolonged exposure to reflux-aggravating factors (e.g., stress, dietary changes) during lockdowns. However, no direct causal relationship with *HP* infection was observed.

Acute and chronic immune stimulation and abnormal response to *HP*, and toxins are the basis of the dyspeptic complaints. Proton pump inhibitors (PPIs) are mostly used for the clinical management of digestive symptoms and as part of *HP* eradication therapy. Recent studies have shown that the use of PPIs increases the susceptibility to severe acute respiratory syndrome-coronavirus-2 infection and influences the risk of developing severe clinical outcomes. *HP* eradication therapy should be administered, and the results should be considered afterwards (3,4,10,27,28).

Household hygiene and staying away from crowded areas may play important roles in preventing the transmission of *HP*. Considering the widespread distribution of *HP* infection, more efforts are necessary. To understand the true scope of the pathophysiology of infection, focusing on GI manifestations.

Study Limitations

We acknowledge that our study has some limitations. Symptoms such as indigestion, heartburn, and reflux may vary depending on the sociocultural characteristics of the patients. The way symptoms are recorded may vary according to the physicians. The patients who underwent endoscopy during the pandemic were selected because they would be more symptomatic, indicating that asymptomatic *HP* infections during the pandemic would be more than those during the pre-pandemic period. Finally, it is not known whether the patients took any medication for dyspeptic complaints before and during the pandemic.

CONCLUSION

Our results revealed that gastric inflammation are strongly correlated with the presence of *HP* and may cause symptoms like epigastric pain, gastric burn, and gastroesophageal reflux. It was thought that dyspeptic complaints and *HP* infection in the gastric mucosa, may have decreased because of the measures taken due to the COVID-19 pandemic, but no significant difference was detected between the two groups in the upper GI tract endoscopies performed before and during the pandemic. In other words, the COVID-19 pandemic did not significantly reduce the spread of *HP*. Although we know much about *HP* today, investigating the underlying factors of GI complaints due to *HP* activity is crucial.

Ethics

Ethics Committee Approval: The study was approved by the Marmara University Scientific Research Ethics Committee (number: 09.2024.802, date: 19.02.2024). During the study, all procedures were carried out according to the principles of the Declaration of Helsinki.

Informed Consent: Informed consent was obtained.

Footnotes

Author Contributions

Concept - E.P., A.C.E., A.C.; Design - E.P., A.C.E., A.C.; Data Collection or Processing - E.P., Ç.A.Ç.; Analysis or Interpretation - A.C.E., Ş.C.Y.; Literature Search - A.C., Ş.C.Y.; Writing - E.P., A.C.E., Ç.A.Ç.

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ORIGINAL ARTICLE
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Incidental identification of elastofibroma dorsi in oncologic PET/CT imaging: a retrospective single-center analysis

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ABSTRACT

Objective: To evaluate the morphological and metabolic characteristics of incidentally detected elastofibroma dorsi (EFD) on F-18 florodeoksiglukoz (FDG) positron emission tomography/computed tomography (PET/CT) and their longitudinal changes in oncologic patients.

Material and Methods: We retrospectively reviewed 42 197 PET/CT scans performed at our institution between January 2019 and September 2023. EFD was incidentally identified in 20 patients (0.05%). Patient demographics, primary malignancy, lesion localization, dimensions, and maximum standardized uptake values (SUV_{max}) were recorded. Measurements were obtained before treatment and at the next 3-month follow-up. Statistical analyses included Mann-Whitney U, Shapiro-Wilk and Spearman correlation tests; significance was set at $p<0.05$.

Results: The cohort comprised 17 females (85%) and 3 males (15%) with a median age of 67 years (range, 47-83). Primary diagnoses were breast cancer (n=8, 40%) and various other malignancies (n=12, 60%). Lesions were bilateral in 75% of cases. Pre-treatment lesion size ranged from 10 to 55 mm; median SUV_{max} was 2.4 (right) and 2.5 (left). No significant differences in baseline size or SUV_{max} were observed between breast and other cancers. A moderate correlation existed between right and left SUV_{max} ($r=0.641$; $p=0.010$). After 3 months, only the left longest diameter showed a statistically significant decrease (median, 45.0 mm vs. 43.0 mm; $p=0.034$), which may reflect measurement variability or positional factors rather than true biological change. SUV_{max} values remained stable.

Conclusion: Incidentally detected EFD on PET/CT exhibits low to moderate and stable FDG uptake and predominantly bilateral localization. Recognition of its characteristic features can prevent unnecessary interventions.

Keywords: F-18 FDG PET/CT, elastofibroma dorsi, SUV_{max}, incidental tumor, oncologic imaging

INTRODUCTION

The integration of positron emission tomography/computed tomography (PET/CT) with F-18 fluorodeoxyglucose (F-18 FDG) is a valuable functional imaging technique in oncology. Initially a research tool, the fusion of PET with CT to create PET/CT facilitated its widespread clinical adoption, offering substantial diagnostic capabilities (1). This modality is crucial in oncological management, encompassing initial diagnosis, staging, restaging, treatment planning, and patient monitoring. Indeed, F-18 FDG PET/CT is routinely employed for these purposes in numerous malignancies (2). However, it is important to recognize that F-18 FDG uptake is not specific to malignant processes. As F-18 FDG is not tumor-specific, its accumulation can also occur in infectious and inflammatory conditions. Nevertheless, malignant lesions, unlike most benign lesions, often exhibit sustained tracer retention during delayed imaging phases (3). This non-specificity can lead to diagnostic challenges, as various benign conditions that demonstrate F-18 FDG uptake can mimic malignancy. For instance, tuberculosis and other granulomatous diseases such as sarcoidosis can exhibit F-18 FDG avidity comparable to that of malignant tissues, posing diagnostic difficulties (4). Elevated F-18 FDG uptake can also be seen in specific physiological states and in various benign lesions, with such benign uptake being reported in over 25% of patients undergoing PET/CT examinations.

Elastofibroma dorsi (EFD) is a benign soft-tissue neoplasm typically located in the inferior subscapular region. Although typically found there, EFD has also been documented in other locations, including the axilla, ischial tuberosity, greater

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trochanter, elbows, and rarely, the stomach, rectum, and omentum. EFD was initially described in 1961 as a slow-growing pseudotumor characterized by the proliferation of fibroblasts and the accumulation of abnormal elastic fibers (5). The reported incidence of EFD varies considerably depending on the age of the population and detection methods. Autopsy studies indicate an EFD prevalence of 7-24% in women and 11-17% in men (6,7). Furthermore, pre-elastofibroma-like morphological changes, including degenerated elastic fibers, have been noted in up to 81% of autopsy cases (7). In a study of 258 patients undergoing chest CT for unrelated reasons, EFD was identified in 2% of patients (8).

The patients with EFD are predominantly asymptomatic. Symptomatic individuals may present with shoulder pain or a palpable, enlarging soft-tissue mass (9,10). Diagnosis is often incidental and is made via CT or magnetic resonance imaging (MRI), based on characteristic imaging features (11). On CT, EFD typically appears as a lenticular, non-encapsulated mass with attenuation similar to adjacent muscle, interspersed with hypodense striations corresponding to entrapped adipose tissue (12).

F-18 FDG PET/CT is an established tool for staging, restaging, monitoring therapy response, and prognostic stratification of diverse malignancies. Its applications range from common adult cancers to pediatric malignancies, where it aids in evaluating treatment efficacy and guiding therapeutic decisions (13). Early identification of treatment-resistant diseases using non-invasive methods, such as PET/CT, is of considerable clinical importance, facilitating timely adjustments to treatment strategies (14). Nevertheless, the literature on F-18 FDG PET/CT characteristics of EFD is primarily confined to sporadic case reports (15,16). Notably, beyond static descriptions, a significant knowledge gap exists regarding potential temporal changes in EFD appearance on sequential PET/CT scans. Elucidating this temporal evolution is essential for accurately differentiating benign EFD from tumor progression, particularly in oncological patients. Therefore, this study aimed to address this gap by evaluating the longitudinal F-18 FDG PET/CT features of incidentally detected EFD in oncologic patients.

MATERIAL and METHODS

Patients

This retrospective, single-center investigation reviewed all 42,197 oncologic F-18 FDG PET/CT scans performed at our institution between January 2019 and September 2024, among which EFD was incidentally identified in 20 patients (incidence rate: 0.05%). Demographic data, primary malignancy classifications, anatomical localizations of the EFD, lesion dimensions, and maximum standardized uptake values (SUV_{max}) values were documented. This investigation exclusively evaluated patients with incidental detection of EFD on F-18 FDG PET/CT.

We obtained approval for this study from the Samsun University Ethics Committee (ethics committee approval no: GOKAEK 2025/2/18, date: 24.01.2025).

F-18 FDG PET/CT Imaging

PET/CT scans were obtained 60 minutes after the injection using an integrated scanner (Philips Medical Systems, USA). All patients fasted for a minimum of 6 hours prior to the intravenous administration of 5 MBq/kg F-18 FDG. The pre-injection blood glucose levels were measured to ensure that they were below 200 mg/dL. During the distribution phase, patients remained in a supine position in a quiet room. Initially, an unenhanced CT scan with 5 mm slice thickness from the base of the skull to the inferior border of the pelvis was performed using a standardized protocol (140 kV and 80 mA). Subsequently, the PET scan was acquired from the base of the skull to the inferior border of the pelvis (8-10 bed positions, 1.5 minutes per bed position) without repositioning the patient on the table. The patient was permitted to breathe normally during PET and CT acquisitions. F-18 FDG PET images were reconstructed with CT-based attenuation correction.

Statistical Analysis

Semiquantitative evaluation of the PET component images was conducted by measuring SUV_{max} to assess the metabolic activity of the EFD. EFD size was determined using the longest and shortest diameters of the transaxial CT component images.

All data were analyzed using STATA/MP v.16 software (StataCorp LLC, Texas, USA). The Shapiro-Wilk test was employed to assess normal distribution, and numerical variables were provided as median (25^{th}-75^{th} percentile) values. Accordingly, Mann-Whitney U test was used to compare the two groups. The association between numerical variables was evaluated using Spearman's correlation analysis, and post-treatment changes were analyzed using the Wilcoxon test. Significance was accepted at $p<0.05$ (*) for all statistical analyses.

RESULTS

A total of 20 EFD patients were analyzed. The cohort included 17 females (85%) and 3 males (15%), with an age range of 47 to 83 years. The most common primary diagnosis among patients was breast cancer (8 patients, 40%), followed by endometrial cancer (3 patients, 15%) and ovarian cancer (3 patients, 15%). The EFD lesions were bilateral in most cases (75%). Initial lesion size ranged from 10 mm to 55 mm. The SUV_{max} values were low (range: 2.0 to 6.8), typically falling between 2.0 and 3.0 (Table 1). F-18 FDG PET/CT findings revealed bone metastases were present in 3 patients (15%), while cervical and axillary lymph node metastases were observed in 3 patients (15%). One patient with malignant melanoma exhibited a subcutaneous hypermetabolic density in the left medial region (5%). One patient with ovarian carcinoma had multiple peritoneal metastatic nodes (5%). Notably, 12

Table 1. Characteristics of patients with incidentally detected elastofibroma dorsi

Patient	Age	Gender	Primary diagnosis	Localization	Size before treatment (mm)	SUV_{max} before treatment	PET/CT findings	Size after treatment (mm)	SUV_{max} after treatment
1	79	Female	Breast	Left	10×55	Left: 2.9	Normal	-	-
2	64	Female	Breast	Right	15×45	Right: 2.2	Bone & Cervical lymph node metastasis	-	-
3	62	Female	Breast	Bilateral	Right: 11×52	Right: 2.1	Bone metastasis	Right: 10×50	Right: 2.0
					Left: 12×45	Left: 2.7		Left: 12×43	Left: 2.5
4	68	Female	Myelodysplastic syndrome	Bilateral	Right: 40×52	Right: 2.4	Normal	Right: 38×52	Right: 2.5
					Left: 35×50	Left: 2.1		Left: 33×48	Left: 2.0
5	80	Female	Breast	Bilateral	Right: 40×51	Right: 2.1	Bone metastasis	Right: 41×50	Right: 2.2
					Left: 35×45	Left: 2.7		Left: 35×45	Left: 2.6
6	67	Female	Endometrium	Bilateral	Right: 32×43	Right: 2.5	Normal	Right: 30×44	Right: 2.5
					Left: 41×51	Left: 2.4		Left: 39×50	Left: 2.5
7	77	Male	Lung	Left	40×52	Left: 2.3	Cervical lymph node metastasis	-	-
8	69	Female	Colon	Right	17×35	Right: 2.6	Recurrence	-	-
9	83	Female	Breast	Bilateral	Right: 37×55	Right: 3.0	Right axillary lymph node metastasis	Right: 38×56	Right: 3.0
					Left: 33×45	Left: 2.6		Left: 33×44	Left: 2.5
10	63	Female	Endometrium	Bilateral	Right: 44×35	Right: 2.8	Normal	Right: 42×35	Right: 2.8
					Left: 40×52	Left: 2.9		Left: 38×50	Left: 2.9
11	64	Male	Ovarian	Bilateral	Right: 35×43	Right: 3.1	Multiple peritoneal metastatic nodules	Right: 34×43	Right: 3.1
					Left: 38×42	Left: 2.9		Left: 38×40	Left: 2.7
12	64	Female	Endometrium	Bilateral	Right: 26×43	Right: 2.1	Normal	Right: 25×40	Right: 2.0
					Left: 34×35	Left: 2.3		Left: 34×37	Left: 2.2
13	71	Female	Colon	Bilateral	Right: 34×43	Right: 2.1	Normal	Right: 32×41	Right: 2.0
					Left: 35×39	Left: 2.2		Left: 34×38	Left: 2.1
14	65	Female	Breast	Bilateral	Right: 42×46	Right: 2.5	Normal	Right: 42×44	Right: 2.3
					Left: 40×42	Left: 2.4		Left: 41×42	Left: 2.5
15	47	Female	Breast	Right	34×58	Right: 2.3	Normal	-	-
16	69	Female	Liposarcoma	Bilateral	Right: 37×39	Right: 3.0	Normal	Right: 38×40	Right: 2.9
					Left: 35×37	Left: 2.7		Left: 34×36	Left: 2.6
17	58	Male	Malignant	Bilateral	Right: 40×42	Right: 2.4	Subcutaneous hypermetabolic densities in	-	-
			melanoma		Left: 41×44	Left: 2.5	the left medial femur		
18	64	Female	Ovarian	Bilateral	Right: 43×45	Right: 6.8	Normal	Right: 43×45	Right: 2.0
					Left: 45×47	Left: 4.5		Left: 45×47	Left: 2.1
19	66	Female	Ovarian	Bilateral	Right: 43×45	Right: 2.0	Normal	-	-
					Left: 45×47	Left: 2.1			
20	69	Female	Breast	Bilateral	Right: 43×45	Right: 2.4	Normal	-	-
					Left: 45×47	Left: 2.5			

PET/CT: Positron emission tomography/computed tomography, SUV_{max}: Standardized uptake values.

patients (60%) had no metastatic involvement based on the F-18 FDG PET/CT findings (Table 1).

Prior to treatment, the mean lesion size was not significantly different between breast cancer and other cancers (Figure 1). Similarly, no association was observed between pre-treatment SUV_{max} values and demographic characteristics. Furthermore, there was no statistically significant correlation between lesion size and SUV_{max} values (Table 2).

Analysis of lesion size and metabolic activity before and after treatment revealed slight reductions in lesion dimensions (Table 1), although statistical significance was observed only in specific cases (Table 3). Notably, left-sided lesions showed a significant decrease in longest size after treatment (45.0 vs. 43.0 mm; p=0.034), while SUV_{max} values remained unchanged (Table 3).

Table 2. Demographic and imaging parameters associated with SUV_{max}

Variables	SUV_{max}			
	Right	p	Left	p
Age	r=-0.52[a]	0.854	r=-0.259[a]	0.351
Gender	2.4 (2.1-2.8)[b]		2.5 (2.3-2.7)[b]	
Female		0.476		
Male	2.7 (2.4-3.1)[b]		2.7 (2.5-2.9)[b]	0.477
Primary diagnosis	2.4 (2.1-2.5)[b]		2.6 (2.5-2.7)[b]	
Breast		0.679		0.680
Others	2.5 (2.1-3.0)[b]		2.5 (2.2-2.9)[b]	
PET/CT findings	2.5 (2.1-2.8)[b]	0.999	2.4 (2.2-2.7)[b]	0.165
Normal				
Abnormal	2.4 (2.1-3.0)[b]		2.7 (2.6-2.7)[b]	
Shortest dimension				
Right	r=0.188[a]	0.502	r=0.145[a]	0.606
Left	r=0.159[a]	0.571	r=0.003[a]	0.992
Longest dimension				
Right	r=-0.193[a]	0.491	r=-0.170[a]	0.544
Left	r=0.090[a]	0.749	r=0.060[a]	0.832
SUV_{max}				
Right	-	-	r=0.641[a]	0.010*
Left	r=0.641[a]	0.010*	-	-

Data were shown as median (IQR) or correlation coefficient. *: Indicates statistical significance at p<0.05, [a]: Spearman's rank correlation, [b]: Mann-Whitney U test, *: p<0.05, PET/CT: Positron emission tomography/computed tomography, SUV_{max}: Standardized uptake values, IQR: Interquartile range.

Table 3. Change of size and SUV_{max} parameters after treatment

Variable	Before	After	p
Shortest dimension			
Right	40.0 (34.0-43.0)[d]	38.0 (31.0-41.5)[d]	0.087
Left	38.0 (35.0-41.0)[d]	34.5 (33.5-38.5)[d]	0.295
Longest dimension			
Right	45.0 (43.0-51.0)[d]	44.0 (40.5-51.0)[d]	0.067
Left	45.0 (42.0-47.0)[d]	43.0 (39.0-46.0)[d]	0.034*
SUV_{max}			
Right	2.4 (2.1-3.0)[d]	2.4 (2.0-2.9)[d]	0.299
Left	2.5 (2.3-2.7)[d]	2.5 (2.2-2.6)[d]	0.201

Data were shown as median (IQR), *: Indicates statistical significance at p<0.05, [d]: Wilcoxon signed-rank test for paired comparisons, SUV_{max}: Standardized uptake values, IQR: Interquartile range.

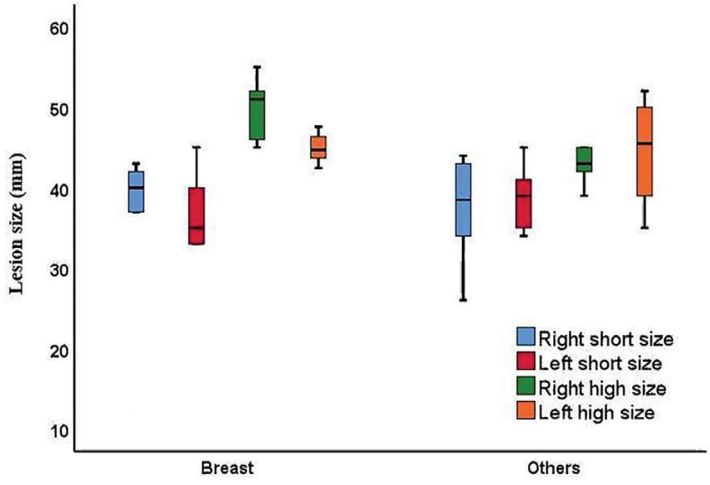

Figure 1. Box plots illustrating the distribution of elastofibroma dorsi lesion dimensions (mm) before oncologic treatment in patients with breast cancer (n=8) versus other primary malignancies (n=12). Within each main group, plots show the distribution for four different measurements: The right shortest dimension (labeled "Right short size"), the left shortest dimension (labeled "Left short size"), the right longest dimension (labeled "Right high size"), and the left longest dimension (labeled "Left high size"). Boxes indicate the interquartile range (IQR), the horizontal line represents the median, and whiskers typically extend to 1.5 times the IQR or the data range if within these limits.

DISCUSSION

EFD is a slow-growing benign connective tissue tumor that is most commonly located in the subscapular region of elderly individuals, particularly in females. With the increasing use of F-18 FDG PET/CT in oncologic imaging, incidental detection of EFD has become more frequent (5). In our study, 20 patients with incidentally detected EFD on PET/CT were analyzed. The majority were female (n=17, 85%), with an age range of 47 to 83 years and bilateral involvement was observed in 15 patients (75%). The predominance of female patients in this cohort is consistent with previous studies reporting a higher prevalence and frequent bilateral occurrence of EFD in elderly women, potentially attributable to hormonal or biomechanical influences (7,17). However, the FDG uptake observed in EFD lesions may pose a diagnostic dilemma, as it can mimic metabolically active malignant lesions. This study evaluated the characteristics of incidentally detected EFD lesions on oncologic F-18 FDG PET/CT, analyzed their temporal treatment-related metabolic behavior, and discussed their clinical implications.

Metabolic Activity and Other Imaging Characteristics

The SUV_{max} values of EFD lesions in our cohort ranged from 2.0 to 6.8, with a median SUV_{max} of 2.4 for the right site and 2.5 for the left sites (Figure 2). Literature findings support the observation that EFD generally exhibits low to moderate FDG uptake, but with a stable metabolic profile over time (9).

EFD, while benign, can mimic other soft tissue masses on imaging, necessitating careful evaluation to avoid misdiagnosis and unnecessary intervention (18). The potential for misclassification highlights the necessity of integrating clinical findings with imaging characteristics and, when uncertainty persists, pursuing tissue diagnosis to definitively exclude malignancy. A comprehensive diagnostic approach, moving beyond SUV_{max} alone, is essential to overcome the diagnostic challenge posed by variable F-18 FDG uptake in EFD. This involves the meticulous integration of key clinical indicators (such as older age, female predominance, and often asymptomatic presentation) with specific imaging patterns. Crucially, the high incidence of bilaterality, observed in 75% of our cohort, has emerged as a powerful diagnostic clue that strongly favors EFD over typically unilateral malignant lesions. When these clinical factors and the robust finding of bilaterality are combined with the characteristic morphological features on CT, the diagnostic confidence for EFD can be significantly increased, often obviating the need for invasive procedures in cases with typical presentations. Ultimately, an accurate diagnosis relies on a combination of imaging features, clinical context, and pathological correlation when necessary, which requires awareness of entities such as low-grade fibromyxoid sarcoma, which can present diagnostic challenges (19). It is essential to note that MRI excels in delineating soft-tissue lesions, relying solely on imaging studies for a definitive histological diagnosis is accurate in only a minority of cases (20). Thus, familiarity with the imaging characteristics of EFD is crucial for radiologists and nuclear medicine physicians to ensure the accurate interpretation of F-18 FDG PET/CT scans in oncologic patients. On CT imaging, EFD typically appears as a lenticular, non-encapsulated lesion with hypodense striations interspersed within the muscular tissue, corresponding to alternating fibrous and fatty components (12). On PET/CT imaging, EFD demonstrates low-to-moderate FDG uptake commonly within the 2.0-3.0 SUV_{max} range, which can help

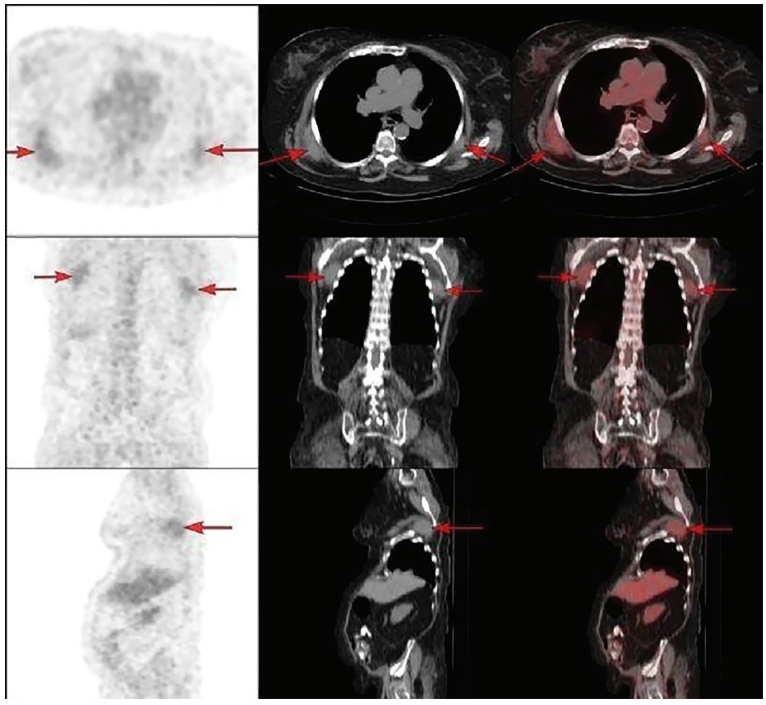

Figure 2. A 67-year-old female patient with a diagnosis of endometrial cancer underwent F-18 FDG PET/CT follow-up, which incidentally revealed findings consistent with elastofibroma dorsi (right SUV_{max}: 2.50- left SUV_{max}: 2.40). The condition manifested as mildly hypermetabolic uptake in soft tissue density within both subscapular regions (red arrows). (From top to bottom; axial, coronal, sagittal and left to right F-18 FDG PET, CT and F-18 FDG PET/CT fusion images are presented).

FGD: Florodeoksiglukoz, $SUV_{max:}$ Standardized uptake values, PET/CT: Positron emission tomography/computed tomography

distinguish it from malignant soft tissue involvement (15,16). These imaging features are crucial in differentiating EFD from malignancies, particularly in oncological patients where soft tissue metastases or sarcomas are a major concern (11).

In our study, lesion sizes ranged from 10 mm to 55 mm, with a median diameter of 45 mm observed bilaterally. However, no statistically significant correlation was found between lesion size and SUV_{max} values, suggesting that the metabolic activity of EFD is not solely volume-dependent but may be influenced by underlying histological characteristics such as stromal composition or vascularity. Importantly, 60% of the patients in our cohort exhibited no evidence of metastatic disease, emphasizing the need for caution in interpreting incidental soft tissue findings in oncologic imaging.

Collectively, these observations support the interpretation of EFD as a benign, degenerative fibroblastic process rather than a hypermetabolic neoplastic entity (7). Nevertheless, in the differential diagnosis of soft tissue lesions such as EFD, a structured approach is essential, particularly to distinguish between neoplastic and non-neoplastic entities. In this context, the World Health Organization's 2013 classification of soft tissue tumors serves as a valuable framework for guiding clinical decision-making, including the appropriate use of biopsy in diagnostically uncertain cases (21).

Pre- and Post-treatment Changes

Few studies have evaluated longitudinal metabolic changes in EFD using F-18 FDG PET/CT (22). In our study, serial 18 F-FDG PET/CT scans revealed no significant changes in SUV_{max} values before and after oncologic treatment ($p>0.05$). In our study, a statistically significant reduction was observed in the longest diameter of left-sided EFD lesions following oncologic treatment, although the absolute magnitude of change was minimal (median: 45.0 mm to 43.0 mm; $p=0.034$). While this dimensional decrease may be incidental, it raises the possibility of subtle structural remodeling in response to systemic therapy or positional factors. Interestingly, existing literature, including the case series by Erhamamci et al. (23), does not report spontaneous or treatment-associated reduction in lesion size, instead focusing on static lesion characteristics and surgical outcomes. This discrepancy may reflect differences in patient selection (symptomatic vs. oncologic surveillance populations), imaging follow-up intervals, or underlying biological behavior. Although elastofibromas are generally considered metabolically and structurally stable, our findings suggest that minor variations in lesion size can occur over time, warranting cautious interpretation. Further prospective imaging studies are needed to determine whether such dimensional changes are reproducible and clinically relevant, or simply represent

measurement variability, mechanical influences, or postural shifts during imaging acquisition.

Study Limitations

This study acknowledges several limitations. Firstly, its retrospective design intrinsically poses risks of selection bias and incomplete clinical documentation. Secondly, as a single-center study, the generalizability of our findings may be constrained by institutional imaging protocols, equipment variations, and patient population characteristics. Thirdly, the relatively small sample size (n=20) limits the statistical power of subgroup analyses, particularly concerning treatment-related changes.

Additionally, the diagnosis of EFD was based solely on imaging characteristics without histopathologic confirmation, which, while ethically justified in typical cases, limits definitive validation. In clinical practice, biopsy is not routinely performed for incidentally detected EFD with classic imaging findings; however, histological confirmation remains essential in atypical or diagnostically equivocal presentations.

Lastly, variations in treatment regimens and follow-up intervals among patients precluded standardized assessment of temporal changes in lesion behavior, thereby limiting conclusions regarding the potential impact of oncologic therapy on EFD morphology or metabolism. Future studies with a prospective design, larger cohorts, and histologic correlation are warranted to address these limitations and to better define the natural course of EFD in oncologic populations.

CONCLUSION

EFD is characterized by its bilateral subscapular localization, low-to-moderate FDG avidity, and stable metabolic behavior as observed on PET/CT, which supports its benign nature. The integration of morphologic and metabolic findings enhances diagnostic specificity and reduces unnecessary interventions. Future research should prioritize the development of standardized imaging criteria and the study of longitudinal behavior to refine oncologic interpretation.

Ethics

Ethics Committee Approval: We obtained approval for this study from the Samsun University Ethics Committee (ethics committee approval no: GOKAEK 2025/2/18, date: 24.01.2025).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Data Collection or Processing - B.K.; Analysis or Interpretation - F.B.; Literature Search - G.S.; Writing - N.B.

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ORIGINAL ARTICLE
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Risk factors for visceral artery pseudoaneurysm in chronic pancreatitis: A retrospective analysis

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ABSTRACT

Objective: Chronic pancreatitis (CP) leads to enduring abdominal pain and functional insufficiency, alongside notable risks posed by vascular complications. Pseudoaneurysms (PSA) are common in CP, necessitate careful management due to potential life-threatening hemorrhage. Literature suggests a 5-10% incidence of gastrointestinal bleeding in CP, often related to PSA affecting nearby arteries. Our study aims to evaluate the prevalence and outcomes of vascular complications in CP, aiding in improved management strategies.

Material and Methods: This retrospective observational study was conducted on the patients diagnosed with CP at a tertiary care center in Northeast India from April 2018 to December 2023. Demographic data and risk factors such as smoking and alcohol use were collected from medical records. The diagnosis and etiological assessment followed the M-ANNHEIM criteria, employing contrast-enhanced computed tomography.

Results: In our study of 86 patients with CP, predominantly male (68.6%), the median age at presentation was 37.4 years. Arterial PSAs were identified in 11 patients (12.79%), with a median onset of 18.2 months from symptom onset. Univariate analysis revealed that male sex (p=0.015), alcohol abuse (p=0.001), smoking (p=0.035), pseudocyst formation (p=0.008), and absence of parenchymal calcification (p=0.002) were significantly associated with PSA development. Interestingly, inflammatory head mass was more prevalent in patients without PSA (49.3% vs. 9.1%, p=0.02), suggesting a potential protective effect. On multivariate analysis, independent predictors of PSA formation included an alcohol abuse [odds ratio (OR): 10.75, 95% confidence interval (CI): 0.967-119.53, p=0.05], a pseudocyst presence (OR: 27.41, 95% CI: 1.591-472.39, p=0.02), and a bulky pancreatic head (OR: 12.72, 95% CI: 2.97-54.51, p=0.0006), while parenchymal calcification remained inversely associated (OR: 0.1279, 95% CI: 0.016-1.02, p=0.05).

Conclusion: Arterial PSA formation in CP is independently associated with alcohol abuse, pseudocysts, and inflammatory head mass, while parenchymal calcification appears protective. Endovascular coiling has emerged as a promising intervention, demonstrating effective management of PSA and successful prevention of hemorrhagic complications.

Keywords: Chronic pancreatitis, vascular complications, pseudoaneurysm, coil embolization

INTRODUCTION

Chronic pancreatitis (CP) is a progressive inflammatory disorder characterized by irreversible damage to the pancreatic parenchyma, leading to persistent abdominal pain and impaired endocrine and exocrine function. While the etiology of CP is multifactorial, involving factors such as alcohol abuse, genetic predisposition, and idiopathic factors, its clinical course is often complicated by the development of vascular complications (1).

Vascular complications in CP encompass a wide range of pathologies, including pseudoaneurysms (PSA), arterial thrombosis, and venous occlusions, presenting significant diagnostic and therapeutic challenges (2). Among these, visceral artery PSA is the most common arterial complication, with potentially life threatening consequences due to risk of severe hemorrhage (3). PSAs are more frequently associated with CP than with acute pancreatitis (AP), posing considerable risk of morbidity and mortality (4).

Previous studies have indicated that vascular complications, notably gastrointestinal bleeding, occur in 5-10% of patients with CP, with a significant portion attributed to bleeding from PSAs. PSAs commonly occur in the arteries near the pancreas,

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such as the gastroduodenal artery (GDA), splenic artery (SA), and superior mesenteric artery. Studies have suggested that PSAs associated with CP necessitate surgical intervention more frequently than those associated with AP (3,4).

Despite advances in diagnostic techniques and therapeutic interventions, the understanding of vascular complications in CP remains limited, particularly regarding their prevalence, risk factors, and clinical outcomes. Much of the existing literature consists of case reports and series highlighting the need for comprehensive studies to elucidate the epidemiology and impact of these complications. In this context, our study aims to investigate the vascular complications of CP through a retrospective analysis of patients managed at a tertiary care center. By examining a large cohort of CP patients, we aim to delineate the prevalence, clinical characteristics, and outcomes of vascular complications, providing valuable insights into their management and prognostic implications.

MATERIAL and METHODS

A retrospective review was conducted on all patients aged 18-75 years diagnosed with CP at a tertiary care center in Northeastern India between April 2018 and December 2022. Exclusion criteria included patients with a PSA attributable to causes other than trauma and those with prior vascular conditions. Patients >75 years old were excluded to reduce heterogeneity and potential bias from age-related comorbidities, that could influence vascular complications and outcomes. Ethical approval was obtained from the Institutional Ethics Committee of All India Institute of Medical Sciences (protocol code-IEC/2022/994, date: 14.12.2022), and the study adhered to the principles outlined in the Declaration of Helsinki as well as local and national regulations. Informed consent was taken from all participants involved in the study. The medical records were thoroughly reviewed, considering the demographic details and risk factors associated with CP, such as smoking and alcohol abuse. Alcohol abuse is defined as chronic intake >80 g/day for men and >60 g/day for women for >5 years. Contrast-enhanced computed tomography (CECT) with the pancreatic protocol has been done for the diagnosis of CP and etiological evaluation has been done according to M-ANNHEIM criteria. Notable features such as pancreatic calcifications, ductal lesions, and pseudocysts were documented. Ductal lesions included main pancreatic duct strictures, dilatation >5 mm, intraductal calculi or hypoechoic ductal nodules seen on CECT. PSA were identified via abdominal computed tomography angiography (CTA), characterised by a hyper-attenuating contrast-enhanced sac adjacent to an artery, with evidence of communication or contrast leakage from a defined vascular territory on digital subtraction angiography (DSA) (5).

Patients who presented with gastrointestinal or intra-abdominal bleeding received immediate resuscitation with intravenous fluids and/or blood transfusions as necessary. Treatment strategies were based on the patient's hemodynamic status. For hemodynamically stable patients, a CTA was conducted to assess PSA. If PSAs were detected, patients underwent DSA followed by endovascular embolization (6). If endovascular embolization was unsuccessful, patients were considered for percutaneous thrombin injection. For hemodynamically stable patients with PSAs amenable to direct percutaneous thrombin injection (i.e., large PSA with narrow neck), the procedure was performed. In cases where patients were hemodynamically unstable, they underwent surgical intervention. The size of PSAs, determined by the maximum diameter in any plane, (and their location) was documented. Patients were followed up every three months for one year to monitor their progress.

Statistical Analysis

The median and the interquartile range (IQR) were used to represent continuous data, whereas the total number of participants and proportion were used to represent categorical data. Baseline bivariate comparisons were performed after the group was stratified according to the occurrence of vascular events. When appropriate, Fisher's exact test or the chi-square test was used to test the categorical variables. After assessing if continuous variables were normal with the Shapiro-Wilk test, the Mann-Whitney U test was used. Risk factors for vascular events in CP patients were identified using a multivariable Cox proportional hazard model. Univariate analysis was performed to assess potential risk factors, with those significant in the univariate analysis included in the final multivariable model. Hazard ratios and 95% confidence intervals (CIs) were calculated. Statistical analysis was conducted using IBM SPSS, version 27.0, with a two-sided p-value of less than 0.05 considered statistically significant.

RESULTS

Table 1 presents the distribution of vessel involvement in cases of arterial PSA. Out of 86 patients, 11 were diagnosed with arterial PSA, representing a prevalence of 12.79%. SA was the most commonly involved vessel, accounting for 45.45% of cases, followed by the GDA and left gastric artery at 18.1% and 27.3% respectively. The proper hepatic artery was involved in 9.09% of cases.

Table 1. Site of arterial pseudoaneurysm (n=11)

Vessel involved	Number of cases (percentage)
Splenic artery	5 (45.45%)
Gastroduodenal artery	2 (18.18%)
Proper hepatic artery	1 (9.09%)
Left gastric artery	3 (27.27%)

Values are presented as number (%).

Table 2 presents the clinical presentation of patients with arterial PSA. The majority of cases were symptomatic (63.6%), with gastrointestinal bleeding being the most common symptom (43%). Hemorrhagic shock was observed in 28.5% of cases, while abdominal pain and decreased hemoglobin levels were reported in 14.2% of cases each. Notably, 36.36% of patients remained asymptomatic despite the presence of arterial PSAs.

Table 3 compares demographic and clinical characteristics between two groups with and without PSA. The median age at presentation was 37 years (IQR 30-45) in the PSA group and 34 years (IQR 28-42) in the non-PSA group. All patients in the PSA group were male (100%), compared to 64% in the non-PSA group (p=0.015). The median duration of symptoms was significantly shorter in the PSA group (18.2 months, IQR 10-26) than in the non-PSA group (32.4 months, IQR 18-48). Regarding etiology, alcohol abuse was markedly higher in the PSA group (90.9% vs. 22.7%, p=0.001). Smoking and pseudocysts were more common in the PSA group (36.4% vs. 12%, p=0.035) than in the non-PSA group (36.4% vs. 5.3%, p=0.008). In contrast, inflammatory pancreatic head mass and parenchymal calcification were more

Table 2. Clinical presentation of patients presented with arterial pseudoaneurysms (n=11)

Clinical manifestation	Number of cases (percentage)
Asymptomatic	4 (36.36%)
Gastrointestinal bleeding	3 (42.8%)
Haemorrhagic shock	2 (28.5%)
Abdominal pain	1 (14.2%)
Decreased haemoglobin	1 (14.2%)

Values are presented as number (%).

Table 3. Comparison of demographic and clinical profiles between patients with and without pseudoaneurysm in chronic pancreatitis

Variables	Pseudoaneurysm (n=11)	No pseudoaneurysm (n=75)	p-value
Age at presentation (years) Median (IQR)	37.7 (30-45)	34 (28-42)	0.265
Sex (male) (percentage)	11 (100%)	48 (64%)	0.015
Duration of symptoms (months), Median (IQR)	18.2 (10-26)	32.4 (18-48)	0.032
Alcohol abuse (percentage)	10 (90.9%)	17 (22.7%)	0.001
Smoker (percentage)	4 (36.4%)	9 (12%)	0.035
Pseudo cyst (percentage)	4 (36.4%)	4 (5.3%)	0.008
Inflammatory head mass (percentage)	1 (9.1%)	37 (49.3%)	0.02
Parenchymal calcification (percentage)	4 (36.4%)	60 (80%)	0.002

Values are presented as number (%), median (IQR), IQR: Interquartile range.

Table 4. Association of various risk factors with pseudoaneurysm formation (n=11)

Variables	Univariate analysis		Multivariate analysis	
	Odds (95% CI)	p-value	Odds (95% CI)	p-value
Male sex	13 (0.74-230)	0.068	-	-
Alcohol intake	34.1 (4.07-286)	0.001	10.75 (0.967-119.53)	**0.05**
Smoking	4.19 (1.02-17.2)	0.002	2.167 (0.277-16.93)	0.461
Pseudocyst	10.1 (2.07-49.7)	0.001	27.41 (1.591-472.39)	**0.02**
Inflammatory head mass	0.103 (0.0125-0.843)	0.012	12.72 (2.97-54.51)	**0.0006**
Parenchymal calcification	0.002 (0.0369-0.552)	0.002	0.1279 (0.016-1.02)	**0.05**

Values are presented as median (IQR), IQR: Interquartile range, CI: Confidence interval.

prevalent in the PSA-non-PSA group (36.4% vs. 80%, p=0.002) compared to the non-PSA group (9.1% vs. 49.3%, p=0.02).

Of the 11 patients diagnosed with PSA, the majority (n=8) were successfully managed with endovascular coiling, achieving a 100% technical success rate without procedural complications. Two patients, whose PSA were anatomically favourable for direct access and demonstrated narrow necks, underwent percutaneous thrombin injection under image guidance. Both procedures were technically successful, with complete thrombosis confirmed on follow-up imaging. One patient, who presented in a state of hemodynamic instability and was not a candidate for radiological intervention, underwent emergency surgical ligation of the bleeding vessel. All patients were monitored post-intervention in a high-dependency setting based on their clinical status. There were no recorded incidents of rebleeding, reintervention, or procedure-related morbidity during the one-year follow-up period. The median length of hospital stay among the 11 PSA patients was 7 days (IQR: 5-10 days), reflecting favorable short-term recovery following timely intervention.

Table 4 presents the univariate and multivariate analyses assessing of risk factors associated with PSA development. On univariate analysis, significant associations were observed with male sex (p=0.068), alcohol intake (p=0.001), smoking (p=0.002), presence of pseudocyst (p=0.001), bulky pancreatic head (p=0.012), and absence of parenchymal calcification (p=0.002). In multivariate logistic regression, alcohol intake [odds ratio (OR): 10.75; 95% CI: 0.967-119.53; p=0.05], pseudocyst (OR: 27.41; 95% CI: 1.591-472.39; p=0.02), and bulky pancreatic head (OR: 12.72; 95% CI: 2.97-54.51; p=0.0006) remained independent predictors of PSA formation. Conversely, parenchymal calcification demonstrated a protective effect (OR: 0.1279; 95% CI: 0.016-1.02; p=0.05).

DISCUSSION

The management of vascular complications in CP remains a significant challenge due to the complex interplay between chronic inflammation, fibrosis, and the vasculature surrounding the pancreas. Among these complications, arterial PSAs stand out due to their high mortality risk if not promptly diagnosed and treated. Our study aimed to examine the incidence, risk factors, clinical presentation, and management outcomes of PSAs in patients with CP, focusing on a cohort from a tertiary care center in Northeastern India.

In our study, we observed an incidence of arterial PSAs in 12.79% of CP patients, which aligns with the broader literature that reports an incidence range of 4-10% (7-9). This relatively high incidence may be attributed to the advanced state of CP in the study population, reflecting the progressive nature of the disease in this region. The frequent involvement of the SA, observed in 45.45% of PSA cases in our study, can be explained by its anatomical proximity to the pancreas. The repetitive inflammation and fibrosis associated with CP can erode the arterial wall, leading to PSA formation. The SA tortuous course and close association with the pancreatic tail make it particularly vulnerable. Our study identified several key risk factors associated with the development of arterial PSAs in CP patients. Alcohol abuse emerged as a significant risk factor, with a strong association observed between heavy alcohol consumption and PSA formation. This is consistent with existing knowledge that alcohol-induced pancreatitis tends to be more severe, leading to more pronounced fibrosis and inflammatory changes, which in turn increase the likelihood of vascular involvement. Mallick et al. (9) highlighted alcoholic pancreatitis as a leading cause of arterial PSA. They reported a significant association between chronic alcohol consumption, pancreatitis, and developing arterial PSAs, particularly involving the SA. The study by Maatman et al. (10) also highlighted the relationship between alcoholic pancreatitis and arterial PSAs, emphasizing a significant link between chronic alcohol, pancreatitis, and the development of arterial PSAs. Olesen et al. (7) proposed three complication clusters for CP: Inflammatory, fibrotic, and pancreatic insufficiency. The inflammatory cluster encompasses complications like pseudocysts, venous thrombosis, pseudoaneurysms, ascites, and upper gastrointestinal bleeding (7).

Smoking, another modifiable risk factor, was also significantly associated with PSA development. Smoking exacerbates pancreatic inflammation and impairs the healing process, thereby increasing the risk of complications such as PSA. This finding underscores the importance of smoking cessation as part of the management strategy for CP patients. Smoking exacerbates pancreatic fibrosis through the activation of pancreatic stellate cells and upregulation of interleukin-22 in mouse models (11). In our study, smoking was significantly associated with arterial PSA formation in univariate analysis but did not retain significance in the multivariate model. This suggests that the observed association may be confounded by other variables, such as alcohol use or pseudocyst formation. Previous studies have variably reported smoking as a contributory factor in CP-related complications; however, its independent role in vascular sequelae such as pseudoaneurysm formation remains inconclusive (12-15). Our findings align with studies where smoking did not emerge as an independent predictor, highlighting the need for further prospective research to clarify its role.

The presence of pancreatic pseudocysts was another significant risk factor identified in our study. Pseudocysts, which result from the encapsulation of pancreatic fluid collections by fibrous tissue, can exert pressure on adjacent vessels, potentially leading to erosion and pseudoaneurysm formation. This finding

is particularly important because it highlights the need for careful monitoring of patients with pseudocysts for early signs of vascular complications. Interestingly, parenchymal calcification, which is typically considered a marker of chronic pancreatic damage, was found to have a protective effect against the development of PSAs. This counterintuitive finding could be due to the stabilization of the pancreas and surrounding structures by the calcified tissue, reducing the likelihood of vessel erosion. However, further research is needed to confirm this hypothesis and fully understand the protective mechanisms involved.

The clinical presentation of PSAs in our study varied widely, with some patients presenting with acute gastrointestinal bleeding or hemorrhagic shock, while others remained asymptomatic despite the presence of sizable aneurysms. This variability underscores the importance of high clinical suspicion and routine surveillance imaging in CP patients, especially those with known risk factors (16). Endovascular coiling emerged as the primary treatment modality for PSAs in our cohort, with excellent outcomes. This minimally invasive approach offers several advantages, including the ability to precisely target the PSA, reduce the risk of rebleeding, and avoid the morbidity associated with open surgical procedures (17-21). Our findings are consistent with other studies that have demonstrated the efficacy of endovascular techniques in managing PSAs, particularly in hemodynamically stable patients. However, in cases where endovascular coiling was not feasible or failed, alternative approaches such as percutaneous thrombin injection were employed. This technique has been increasingly recognized as a viable option for treating select cases of PSAs, particularly when the anatomy is not favorable for coiling. The success of these interventions in our study highlights the importance of a multidisciplinary approach involving interventional radiologists, gastroenterologists, and surgeons to optimize outcomes for CP patients with vascular complications.

Study Limitations

Despite the valuable insights provided by our study, several limitations must be acknowledged. The retrospective design introduces potential bias due to reliance on the accuracy and completeness of medical records. The relatively small sample size restricts the generalizability of our findings, particularly concerning the prevalence and risk factors of arterial PSAs in diverse populations. Moreover, the absence of detailed data on inflammatory markers and other potential risk contributors limits our understanding of PSA pathophysiology. The observed protective effect of parenchymal calcification warrants further exploration in larger, prospective studies. Additionally, although endovascular coiling demonstrated favorable outcomes, data on its long-term durability and recurrence risk remain limited. Future research should include broader clinical and laboratory parameters and longer follow-up to refine risk stratification and treatment strategies.

CONCLUSION

In conclusion, arterial PSA formation in CP is independently associated with alcohol abuse, inflammatory head mass, and pseudocyst formation, while parenchymal calcification may offer a protective effect. These findings underscore the importance of focused surveillance in high-risk patients and support endovascular coiling as the treatment of choice, while emphasizing the need for prospective studies to optimize long-term management.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Institutional Ethics Committee of All India Institute of Medical Sciences (protocol code-IEC/2022/994, date: 14.12.2022), and the study adhered to the principles outlined in the Declaration of Helsinki as well as local and national regulations.

Informed Consent: Informed consent was taken from all participants involved in the study.

Footnotes

Author Contributions

Concept - U.A., K.P.; Design - U.A., K.P.; Data Collection or Processing - S.Y., R.N.P., B.N.S., K.K.; Analysis or Interpretation - S.Y., R.K., B.N.S., K.K.; Literature Search - U.A., Ra.K., K.P., R.K., R.N.P., K.K.; Writing - U.A., S.Y., R.K., K.P., Ra.K., R.N.P., B.N.S. K.K.

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CASE SERIES
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Gastrointestinal schwannomas: A case series of 9 patients and literature review

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ABSTRACT

Gastrointestinal schwannomas are benign, slow-growing, rare tumors comprising 2-6% of all mesenchymal tumors of the gastrointestinal tract and 0.2% of all gastric neoplasms. In the gastrointestinal system, schwannomas are mostly observed in the stomach, followed by the colon and rectum. In this case series, we present the clinicopathological results of 9 cases, along with a literature review. A retrospective analysis was conducted on nine patients diagnosed with gastrointestinal schwannoma in a single institution. Tumors were located in the small intestine and stomach, with an average tumor size of 4.6 cm (range: 1.8-8.5 cm). Diagnoses were incidental in most cases, with only four patients presenting symptoms such as epigastric pain and changes in bowel habits. Histopathological characteristics of tumors were studied. Surgical resection with negative margins was performed in 8 cases. Histopathological analysis confirmed schwannomas characterized by solid, homogeneous, spindle-cell structures without cystic changes or necrosis. Immunohistochemically, all tumors were S-100 positive, with variable expression of other markers. Desmin was negative in seven samples. One gastric schwannoma showed focal smooth muscle actin positivity, while others were negative. The Ki-67 index ranged from 0% to 6%, and c-Kit was negative in all cases. DOG-1 expression was examined in four cases, showing focal positivity in small bowel schwannoma and negativity in three gastric schwannomas. Gastrointestinal schwannomas are predominantly benign tumors, more common in women, and typically occur in the sixth decade of life. While imaging and endoscopic techniques help in diagnosis, definitive diagnosis relies on histopathological analysis. Surgical resection remains the gold standard for treatment.

Keywords: Gastric schwannoma, intestinal schwannoma, mesenchymal tumor

INTRODUCTION

Schwannomas were first described by Verocay in 1910 and examined pathologically by Stout in 1935 (1,2). Gastrointestinal system schwannomas were first described by Daimaru in 1988 as generally benign tumoral structures, different from central nervous system schwannomas (3).

Schwannomas are slow-growing, generally benign tumors arising from Schwann cells in the nerve sheath. The majority of cases are seen in the cranial nerves, with the 8th cranial nerve, being the most common. They can also be seen in the peripheral nerves in extremities, the spinal cord, and the central nervous system (4,5). Schwannomas are rarely seen in the gastrointestinal system and constitute about 2-6% of all mesenchymal tumors, including gastric tumors. It constitutes 0.2% of neoplasias and 4% of gastric benign neoplasias (6). In the gastrointestinal system, schwannomas are mostly observed in the stomach at 60%, followed by the colon and rectum at 3%) (7,8). Their occurrence within the small intestine and rectum is very rare. Although gastric schwannomas are generally asymptomatic, they can present with epigastric pain, swelling, hemorrhage, changes in bowel habit, or perforation (9-11).

Gastrointestinal tract schwannomas are generally asymptomatic, submucosal structures detected incidentally during laparoscopy, laparotomies, or imaging (6,12). Although computerized tomography (CT) imaging, endoscopy, endoscopic ultrasonography (EUS), colonoscopy, and endoscopic fine needle aspiration biopsy (FNAB) are helpful in the diagnosis of schwannomas, they can be confused with other mesenchymal tumors such as gastrointestinal stromal tumors (GIST), gastrointestinal autonomic nerve tumors (GANT), and leiomyosarcoma, and the

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differential diagnosis is made by postoperative pathological and immunohistochemical examination of the specimen (13).

Gastrointestinal schwannomas are nerve sheath-differentiated tumors that show S100 and glial fibrillary acidic protein (GFAP) positivity (14,15). Gastrointestinal schwannomas are considered largely benign tumoral structures, and the most commonly performed treatment is surgical resection. Cases of local recurrence due to inadequate resection have been reported in the literature (16). Our aim in this study is to examine the clinical, histopathological, and immunohistochemical features of gastrointestinal tract schwannomas in 9 cases observed at our clinic.

MATERIAL and METHODS

The study included 9 patients who were diagnosed with gastrointestinal schwannoma at a single institution between January 2017 and August 2022. Patient information was collected regarding clinicopathological parameters. Tumor locations were confirmed through an endoscopic examination, chart review. Histologically, tumors were confirmed using parameters like smooth muscle actin (SMA) and desmin. The Ki-67 index was obtained for all patients. The positivity with S100 and c-Kit was also noted.

The study was performed in accordance with the ethics guidelines of the Helsinki Declaration and was approved by the Local Ethics Committee of İstanbul University-Cerrahpaşa (approval number: E-83045809–604.01-978438, date: 03.05.2024). All patients provided written informed consent prior to their inclusion in the study.

Statistical Analysis

We did not perform any statistical analysis in this study.

RESULTS

In this study, five male and four female patients were diagnosed with gastrointestinal tract schwannoma. The average age was 63, the youngest patient was 30 years old, and the oldest patient was 88 years old. One tumor was seen in the small intestine (n=1), tumors and 8 tumors were observed in the stomach (n=8). The average tumor size was 4.6 cm, the smallest was 1.8 cm, and the largest was 8.5 cm. Among these 9 cases, 1 was detected in the duodenum, 3 in the gastric antrum, 3 in the gastric fundus, and 2 in the lesser curvature of the stomach.

Only 4 of the patients were admitted to the hospital with complaints of epigastric pain radiating to the back, nausea, vomiting, change in bowel habits, and abdominal pain. Of the other five patients, the diagnosis was made incidentally during imaging, endoscopy, and surgery performed for other reasons.

In one of the cases where incidental diagnosis was made, this was achieved via subtotal gastrectomy during a Whipple procedure for a pancreatic tumor. In another case, the diagnosis was made from a CT taken during the follow-up period for kidney stones. In the other seven cases, the diagnosis was made as a result of endoscopic evaluations performed for follow-up purposes. On CT imaging, schwannomas were observed as round, homogeneous, exophytic lesions with contrast enhancement in the stomach. Upper gastrointestinal endoscopy was performed in 4 of the patients, revealing a submucosal smooth-surfaced exophytic lesion on the stomach wall. For further evaluation, EUS and contrast-enhanced abdominal CT were performed in the cases that revealed hypoechoic heterogeneous submucosal tumors originating from the gastric muscularis propria. Preoperative diagnosis of schwannoma was not made by biopsy in any of the cases.

Resection with negative surgical margins was performed in 8 of the cases, and the tumor was found adjacent to the surgical margin in only 1 case. The preliminary diagnosis was pancreatic tumor in 1 patient, GIST in 5 patients, gastrointestinal sarcoma in 1 patient, and desmoid tumor in 1 patient. The Whipple procedure was performed on the patient who was operated on for a pancreatic tumor, and incidental gastric schwannoma was detected in the postoperative subtotal gastrectomy material. Of the remaining gastric schwannoma cases, 5 underwent subtotal gastrectomy, 1 underwent wedge resection, and 1 underwent total gastrectomy. The open technique was used in all cases. In the case of small bowel schwannoma, segmental small bowel resection was performed (Figures 1-4).

While no morbidity or mortality was observed in any case during the first 5 years of postoperative follow-up, 1 patient died in the 7th postoperative year. In all cases, the diagnosis of schwannoma was confirmed histopathologically. As a result of pathological examinations, gastrointestinal schwannoma tumors were reported to be solid, homogeneous, dense, and spindle cell

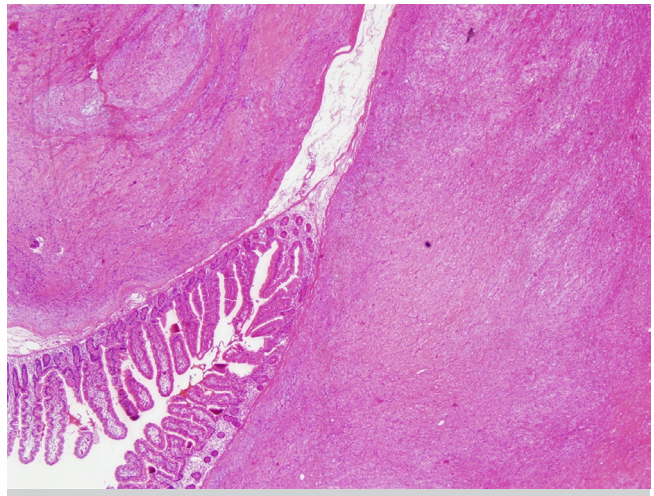

Figure 1. Well circumscribed nodular lesion in submucosa of the intestine (hematoxylin and eosin, X40).

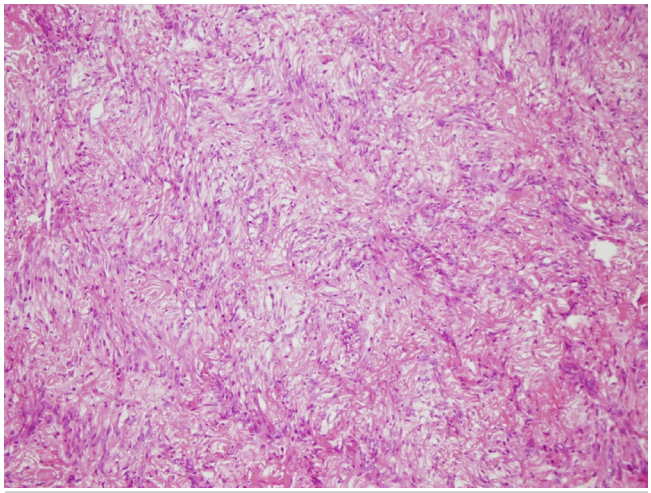

Figure 2. Hypercellular areas in schwannoma (Antoni A type) (hematoxylin and eosin, X200).

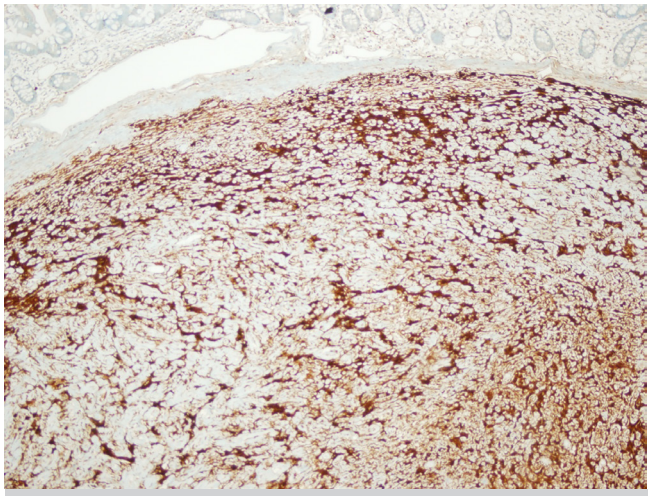

Figure 3. S100 shows strong and diffuse positivity for schwannoma.

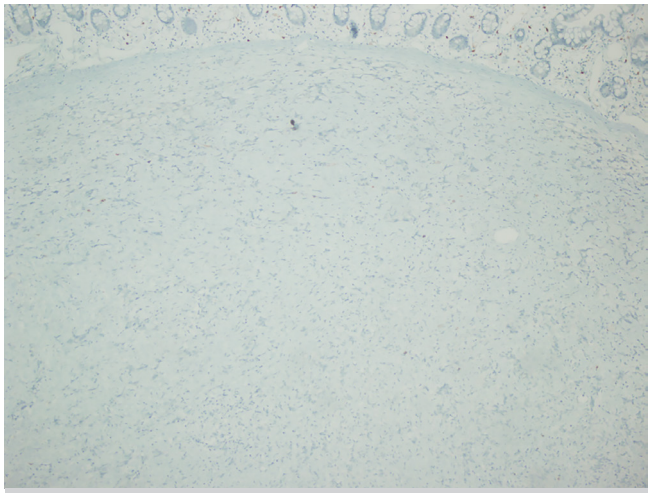

Figure 4. Tumor cells show negative c-Kit immunhistochemistry (ABC method, X100).

tumors. Cystic change and areas of necrosis were not seen in any of the cases.

The mitotic rate was found to be less than 5/50 in all gastric schwannoma cases. In pathological examination, all samples were found to be positive for S-100 (n=4 samples positive and n=5 samples strongly positive) (Table 1). Desmin was found to be negative in 7 of the samples, and SMA were not observed in both a gastric case nor in the small intestine tumor. While only one gastric schwannoma showed SMA focal positivity, SMA expression was found to be negative in the remaining gastric schwannomas. Ki-67 and c-Kit were studied in all patients except the pancreatic tumor patient who had a Whipple procedure. While the Ki-67 rate of the cases was between 0-6%, c-Kit was reported as negative in all cases. In the study, DOG-1 expression was analyzed in only 4 cases, and was focally positive in small bowel schwannoma and negative in the other 3 gastric schwannoma cases. During the 5-year postoperative follow-up period, no gastrointestinal side effects such as recurrence, weight loss, bloating, and dyspepsia were observed in any patient.

DISCUSSION

Gastrointestinal schwannomas are slow-growing, mostly asymptomatic gastrointestinal mesenchymal tumors, first identified by Daimaru with S-100 immunohistochemical staining (2). These structures, which have characteristics different from central nervous system schwannomas, constitute 2-6% of mesenchymal tumors of the gastrointestinal tract (16-18). Gastric schwannomas constitute 0.2% of all gastric tumors, 6.3% of gastric mesenchymal tumors and 4% of gastric benign tumors (19,20).

Gastrointestinal schwannomas are a group of non-epithelial tumors that differ from leiomyomas, leiomyosarcomas, GANTs, and GISTs. Although they can originate from different parts of the gastrointestinal system, they are most commonly found in the stomach (60-70%), followed by the colon and are rarely in the small intestine and esophagus (21,22). Gastric schwannomas most commonly arise from the stomach corpus (50%) followed by the gastric antrum (32%) and the gastric fundus (18%). In our study, three of the gastric schwannomas originated from the gastric antrum, three from the fundus, and two from the lesser curvature.

Our study included four male and five female patients who were diagnosed with gastrointestinal tract schwannoma according to the results of postoperative pathological examination. The average age of the patients was determined to be 58.8 years and ranged from 30 to 89 years. These findings correlate with other studies showing that gastrointestinal tract schwannomas are most common in the 5th and 6th decades of life and are more common in women (11). There are studies in the literature showing that the incidence of intestinal schwannomas is almost

Table 1. Immunohistochemical examinations of all specimens involved

Patient	Location	SMA	Desmin	Ki-67	S100	c-Kit
1	Duodenum	Negative	-	-	Positive	Negative
2	Antrum	Negative	Negative	3%	Strongly positive	Negative
3	Antrum	Negative	-	0-1%	Positive	Negative
4	Fundus	Negative	Negative	1-3%	Strongly positive	Negative
5	Fundus	Negative	Negative	5%	Strongly positive	Negative
6	Lesser curvature	Negative	Negative	2-3%	Positive	Negative
7	Fundus	Focally positive	Negative	2-3%	Strongly positive	Negative
8	Lesser curvature	Negative	Negative	5%	Strongly positive	Negative
9	Antrum	Negative	Negative	1-2%	Positive	Negative

SMA: Smooth muscle actin.

equal in men and women, and the average patient age is 60-65 years (23).

On CT images, schwannomas are generally seen as hypodense, well-circumscribed, solid structures adjacent to the stomach wall, without cystic change necrosis, calcification, and with homogeneous exophytic or intramural extension as well as spherical, oval, or multilobulated contours. CT scans are helpful in visualizing the location and invasion of the tumor and distinguishing it from GIST. On CT imaging, schwannomas, unlike GISTs, are homogeneous, strong enhancing lesions that do not show hemorrhage, necrosis, cystic change, or calcification (24). Also, since the preoperative differential diagnosis often includes GIST, biopsy is sometimes contraindicated in suspected GIST due to risks such as capsular rupture or peritoneal seeding.

During endoscopy, they are generally seen as elevated submucosal lesions, and a central ulcer is observed in about 25-50% of the cases (25). In 4 of the 9 in our series, a submucosal smooth-surfaced, exophytic lesion was observed on the stomach wall during endoscopy. While EUS-guided FNAB is helpful in the diagnosis of submucosal schwannomas in the upper gastrointestinal tract, it is not definitive in the diagnosis of deeper-seated lesions.

Gastrointestinal schwannoma cells usually show S-100 protein and GFAP positivity. They originate from the submucosally located myenteric plexus (Auerbach's plexus) of the gastrointestinal tract and, to a lesser extent, from the Meissner plexus (26). Macroscopically, schwannomas are round, fusiform, grey-white structures with well-defined borders. Although microscopically gastrointestinal schwannomas are generally well-circumscribed, unlike other schwannomas, they are not encapsulated or surrounded by epineurium. Nuclear palisading, xanthoma cells, vascular hyalinization, and dilatation seen in other soft tissue schwannomas are not observed in gastric schwannomas (27). In our study, the histopathological diagnosis of schwannoma was accepted in all cases, and similar to previous studies, microscopic pathological examination revealed that the schwannomas had a solid, homogeneous structure, and a structure consisting of spindle cells. While no area of necrosis was observed in any of the specimens, the submucosa, the muscularis propria, and subserosal involvement were generally observed. While cytological atypia was observed in 3 cases, ulceration, bleeding, or perforation was not observed in any of them. Since gastric schwannomas rarely exhibit malignant properties, tumor size and mitotic activity are not of great importance in terms of prognosis. In our study, the average tumor size was determined to be 4.6 cm, with a range of (range 2.5 cm-8.5 cm).

The immunohistochemical pattern of schwannomas is important in distinguishing them from other GI mesenchymal neoplasias. Vimentin, GFAP, and S100 proteins are known to be expressed by gastrointestinal schwannoma cells. In various studies, S100 positivity and CD34 positivity were observed in gastric schwannomas, whereas CD117, SMA, actin, HHF35, melan A, HMB45 and desmin were typically negative (27-29). GIST is typically positive for CD34 and CD117 (30,31). In our study, while immunohistochemical examinations of all specimens showed strong positivity for S100, no immune reactivity was detected for DOG1, c-Kit (CD117), CD34, desmin, and SMA.

The incidence rate of gastrointestinal schwannomas is approximately one per 45 in comparison to GISTs (27). While GISTs, appear heterogeneous on CT due to the presence of necrosis, hemorrhage, and cystic degenerative changes, schwannomas appear homogeneous on CT. In these cases, immunohistochemistry is extremely important for differential diagnosis. GISTs are macroscopically distinguished from the yellow and white structure of gastric schwannomas by their pink-hemorrhagic structure.

Another differential diagnosis of gastrointestinal schwannoma is primary and secondary lymphomas due to the similarity in CT images. The presence of adenopathy in the surrounding tissue on imaging distinguishes lymphoma from gastrointestinal

schwannoma. Other entities in the differential diagnosis are sarcomas, metastatic melanomas, and gastrointestinal adenocarcinomas.

Studies have shown that most gastrointestinal schwannomas are benign. In this respect, it is important to distinguish them from GISTs, which show malignant features in 10-30%, and GANTs, which have a recurrence and metastasis rate of more than 55% (32-34). There are also a few very rare cases of malignant schwannoma in children reported in the literature (35). Studies have shown that the standard treatment for benign schwannomas is surgical resection with negative margins and that there is no need for radical surgeries or extended resections. Radical surgery is typically the management of choice for malignant schwannomas, and the role of chemoradiotherapy in treatment is unclear (36). No malignancy was observed in our study. Total resection was considered the primary treatment method in these cases due to the > uncertainty of thepreoperative diagnosis, and long-term results were favorable.

CONCLUSION

Gastric schwannomas, different from soft tissue and central nervous system schwannomas, are rare, slow-growing, usually asymptomatic, originate from neuronal Schwann cells, and are tumors that are generally benign, more common in women, and in the 6th decade. Radiological imaging, EUS, and endoscopic FNAB help in the diagnosis, and the definitive diagnosis can be made after postoperative immunohistochemistry and histopathological examinations. The treatment of choice is complete surgical resection, since it is mostly benign except for a few reported cases.

Ethics

Informed Consent: All patients provided written informed consent prior to their inclusion in the study.

Footnotes

Author Contributions

Concept - S.S.U., E.E.; Design - S.S.U., E.E.; Data Collection or Processing - S.S.U., E.E., N.G.; Analysis or Interpretation - S.S.U., E.E., Ş.B.; Literature Search – E.E., N.G., Z.Ö., N.K., Ş.B.; Writing - E.E., N.G., Z.Ö., N.K., Ş.B.

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

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CASE REPORT
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Evaluation of pediatric prostatic and retroperitoneal embryonal rhabdomyosarcoma with high Ki-67-case series study

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ABSTRACT

Embryonal rhabdomyosarcoma (ERMS) is a highly aggressive pediatric malignancy that can develop in various anatomical locations. This case series presents four pediatric patients diagnosed with ERMS, including one with the uncommon presentation of prostatic rhabdomyosarcoma. By analyzing clinical features, treatment strategies, and outcomes, this study aims to provide insights into the challenges of managing this malignancy in different anatomical sites.

Keywords: Embryonal rhabdomyosarcoma, Ki-67 proliferation index, children, rhabdomyosarcoma recurrence

INTRODUCTION

Embryonal rhabdomyosarcoma (ERMS) is a rare and aggressive pediatric malignancy which can manifest in various anatomical locations. This case series examines four pediatric patients diagnosed with ERMS, including one with the uncommon presentation of prostatic rhabdomyosarcoma. By analyzing their clinical features, treatment strategies, and outcomes, this series aims to shed light on the variability and challenges of managing this rare malignancy in different anatomical locations.

CASE REPORTS

Case 1

A 2-year-old male patient presented with a recurrent mass on the left side of his back, previously diagnosed as rhabdomyosarcoma. Physical examination revealed a firm, palpable mass extending from the 10th to 12th ribs, reaching the kidneys. An incision scar from a prior surgery at 10 months of age was noted. Computed tomography (CT) showed the tumor extending to the spleen and kidney, with no signs of metastasis (Figure 1A).

The previous incision site was reopened for surgical access. The tumor originated subcutaneously. Infiltrated the muscles, paravertebral fascia, and diaphragm It was invasive to the 10th, 11th, and 12th ribs, all excised along with the mass.

However, 11 weeks post-surgery, the patient returned with a recurrent mass. Another surgery was performed to remove the tumor in the left upper thoracic region. Pathology confirmed ERMS with clear surgical margins, with the Ki-67 proliferation index reported at 75%. Immunohistochemical staining also showed positive desmin, SMA, FLI-1, and myogenin results.

No fluorodeoxyglucose-18 (FDG) uptake on PET-CT after resection (Figure 1B). Despite complete excision, the patient developed a recurrent tumor protruding from the skin near the vertebral column at the L1-L2 levels, extending toward

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the aorta (Figure 1C, D). This tumor was excised after being dissected from the aorta and diaphragm. Additionally, those areas were marked for radiotherapy with titanium clips. The tumor was classified as stage III and high risk according to Children's Oncology Group (COG) risk stratification (Table 1). Subsequently, the patient underwent multiple surgeries in his home country due to recurrent disease and received chemotherapy and radiotherapy. The patient received a chemotherapy combination containing vincristine, irinotecan, and temozolomide. After chemotherapy, a total radiotherapy dose of 50.4 Gy was applied to the primary tumor site in 33 sessions. Three months after completing the treatment, recurrence developed in the primary site. Repeated operations and chemotherapy courses were unsuccessful, and the patient ultimately succumbed.

Case 2

A 1-year-old male patient presenting with an intra-abdominal mass was admitted to our hospital. Following chemotherapy, ultrasonography (USG), revealed grade 3 hydronephrosis in the left kidney and grade 1 hydronephrosis in the right kidney, with dilated ureters, more pronounced on the left side. Additionally, a mass measuring approximately 100x43 mm was detected, displacing the bladder superolateral to the left and positioned posterior to the bladder. A Doppler USG further characterized the mass as a hypervascular, mixed echogenic, well-circumscribed solid mass. Magnetic resonance imaging (MRI) confirmed the presence of an intrapelvic retroperitoneal malignant solid mass measuring 12.5×10 cm (Figure 2A).

A few days later, triphasic abdominal CT revealed a larger tumor, measuring 13x8x10.5 cm, located retroperitoneally and displacing the bladder anteriorly. The mass displayed extensive necrotic areas and non-homogeneous opacification of vascular structures but showed no signs of invasion. It was also compressing the left ureter, leading to a decision to proceed with surgical intervention.

During surgery, cystoscopy revealed significant hypertrophy of the bladder and urethra, necessitating a biopsy. A firm, encapsulated mass was found occupying the entire pelvis, extending above the umbilicus, and originating from the prostate, with attachments to the bladder and colon. The mass,

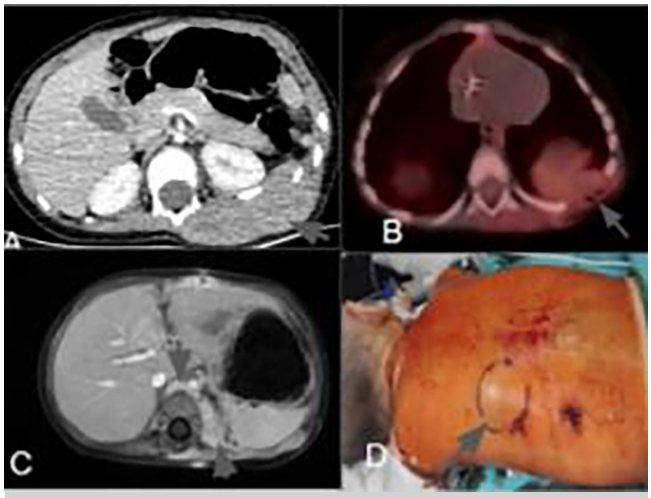

Figure 1. A. CT image of the retroperitoneal mass near the spleen and kidney. **B.** PET-CT image pre-resection metabolic activity. **C.** MRI of recurrent tumor at L1-L2 levels. **D.** Postoperative view; showing the recurrent tumor site.

PET-CT: Positron emission tomography-computed tomography, MRI: Magnetic resonance imaging

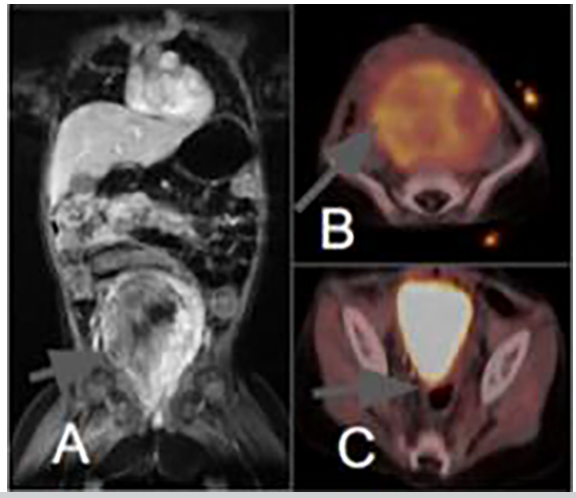

Figure 2. A. Preoperative MRI showing a large prostatic tumor displacing the iliac vessels laterally. **B.** PET-CT prior to surgery, confirming metabolic activity. **C.** Postoperative PET-CT: Indicating no metabolic activity.

PET-CT: Positron emission tomography-computed tomography, MRI: Magnetic resonance imaging

Table 1. Patient and clinical characteristics with risk group stratification according to the children's oncology group

Case	Age (years)	Tumor location	Tumor size (cm)	Lymph node involvement	Distant metastasis	Surgical resection	Ki-67 index (%)	Stage	Risk group
1	2	Paravertebral	Extensive	No	No	Multiple, incomplete	75	III	High
2	1	Prostate	12-13	Para-aortic, iliac	No	Complete	25	IIB	Intermediate
3	7	Retroperitoneum	4.5	No	No	Complete	2	III	Intermediate
4	4	Pelvic	5x3x5.5	Retroperitoneal	Iliac bone	Incomplete	75	IV	High

approximately 12-13 cm in size, caused right-sided ureteral dilation with minimal dilation on the left. It was fully resected.

Additionally, both para-aortic and iliac lymph node dissections were performed, and the prostate was excised along with the tumor. Titanium clips were placed to mark the dissection area.

Immunohistochemical staining of the surgical samples showed a Ki-67 proliferation index of 25%, along with positive CD34, p53, and S100 staining. A bladder biopsy revealed a Ki-67 index of 35-45%, with focal positive staining for myogenin, desmin, and MSA. WT1 displayed cytoplasmic staining, consistent with ERMS. The tumor was classified as stage IIB and intermediate risk (Table 1).

Following surgery, the patient was referred to the department of oncology for a comprehensive treatment plan that included chemotherapy. One-month post-surgery, an abdominal MRI showed no residual intra-abdominal mass. The patient underwent combination chemotherapy with vincristine, actinomycin, and cyclophosphamide, followed by a total of 41.4 Gy of radiotherapy to the primary tumor site in 23 sessions.

Nine months later, after completing chemotherapy, a PET/CT scan indicated an almost complete therapeutic response, with no pathological FDG uptake suggestive of residual tumor tissue (Figure 2B, C). The patient has remained in good health for the past three years.

Case 3

A 7-year-old female patient was admitted with an intra-abdominal mass previously diagnosed as rhabdomyosarcoma. She had undergone surgery five years earlier.

Physical examination revealed a Pfannenstiel incision scar, growth retardation, a skin rash, and thrombocytopenia on blood analysis. MRI identified a retroperitoneal mass, although no significant tumor focus was detected during cystoscopy (Figure 3A). Biopsies were obtained from suspected regions.

PET-CT imaging showed uptake on the left side of the bladder and lymphadenopathy (LAP) involvement (Figure 3B). During surgery, a 4.5 cm mass was found adhering to and surrounding the left ureter, left external and internal iliac vessels, the iliac vein, bladder, and uterus. The mass extended from the left lateral bladder to the vulva. Complete resection was achieved, and titanium clips were placed to mark the borders of the resection area.

The mass appeared firm and exhibited a dirty yellow coloration. A retroperitoneal lymph node dissection was performed, though no significant pathological lymph node involvement was identified. Biopsies were obtained from the omentum and lymph nodes in the iliac chain and para-aortic region. A tumor-free surgical margin was achieved, and no tumor cells were found in the bladder. The tumor was classified as stage III, intermediate risk (Table 1).

Immunohistochemical staining showed a Ki-67 proliferation index of 1-2%, indicating a low proliferation rate. The patient has remained disease-free for one year, with no recurrence observed. Post-surgery, the patient was referred to the department of oncology for a multi-modal treatment plan, which included chemotherapy and radiotherapy. Both chemotherapy and radiotherapy were subsequently administered. All treatment courses were unsuccessful, and the patient ultimately passed away.

Case 4

A 4-year-old male patient was referred to our hospital after undergoing surgery at another center earlier in the year, where complete removal of the mass could not be achieved. The patient was subsequently started on chemotherapy and referred for further treatment.

Physical examination revealed no remarkable findings. The midline incision was intact without dehiscence, and a nephrostomy catheter was present on the right side due to hydronephrosis. The USG indicated grade IV hydronephrosis in the right kidney, with marked dilation of the proximal ureter, while the distal ureter was not visualized. A small fusiform LAP was identified in the retrocaval region at the right renal level. Lower abdominal MRI revealed a 5x3x5.5 cm mass with dense components and septations, extending from the right iliac chain toward the bladder and rectum. The mass appeared cystic and necrotic, involving the right internal iliac vascular structures and displacing the external iliac vascular structures anteriorly. A focal lesion, measuring 15x6 mm and showing mild contrast enhancement, was also noted on the left iliac bone (Figure 4A).

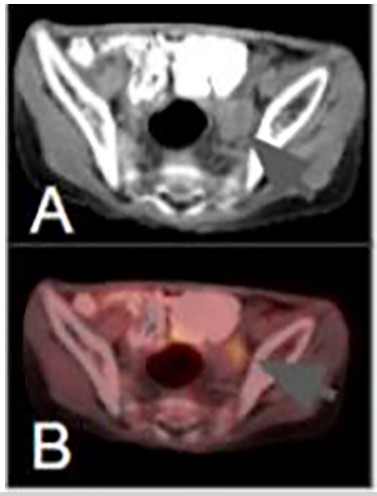

Figure 3. A. MRI image showing recurrent retroperitoneal tumor near iliac vessels and bladder. **B.** Preoperative PET-CT image demonstrating pathological FDG uptake near the left bladder and lymph nodes.

PET-CT: Positron emission tomography-computed tomography, MRI: Magnetic resonance imaging, FDG: Fluorodeoxyglucose

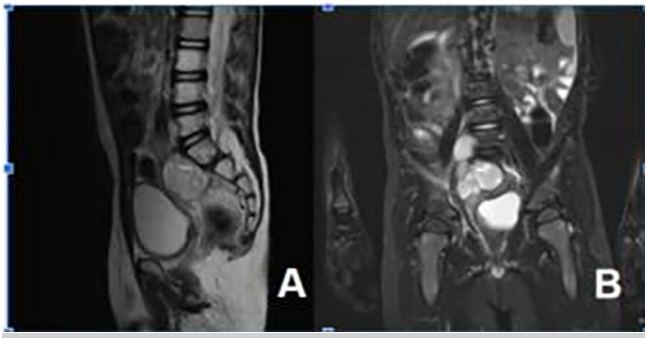

Figure 4. A. Preoperative MRI of the retroperitoneal mass near the iliac vessels and rectum. **B.** Postoperative MRI confirming residual tumor progression in the distal right psoas muscle and recurrence near iliac structures.

MRI: Magnetic resonance imaging

During the operation, the mass, measuring approximately 5x3x5.5 cm, was carefully dissected from critical anatomical structures, including the aorta, vena cava, right ureter, bladder, and rectum in the retroperitoneal area. Notably, a thrombus extending distally from the confluence of the vena cava and iliac veins was identified and addressed. Due to significant tumor invasion into the lower ureter and proximal rectum, en bloc resection of the affected ureteral segment, a 5 cm portion of the rectum, and the retroperitoneal mass, was performed. Adhesions from prior surgeries were meticulously removed to facilitate clear margins. Titanium clips were strategically placed to mark resection boundaries for subsequent radiotherapy, and a retroperitoneal lymph node dissection extended to the superior mesenteric artery.

Reconstruction involved a side-to-end anastomosis between the lower sigmoid colon and rectum to restore bowel continuity. Postoperative biopsies confirmed the presence of residual tumor cells at the margins, indicating the need for further oncological management.

Immunohistochemical staining of the surgical samples indicated a Ki-67 proliferation index at 75% with focal positive staining for myogenin, while desmin showed cytoplasmic staining, which is characteristic of ERMS. Two months post-surgery, the cystic necrotic mass in the distal portion of the right psoas muscle, measuring 7x2.6x1.7 cm and located near the right iliac vascular structures, was causing mild compression. Compared to a previous scan, the lower component of the mass had been resected, though progression was noted in the remaining upper portion revealed on MRI (Figure 4B). A hypointense fusiform lesion was also observed on the right iliac bone. The tumor was classified as stage IV and high risk (Table 1).

DISCUSSION

The Ki-67 proliferation index is a valuable marker in assessing tumor aggressiveness and prognosis in ERMS, particularly in recurrent cases. Studies indicate that higher Ki-67 expression is associated with increased tumor proliferation, poor differentiation, and a heightened risk of recurrence (1-3). In recurrent ERMS, Ki-67 may indicate the tumor's response to treatment and the likelihood of further progression.

While the role of Ki-67 in initial diagnosis and risk stratification is well-established, its utility in monitoring recurrent disease is gaining attention, offering the potential for tailoring aggressive treatment strategies.

Incorporating Ki-67 into the evaluation of recurrent ERMS could improve prognostication and guide decisions regarding the intensity of salvage therapy and multimodal approaches (4,5). Our study found a strong correlation between local recurrence and the Ki-67 proliferation index in pediatric patients with ERMS. Unfortunately, patients with high Ki-67 index and retroperitoneally located tumors demonstrate a higher likelihood of recurrence, even after complete resection. This is mainly attributed to the close anatomical relationship between these tumors and critical structures, including the iliac arteries, veins, ureters, and sacral plexus.

Additionally, the presence of microinvasions in this region further increases the risk of recurrence, making complete surgical clearance challenging. While tumor size is generally considered a prognostic factor, one of our cases showed no recurrence during follow-up despite a large mass originating from the prostate. This may be due to the prostate's encapsulated nature, which allowed for complete resection and thereby helped prevent recurrence, even with a high Ki-67 index.

The primary goal of surgical management in ERMS is achieving complete resection with clear margins, which is crucial for local control. However, complete resection is sometimes challenging due to the infiltrative nature and location. Achieving a clear margin for resection is challenging when the ER source originates from retroperitoneal muscle tissue. Adjuvant chemotherapy plays a crucial role in managing micrometastatic disease and improving overall survival rates. In some cases, radiotherapy significantly improves patient outcomes. In instances where complete surgical resection is not feasible due to proximity to critical structures and recurrences, a biopsy followed by neoadjuvant chemotherapy may be helpful to shrink the tumor and make a subsequent resection feasible (6-11).

In conclusion, our findings suggest that a low Ki-67 index and complete surgical removal significantly reduce the risk of tumor recurrence. However, even with full excision, recurrences were noted in retroperitoneal tumors with a high Ki-67 index. In contrast, for embryonal sarcomas originating from the prostate, recurrence rates were reduced despite the tumor's large size and high Ki67 index, likely due to complete removal. These findings highlight the crucial role of tumor location in prognosis,

particularly in achieving complete resection. Moreover, our cases illustrate a strong association between tumor recurrence and high Ki-67 index levels in rhabdomyosarcoma. The recurrence rate appears to be lower in prostatic tumors, which benefit from the encapsulation characteristic of the organ.

Ethics

Informed Consent: Informed consent forms were signed by parents of each patient.

Footnotes

Author Contributions

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

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CASE REPORT
Turk J Surg 2025;41(3):338-342

Retroperitoneal duodenal perforation following biliary stent migration: A case report and review of conservative management

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ABSTRACT

Endoscopic biliary stenting is a widely adopted technique for managing bile duct injuries post-cholecystectomy. However, its complications can have severe consequences. Although rare compared to other endoscopic retrograde cholangiopancreatography-related complications, duodenal perforation due to stent migration carries a significant risk of morbidity and mortality. While biliary stenting is often considered a less invasive alternative to surgery, timely recognition and management of potential complications remain crucial. We present a case of duodenal perforation due to biliary stent migration in a 49-year-old woman following laparoscopic cholecystectomy, emphasizing the effectiveness of conservative management, including the key role of interventional radiology, in selected patients.

Keywords: Biliary injury, biliary stent, ERCP, duodenum, perforation, management

INTRODUCTION

Biliary injury is a known complication of cholecystectomy, one of the most frequently performed general surgical procedures worldwide; occurring in approximately 0.3-0.6% of laparoscopic cases (1). Management depends on the extent of the injury and the patient's clinical condition. Endoscopic retrograde cholangiopancreatography (ERCP) with stent placement is an effective intervention in cases without full-thickness bile duct injury (type E) (2), particularly in experienced centers. However, ERCP-related complications can occur, including bleeding, leakage, and obstruction, with duodenal perforation due to stent migration being a rare but serious outcome (3-5).

The overall incidence of biliary stent migration is reported to be between 5% and 10%, with duodenal perforation occurring in only a small subset of cases (6,7). Identified risk factors for migration include inappropriate stent length, inadequate anchoring, and patient-specific anatomical variations (8,9). Furthermore, migrated stents may cause intestinal perforation, biliary peritonitis, or even cecal perforation in rare cases (10,11). To mitigate these risks, stent selection should be tailored to individual patient anatomy, and securing techniques should be optimized (12,13).

Here, we report a case of retroperitoneal duodenal perforation secondary to biliary stent migration and its successful conservative management.

For this case report, informed consent was obtained from the patient (or their legal guardian) for the publication of clinical details and any accompanying images. The patient was informed about the purpose of the report, and their anonymity was ensured by omitting any identifying information.

CASE REPORT

A 49-year-old female with a history of hypertension underwent laparoscopic cholecystectomy for calculous cholelithiasis at an external center in December 2024. She was referred to our center with suspected biliary injury. Upon admission, laboratory tests revealed elevated direct bilirubin (total: 1.59 mg/dL; direct: 0.83 mg/

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dL), alkaline phosphatase (500 U/L; normal: 35-104 U/L), and AST (38 U/L; normal: 0-32 U/L), while other parameters were within normal limits.

Abdominal ultrasound revealed a 2 cm loculation in the cholecystectomy area. A hepatocyte-specific contrast-enhanced magnetic resonance cholangiopancreatography performed at the referring center suggested a possible Strasberg type E injury (Figure 1). After evaluation by our radiology team, ERCP was performed and revealed a biliary leak compatible with Strasberg type A (Figure 2). A 10 cm, 8F biliary stent was placed endoscopically.

During follow-up, persistent biliary leakage and rising bilirubin levels necessitated a stent revision. Following the second procedure, the patient was clinically stable and discharged. However, on post-discharge day five, she presented with severe abdominal pain. Abdominal computed tomography (CT) demonstrated stent migration into the third portion of the duodenum, with evidence of perforation and retroperitoneal abscess formation (Figure 3).

A multidisciplinary team including general surgeons, radiologists, and gastroenterologists opted for conservative management with radiological percutaneous drainage. Interventional radiology successfully drained the abscess under ultrasound guidance, and the stent was removed endoscopically a few days later (Figure 4). The patient was started on a liquid diet on the first day after stent removal and progressed to a full diet. The repeat contrast-enhanced CT confirmed resolution of the abscess without contrast extravasation. The percutaneous catheter was removed and the patient was discharged uneventfully on oral antibiotics. At the 3-month follow-up after discharge, the patient was in good general condition with no complaints. No further intervention was required, and repeat imaging confirmed the permanent resolution of the retroperitoneal collection.

DISCUSSION

Endoscopic procedures are essential in the management of biliary injuries, offering a minimally invasive approach. However, complications such as biliary stent migration leading to duodenal perforation pose significant risks. Although rare, these complications require prompt diagnosis and intervention to prevent morbidity and mortality (5,14).

ERCP-associated perforations commonly occur during sphincterotomy, stent placement, or endoscopic manipulation (3). Duodenal perforation due to stent migration is particularly uncommon (4). Studies have shown that perforations associated with ERCP occur in approximately 0.3% to 1% of cases, with higher morbidity associated with delayed diagnosis and treatment (6,14). Risk factors include inappropriate stent selection, technical errors and limited operator experience. Literature suggests that the use of fully covered stents may reduce the risk of migration, whereas uncovered stents are more prone to dislodgement. As this issue is the subject of another study, further randomised trials are warranted to determine optimal stent selection strategies (7).

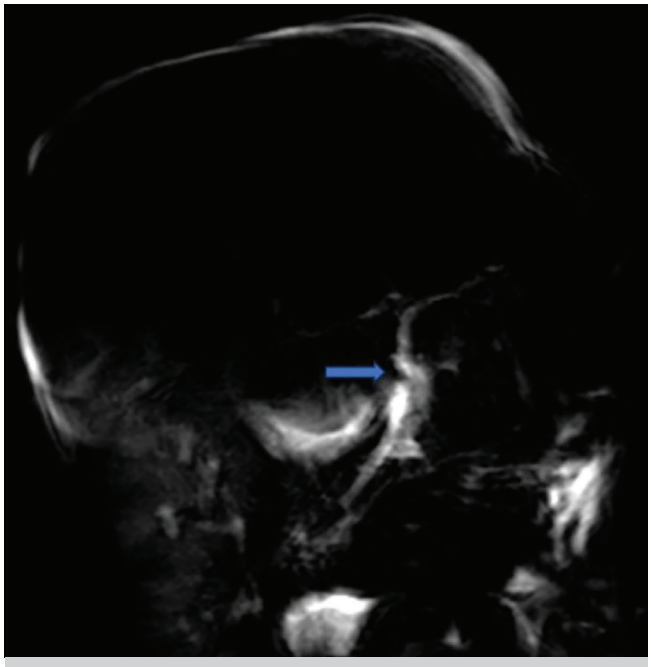

Figure 1. MRCP scan (the blue arrow shows the suspected injury located below the confluence of the extrahepatic bile duct).

MRCP: Magnetic resonance cholangiopancreatography

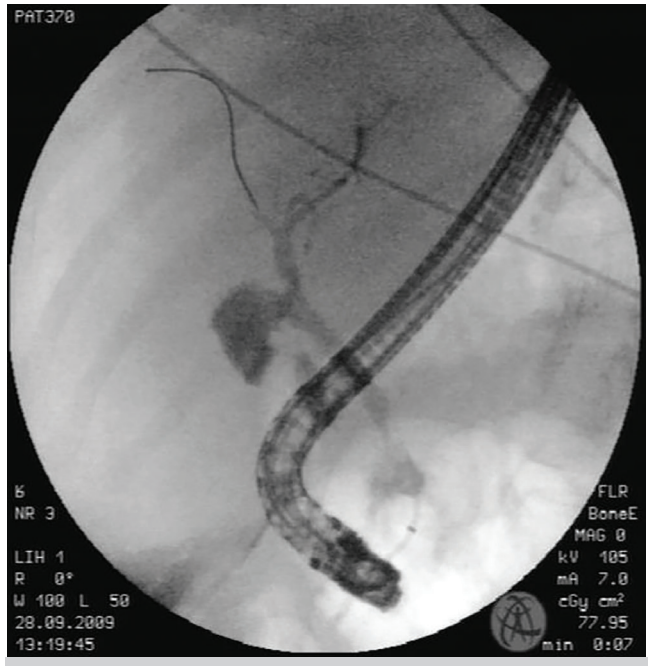

Figure 2. Cholangiography image taken during the ERCP procedure.

ERCP: Endoscopic retrograde cholangiopancreatography

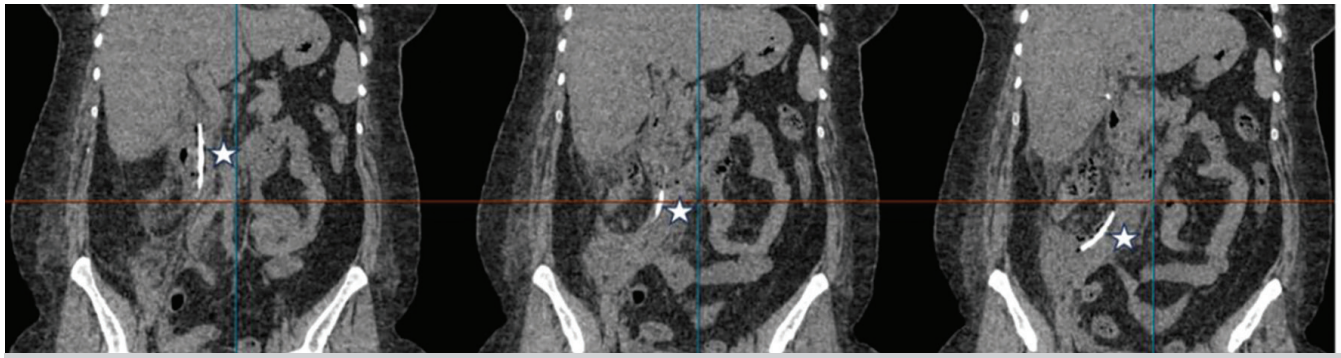

Figure 3. CT scan (the white star marks the biliary stent perforating the duodenum and extending into the retroperitoneal space).
CT: Computed tomography

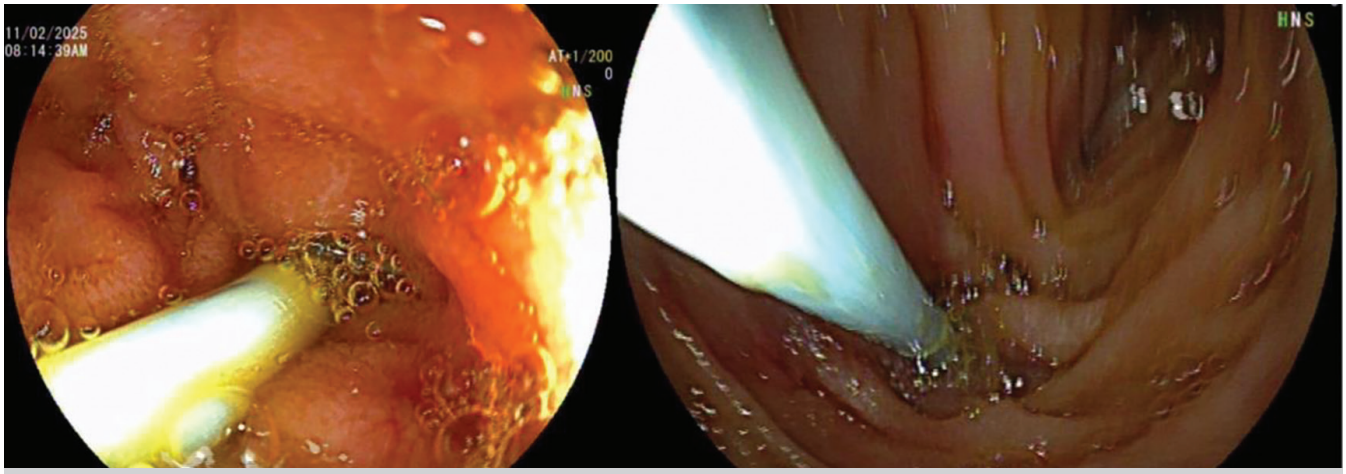

Figure 4. Endoscopic view of the biliary stent perforating the duodenal wall.

Management depends on the location and severity of the perforation. In our case, the decision to manage conservatively was based on several key clinical factors—the patient remained hemodynamically stable, there was no evidence of generalised peritonitis, and imaging confirmed that the perforation and resulting abscess were localized to the retroperitoneal space. These findings were consistent with a contained injury with no ongoing leakage into the peritoneal cavity. Cases of retroperitoneal duodenal perforation may be amenable to conservative management, particularly if the injury is self-contained (15). Endoscopic retrieval of dislodged stents, image-guided percutaneous drainage performed by interventional radiology, and close clinical monitoring are key strategies to avoid surgical intervention. However, if patients develop peritonitis, sepsis or progressive imaging findings, early surgical intervention is imperative.

Recent studies emphasise the importance of individualised treatment strategies. Dumonceau et al. (4) highlight that prophylactic stenting techniques and appropriate stent selection can significantly reduce complications. In addition, Fujisawa et al. (7) discuss novel stent designs aimed at reducing migration rates. In some cases, fully covered self-expanding metal stents have been proposed to minimise the risk of migration (16). In addition, new advances in biodegradable stents may offer future alternatives to reduce complications associated with long-term stent placement (17).

Cross-sectional imaging with IV contrast is essential to assess the extent of perforation, abscess formation and adjacent anatomical involvement. In our case, percutaneous drainage served as an important insurance policy until oral feeding could be safely resumed without recurrence of symptoms. This highlights the importance of a stepwise approach, balancing conservative and invasive management strategies.

Long-term follow-up studies suggest that while non-surgical management can be effective, close follow-up after discharge is essential. Patients with previous ERCP complications, including stent migration, may benefit from scheduled follow-up, additional imaging and multidisciplinary consultation. In

addition, understanding patient-specific risk factors, including anatomical variations and procedural history, may help make informed decisions about stent type and placement duration. Given the challenges of stent migration, future advancements should focus on improving stent design, including self-expanding stents with anti-migration mechanisms (7). Training in ERCP techniques is also essential to reduce procedural risks (8). In addition, advances in bioresorbable stents and improved endoscopic techniques may help to minimise complications.

To aid clinical decision making, we have included a simplified flowchart (Figure 5) outlining the key criteria that guide the selection between conservative and surgical management in patients with duodenal perforation due to biliary stent migration.

CONCLUSION

Duodenal perforation after ERCP-related biliary stenting is associated with a high risk of morbidity and mortality, with reported mortality rates between 10% and 30% in some series (18). Early diagnosis and intervention are essential. While conservative management, including endoscopic stent removal and percutaneous drainage, is feasible in selected cases, prompt surgical intervention remains crucial in patients with worsening sepsis, persistent leakage, or peritonitis.

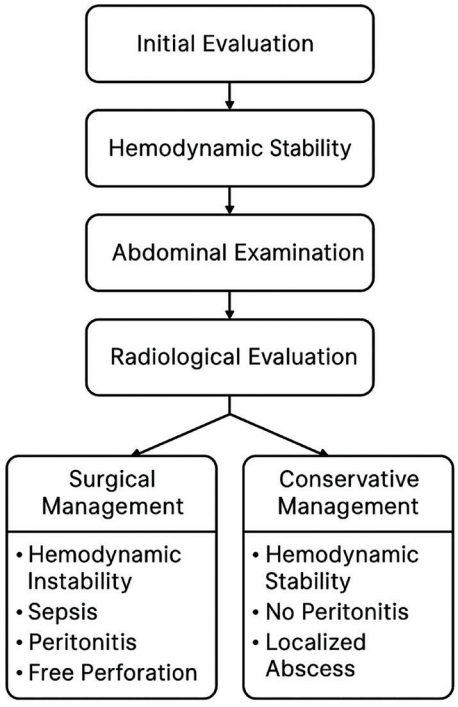

Figure 5. Decision-making algorithm summarizing the criteria for conservative versus surgical management in patients with duodenal perforation secondary to biliary stent migration.

Ethics

Informed Consent: For this case report, informed consent was obtained from the patient (or their legal guardian) for the publication of clinical details and any accompanying images. The patient was informed about the purpose of the report, and their anonymity was ensured by omitting any identifying information.

Footnotes

Author Contributions

Surgical and Medical Practices - R.R.E.S., T.Ö., F.B., O.A.; Concept - F.B., O.A.; Design - O.A.; Data Collection or Processing - R.E.S., T.Ö., F.B.; Analysis or Interpretation - R.R.E.S., F.B., O.A.; Literature Search - R.R.E.S., T.Ö.; Writing - R.R.E.S., T.Ö.

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

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LETTER TO THE EDITOR
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Microbiome, mechanics, and morphology: Rethinking the etiopathogenesis of pilonidal sinus disease

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Keywords: Pilonidal sinus, pilonidal sinus disease, interglueal fold, interglueal fold depth, natal cleft, microbiome

Dear Editor,

We read with great interest the article by Maak et al. (1) titled "Intergluteal fold depth has no influence on pilonidal sinus disease development". This research investigates the long-standing relationship between intergluteal fold (IGF) depth and the onset of primary pilonidal sinus disease (PSD) and determined that IGF depth did not serve as an independent risk factor for PSD. This result deserves additional scrutiny as it directly refutes established surgical assumptions and guideline conclusions.

Akinci et al. (2) initially emphasized the importance of natal cleft morphology in the development of PSD, stating that individuals with PSD exhibit deeper natal clefts, thus justifying the use of cleft lift treatments such as the Karydakis and Bascom techniques. These surgical techniques, which were supported by guidelines including the German Society of Coloproctology and the European Society of Coloproctology, aim to reduce recurrence by flattening the natal cleft (3,4). This practice is assumed to relieve the mechanical forces that trap the hairs. However, the results of Maak et al. (1) urge a reevaluation of this paradigm. Maak et al. (1) utilised a standardised, minimally compressive measurement technique. The authors found that the greatest IGF depth occurred distally in the anus, a region rarely affected by PSD. However, the disease is most often seen in the cranial third, where the IGF depth is least. This discrepancy suggests that IGF depth alone may not be sufficient to explain the onset of PSD. This result is consistent with more recent studies emphasizing the role of hair shaft biomechanics rather than static anatomic measurements.

Bosche et al. (5) have shown that sharp, rootless occipital hairs can embed into the skin under friction forces independent of IGF depth. Furthermore, 3D modelling studies now suggest that soft tissue architecture and motion vectors, rather than depth, may create environments conducive to hair emplacement (6). Pilonidal sinus tracts have shown distinct microbial signatures compared to adjacent healthy skin, with a predominance of anaerobic and biofilm-forming bacteria such as Prevotella and Finegoldia species (7). Recent studies using 16S rRNA sequencing suggest that microbiome dysregulation may contribute to the pathogenesis and chronicity of PSD (8). These findings suggest that the local microbiota may play a role in maintaining chronic inflammation, impeding wound healing, and possibly initiating sinus formation. Targeted antimicrobial therapies, biofilm-disrupting agents, and microbiome-based interventions may complement surgical management, particularly in recurrent or refractory cases. Incorporating microbiome profiling into future PSD studies may thus unlock new diagnostic and therapeutic strategies.

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Effective management of PSD increasingly demands a shift from a purely morphological focus to a multifactorial, precision-based approach. Strategies should integrate patient-specific biomechanical variables such as hair orientation and anchoring, IGF microclimate, and the effects of posture and gluteal compression during prolonged sitting.

In conclusion, multicenter studies with a patient-centered approach integrating biomechanical modeling, microbiome profiling, and hair flow dynamics are needed to provide a deeper and more holistic understanding of PSD pathogenesis and recurrence. Future studies with such integrated approaches may form the basis for PSD guideline updates.

Footnotes

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LETTER TO THE EDITOR
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Children are not just small adults: Comment on "Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) for pediatric mesenchymal hamartoma: A case report" by Caballes et De Lara

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Keywords: Gastrointestinal surgery, general surgery, laparotomy

Dear Editor,

We read with great interest the recent case report by Caballes and De Lara (1) on the use of Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) in an infant with mesenchymal hamartoma. While we acknowledge the authors' efforts in managing a complex case and congratulate the team for the successful surgery, we would like to highlight important concerns regarding the rationale for applying ALPPS in pediatric patients, particularly in light of recent evidence on the role of the future liver remnant (FLR) in children (2).

There is an increasing number of case reports on the application of ALPPS and portal vein embolization in children undergoing hepatectomy (3-11). However, we strongly believe that more evidence is needed to justify the use of these techniques in children. Our recent study on posthepatectomy liver failure (PHLF) in children (2) (published in the Annals of Surgery), based on a cohort of 125 major pediatric hepatectomies, demonstrated that PHLF is exceedingly rare in this population. We found that children have a significantly higher liver volume-to-body weight ratio than adults, with sufficient FLR even in cases where the remnant volume was <20% of total liver volume. Furthermore, we identified no clinically relevant PHLF in our cohort, even among patients undergoing extensive hepatectomies, including right trisectionectomies. These findings call into question the need for FLR augmentation strategies such as ALPPS in pediatric patients, which are based on thresholds derived from adults, and primarily justified in adults due to the risk of PHLF.

ALPPS, initially developed to address the risk of insufficient FLR in adults, has not been systematically evaluated in children and may expose them to unnecessary risks (12), including increased morbidity and compromised oncological outcomes due to the acceleration of tumor progression reported in some case reports (13).

Given these findings, we urge caution in the application of adult-derived surgical strategies in pediatric liver tumors (2). We advocate for a more tailored approach that considers the unique regenerative capacity of the pediatric liver and the low incidence of PHLF in children. Preoperative volumetry should be interpreted with pediatric-specific thresholds in mind, and decisions regarding two-stage hepatectomy, and surgical strategies in general, should be made with caution, trying to understand the pediatric liver physiology.

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We appreciate the opportunity to discuss this important topic and hope that our observations will contribute to an evidence-based approach to liver surgery in pediatric patients.

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