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FROM THE EDITOR-IN-CHIEF'S DESK

Coding the Mind: Joy as a State of Being, Science as a State of Academic Writing

Joy and academic writing may seem unrelated, but they connect through mindset. Both require intention over impulse, focus over distraction, clarity over noise, and, importantly, honesty over pretense. A joyful mind can produce better science, and honest writing helps develop a grounded mindset. Joy isn't something you find deliberately; it's something we cultivate through mindful effort. Academic writing isn't spontaneous; it results from disciplined thinking and effort. It's not just a collection of citations or a formulaic layout; it demands clarity, precision, and the courage to face uncertainty. When we write, we're not merely recording data; we're shaping knowledge and bridging the gap between discovery and understanding. Our secondary goal is not only to achieve pure scientific results but also to publish findings in a desired journal, which brings additional joy.

I believe academic writing suffers when rushed, ego-driven, or lacking depth. Today, artificial intelligence seems to speed up the process. AI has quickly become part of academic fields, providing tools for literature synthesis, data interpretation, and manuscript drafting. While AI can improve efficiency, its misuse poses serious risks. In the last three months, the Turkish Journal of Surgery has received many manuscripts generated by AI without verifying their accuracy. Our editorial team has dealt with fabricated drafts containing incorrect journal names, mismatched authorships, and even non-existent articles. This demonstrates that overreliance on AI risks reducing authors' accountability for their content and weakening scientific rigor. "Shortcut culture" is too dangerous, especially when encouraged by AI, because it leads authors to skip reading the primary literature and lose critical thinking. Therefore, we now require authors to fully disclose AI use; failure to do so is a serious ethical violation. This insight reveals an interesting parallel: AI is programmed by humans, and humans are "programmed" by their mindset.

As we near the end of the year, my words might sound like a complaint. However, my intention is not to vent frustrations as an editor, but to reflect on our current situation with our readers.

I conclude this year's final issue by wishing everyone a productive and joyful 2026. As always, I thank our readers.

"Happy New Year and Merry Christmas".

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

ORIGINAL ARTICLE
Turk J Surg 2025;41(4):347-354

Long-term outcomes of extended versus segmental resection for transverse colon cancer: A population-based analysis based on the SEER database

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ABSTRACT

Objective: To investigate long-term cancer-specific outcomes associated with extended versus segmental colectomy (SC) in patients with stage I-III transverse colon adenocarcinoma using a large, population-based cohort.

Material and Methods: Patients who diagnosed with transverse colon cancer undergoing curative-intent colectomy were identified from the surveillance, epidemiology, and end results database (2013-2019). Surgical procedures were categorized as extended colectomy (EC) or SC based on standardized procedural coding. 1:1 propensity score matching was performed to reduce selection bias and balance baseline characteristics. Cancer-specific survival (CSS) was analyzed using multivariable Cox proportional hazards regression.

Results: Among 18,799 eligible patients, 58% underwent EC. EC was more frequently performed in individuals with higher tumor stage (p<0.01) and those receiving adjuvant chemotherapy (26% vs. 23%, p<0.01). After matching (n=7.904 in each group), EC was associated with a higher rate of adequate lymphadenectomy (>12 lymph nodes retrieved: 94% vs. 89%, p<0.01). Five-year overall survival did not differ significantly between groups (65.6% for EC vs. 66.9% for SC, p=0.074). However, SC was associated with a modest but statistically significant improvement in CSS (84.3% vs. 81.7%, p<0.01). In adjusted analysis, surgical extent (HR=0.8376, p<0.001), along with age, sex, tumor grade, stage, and lymph node yield, were independently associated with CSS.

Conclusion: While EC is more commonly utilized in advanced-stage disease and facilitates higher lymph node retrieval, SC offers comparable—and potentially superior—CSS in selected patients. These findings support the consideration of a tailored surgical strategy based on tumor biology and individual patient characteristics.

Keywords: Transverse colon, segmental colectomy, extended colectomy, SEER, survival

INTRODUCTION

Transverse colon cancer constitutes a relatively uncommon subtype of colorectal malignancy, accounting for approximately 10% of all cases (1). Due to its anatomical position adjacent to major vascular and visceral structures, these tumors often present at more advanced stages and exhibit a higher propensity for local invasion. Surgical management is particularly complex, owing to the significant anatomical variability and the requirement for meticulous, individualized operative planning. This complexity is further magnified in minimally invasive approaches, which demand advanced technical expertise. As a result, transverse colon tumors are frequently excluded from randomized controlled trials comparing laparoscopic and open colorectal surgery (2,3).

Embryologically, the transverse colon arises from both the midgut and hindgut, resulting in a complex vascular architecture and heterogeneous lymphatic drainage (4). This dual origin complicates the standardization of resection techniques and contributes to the lack of consensus on optimal surgical management. Unlike right- or left-sided colon cancers, transverse colon tumors lack uniform treatment protocols. Surgical options include segmental colectomy (SC), extended right or left hemicolectomy, and subtotal colectomy, with the choice often dictated by tumor location, anatomical considerations, and surgeon experience (5,6).

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Previous studies addressing surgical strategies in this region have often included tumors at the hepatic or splenic flexures, rather than isolated mid-transverse lesions (7-9). As a result, much of the available literature focuses on extended hemicolectomies, limiting its applicability to true transverse colon cancers. In the absence of high-quality, focused data, there remains no clear consensus regarding the optimal extent of resection. Consequently, the choice between segmental and extended colectomy (EC) remains subjective and varies across institutions (10).

To address this knowledge gap, we conducted a population-based study using surveillance, epidemiology, and end results (SEER) database to compare long-term oncologic outcomes between extended and SC in patients with stage I-III transverse colon adenocarcinoma.

MATERIAL and METHODS

Patient Selection

Patients diagnosed with stage I-III adenocarcinoma of the transverse colon who underwent curative-intent surgical resection between 2013 and 2019 were identified using the SEER database. As a nationally representative and population-based cancer registry, SEER compiles comprehensive and standardized data on cancer incidence, treatment modalities, and patient outcomes across multiple U.S. regions, serving as a valuable resource for large-scale epidemiologic and outcomes research.

Eligible cases were identified using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) code C18.4, corresponding to tumors located in the transverse colon. The following exclusion criteria were applied: Presence of stage IV disease at diagnosis; histologic subtypes other than conventional adenocarcinoma, including signet-ring cell carcinoma (8490/3) and mucinous adenocarcinoma (8480/3, 8481/3); concurrent or prior primary malignancies; unknown tumor site; incomplete staging information (T or N stage); synchronous or recurrent tumors; and missing survival data.

Surgical Classification

Surgical procedures were categorized using SEER procedure codes as follows:

EC: Defined as either a subtotal or hemicolectomy involving the transverse colon (SEER surgical code 40), or a total colectomy extending from the cecum to the rectosigmoid junction (code 50).

SC: Defined as a localized or partial resection confined to the transverse colon (code 30).

Variables and Outcomes

Demographic data, tumor-related variables, and survival outcomes—including overall survival (OS) and cancer-specific survival (CSS)—were compared between the EC and SC groups. The primary outcome was long-term survival stratified by the type of surgical resection.

Statistical Analysis

Descriptive statistics were employed to summarize baseline patient and tumor characteristics. Continuous variables were reported as means with standard deviations or medians with interquartile ranges (IQR), while categorical variables were summarized as counts and percentages. OS and CSS were estimated using Kaplan-Meier curves, and group comparisons were performed using the log-rank test.

To reduce selection bias and ensure comparability between groups, 1:1 propensity score matching (PSM) was conducted using a nearest-neighbor algorithm without replacement. Matching variables included age, sex, tumor stage, histologic grade, and chemotherapy administration. Following matching, multivariable Cox proportional hazards models were used to identify independent predictors of CSS. Hazard ratios (HRs) with 95% confidence intervals were reported. A two-sided p-value <0.05 was considered statistically significant. All analyses were performed using R software (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria).

Ethical Approval

The study protocol was reviewed and approved by the Ethics Committee of Acıbadem University (approval number: 2025-09/352, date: 12.06.2025). As the analysis was conducted using anonymized, publicly available data from the SEER database, the committee determined that the study met the criteria for formal approval without additional ethical requirements.

RESULTS

Patient Cohort

A total of 37,900 patients diagnosed with transverse colon cancer were initially identified from the SEER database. After applying exclusion criteria—stage 0, stage IV, or unknown disease stage (n=4.622); histologic subtypes other than adenocarcinoma (n=5.495); absence of surgical intervention (n=3.415); and incomplete data or other predefined exclusions (n=5.569)—a final analytic cohort of 18,799 patients was established (Figure 1). Of these, 10,895 patients (58%) underwent EC, while 7.904 patients (42%) received SC.

Trends in Surgical Approach

Temporal trends in surgical management from 2013 to 2019 are illustrated in Figure 2. The proportion of patients undergoing EC gradually increased during the study period. In contrast, the use of SC initially rose but subsequently declined, indicating a shift in practice patterns favoring extended resections in recent years.

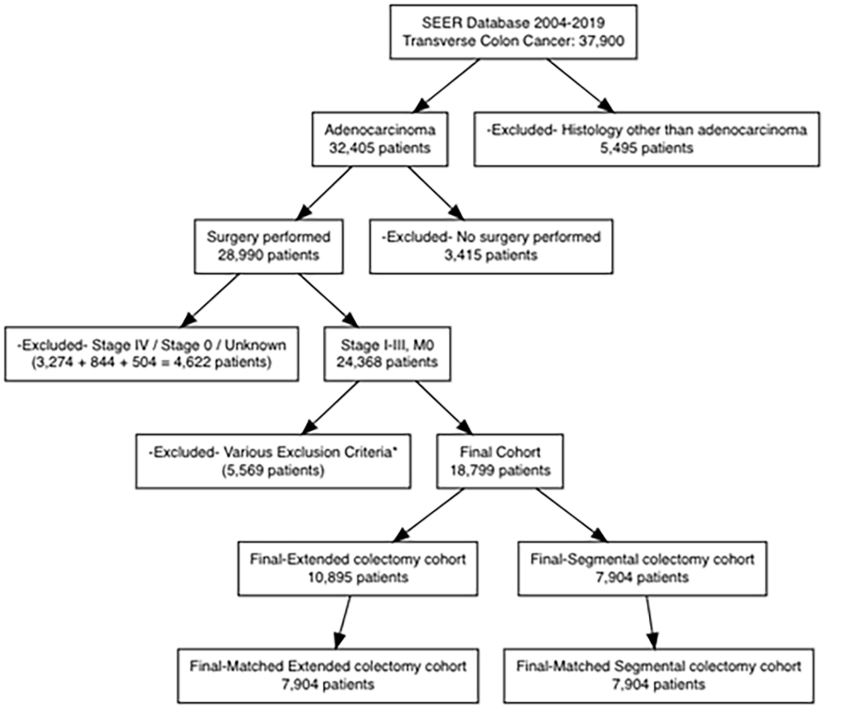

Figure 1. Flowchart of patient selection.

*The following exclusion criteria were applied: surgery not EC or SC (2,758 patients), diagnosed at autopsy (708 patients), incomplete follow-up dates/0 days of survival (780 patients), died within a month after surgery (624 patients), unknown/missing death information (98 patients), unknown/missing grade information (516 patients) and received radiation (85 patients).

EC: Extended colectomy, SC: Segmental colectomy, SEER: Surveillance, epidemiology, and end results

Baseline Characteristics Before Matching

Table 1 presents the unadjusted demographic and clinicopathologic features of the EC and SC groups. Patients undergoing SC were slightly older (median age: 72 vs. 71 years, p<0.01) and had a lower proportion of males (48% vs. 50%, p=0.003). SC was more frequently performed for well-differentiated tumors (11% vs. 9%, p<0.01), whereas poorly differentiated tumors were more common in the EC group. In terms of stage, SC was predominantly used for stage I tumors (31% vs. 26%, p<0.01), while EC was more often selected for stage II and III disease. Additionally, a higher proportion of EC patients received adjuvant chemotherapy (26% vs. 23%, p<0.01).

Post-Matching Characteristics

After 1:1 PSM, 7.904 patients remained in each group (Table 2). Baseline characteristics were well balanced. Mean age was comparable between EC and SC groups (71±12 vs. 70±12 years, p=0.53), and male gender distribution was identical (48% in both groups, p=0.83). Tumor grades were similarly distributed, with moderately differentiated tumors being the most common (75% vs. 73%, p=0.08). Stage distribution and receipt of chemotherapy were also equivalent (tumor stage, p=0.78; chemotherapy, p=0.30). Notably, EC remained associated with a higher rate of adequate lymph node retrieval (>12 nodes: 94% vs. 89%, p<0.01) (Table 3).

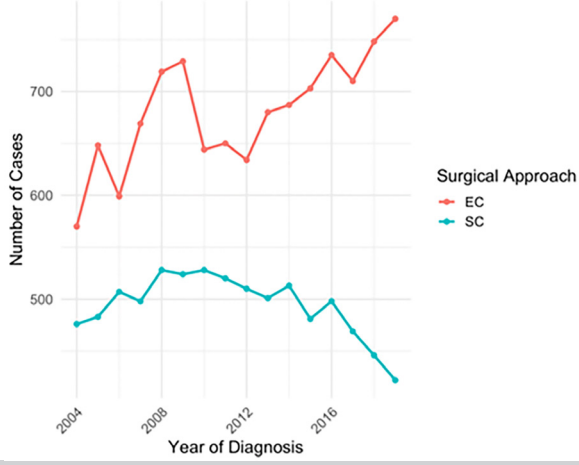

Figure 2. Distribution of surgical approaches performed over study periods.

EC: Extended colectomy, SC: Segmental colectomy

Table 1. Comparison of demographics and pathological characteristics of patients with transverse adenocarcinoma between extended and segmental colectomy

		Extended colectomy n=10,895 (58%)	Segmental colectomy n=7.904 (42%)	p-value
Age	Mean ± SD	69±13	70±12	<0.01
	Median (IQR)	71 (19)	72 (18)	
Gender	Male	5465 (50)	3788 (48)	0.003
Ethnicity	Caucasian	8704 (81.4)	6409 (83.1)	0.009
	African-American	1285 (12.0)	826 (10.0)	
	Other/unknown	906 (6.6)	669 (6.9)	
Marital status at diagnosis	Partnered	5868 (54)	4215 (53)	0.69
	Unpartnered	4570 (42)	3343 (42)	
	Unknown	457 (4)	346 (5)	
Grade	Well differentiated	1008 (9)	853 (11)	<0.01
	Moderately differentiated	7877 (72)	5800 (73)	
	Poorly differentiated	1785 (16)	1106 (14)	
	Undifferentiated	225 (2)	145 (2)	
Stage	Stage I	2815 (26)	2444 (31)	<0.01
	Stage II	4646 (42)	3088 (39)	
	Stage III	3434 (32)	2372 (30)	
Chemotherapy	Yes	2808 (26)	1813 (23)	<0.01

Data are expressed as number (percentage) or mean ± SD. IQR: Interquartile range, SD: Standard deviation.

Table 2. Demographics and pathological characteristics of patients with transverse adenocarcinoma by surgical approach after matching

		Extended colectomy n=7.904	Segmental colectomy n=7.904	p-value
Age	Mean ± SD	71±12	70±12	0.53
	Median (IQR)	73 (18)	72 (18)	
Sex	Male	3802 (48)	3788 (48)	0.83
Race	Caucasian	6343 (80.2)	6409 (83.1)	0.18
	African-American	866 (11.0)	826 (10.0)	
	Other/unknown	695 (8.8)	669 (6.9)	
Marital status at diagnosis	Partnered	4180 (53)	4215 (53)	0.55
	Unpartnered	3398 (43)	3343 (42)	
	Unknown	326 (4)	346 (5)	
Grade	Well differentiated	781(10)	853 (11)	0.08
	Moderately differentiated	5891 (75)	5800 (73)	
	Poorly differentiated	1114 (14)	1106 (14)	
	Undifferentiated	118 (1)	145 (2)	
Stage	Stage I	2404 (30)	2444 (31)	0.78
	Stage II	3119 (40)	3088 (39)	
	Stage III	2381 (30)	2372 (30)	
Chemotherapy	Yes	1759 (22)	1813 (23)	0.3

Data are expressed as number (percentage) or mean ± SD. IQR: Interquartile range, SD: Standard deviation.

Survival Analysis

Figure 3 displays Kaplan-Meier survival curves comparing surgical approaches.

Panel A shows 5-year OS, which did not differ significantly between EC and SC (65.6% vs. 66.9%, p=0.074).

Panel B illustrates 5-year CSS, where SC was associated with a significantly improved outcome compared to EC (84.3% vs. 81.7%, p<0.01). The median survival time was 55 months (IQR: 26-101) for the EC group and 60 months (IQR: 29-106) for the SC group, and this difference did not reach statistical significance (p=0.07, log-rank test).

Multivariable Analysis

Multivariable Cox proportional hazards modeling identified several independent predictors of CSS (Table 4). SC was associated with a lower risk of cancer-specific mortality compared to EC (HR =0.8376, p<0.001). Additional independent predictors of poorer CSS included increasing age (HR =1.0316 per year, p<0.001), male gender (HR =1.0864, p=0.0305), higher tumor grade, advanced stage (both p<0.001), and greater lymph node yield, which was associated with improved survival.

DISCUSSION

This large, population-based study compared EC and SC in patients with transverse colon adenocarcinoma, utilizing data from over 18,000 individuals. The findings revealed a clear temporal shift in surgical practice, with increasing use of EC and a corresponding decline in SC after 2010. This trend may reflect heightened concerns regarding oncologic adequacy, particularly in relation to lymph node staging and margin clearance.

Table 3. Comparison of lymph node retrieval and median survival time between surgical approaches

		Extended colectomy n=7.904	Segmental colectomy n=7.904	p-value
Number of retrieved regional lymph node	<12 nodes	481 (6.1)	858 (10.9)	<0.01
	12-16 nodes	2154 (27.2)	2595 (32.8)	
	17+ nodes	5240 (66.3)	4421 (55.9)	
	Unknown/missing	29 (0.4)	30 (0.4)	
	Mean ± SD	21±12	15±9	
	Median (IQR)	18 (13-25)	14 (9-18)	
Median survival time, months		55 (26-101)	60 (29-106)	0.07

Data are expressed as number (percentage) or median (interquartile). IQR: Interquartile range, SD: Standard deviation.

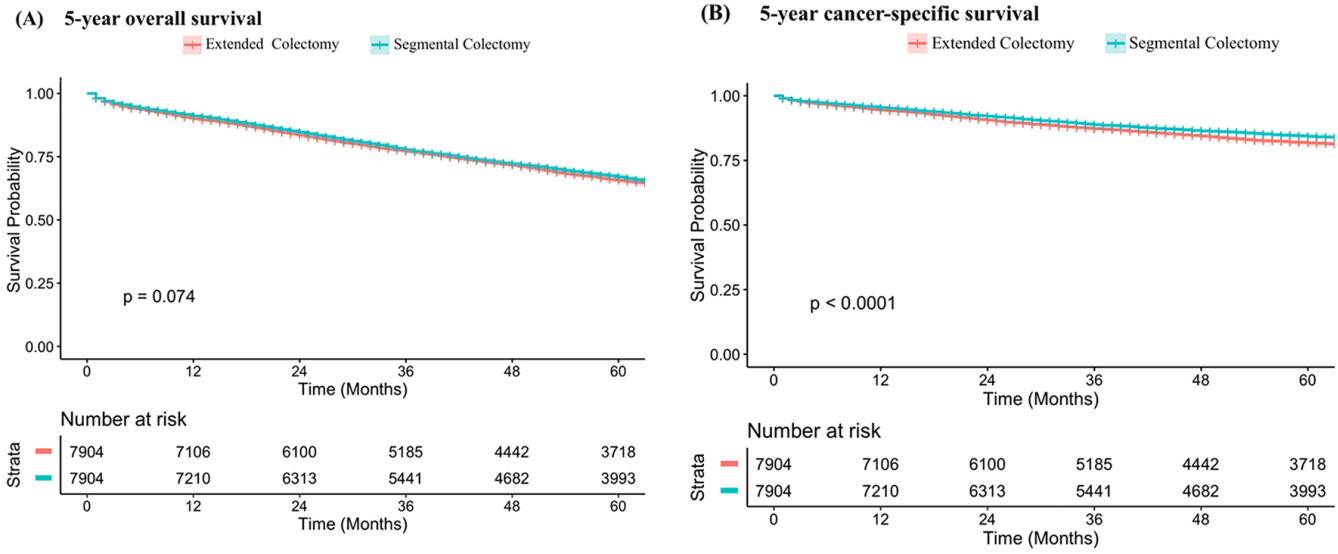

Figure 3. Kaplan-Meier estimates of 5-year overall and cancer-specific survival by resection type after matched analysis. **(A)** Five-year overall survival: EC 65.6% vs. SC 66.9% (p=0.074). HR =0.9574 (95% CI: 0.9081-1.0090), **(B)** Five-year cancer-specific survival: EC 81.7% vs. SC 84.3% (p<0.01). HR =0.8376 (95% CI: 0.7748-0.9057). Survival probabilities estimated by the Kaplan-Meier method; HRs and 95% CIs derived from multivariable Cox proportional hazards models.

EC: Extended colectomy, SC: Segmental colectomy, CI: Confidence interval, HRs: Hazard ratios

Table 4. Multivariable Cox regression results for cancer-specific survival

Variable	Hazard ratio	Lower-95-CI	Upper-95-CI	p-value
Surgical approach (SC vs. EC)	0.8376	0.7771	0.9029	<0.001
Age (per year increase)	1.0316	1.0277	1.0354	<0.001
Sex (male vs. female)	1.0864	1.0078	1.1712	0.0305
Grade G2 (vs. G1)	1.0661	0.9207	1.2344	0.3922
Grade G3 (vs. G1)	1.396	1.1851	1.6445	<0.0001
Grade G4 (vs. G1)	1.4082	1.0703	1.8528	0.0145
Stage II (vs. Stage I)	2.1758	1.9235	2.4613	<0.001
Stage III (vs. Stage I)	5.8368	5.1337	6.6363	<0.001
Chemotherapy (yes vs. no)	0.7793	0.706	0.8602	<0.001
12-16 Lymph nodes examined	0.8137	0.7088	0.9341	0.0034
17+ Lymph nodes examined	0.7998	0.7026	0.9105	<0.0001

SC: Segmental colectomy, EC: Extended colectomy, CI: Confidence interval, G: Grade of differentiation.
Note: The number of retrieved regional lymph nodes with unknown information was excluded from the multivariable Cox regression model due to its representation of missing or unknown data, which does not provide meaningful information for analysis.

Prior to PSM, SC was more frequently performed in older patients and those with early-stage or well-differentiated tumors, whereas EC was more common in patients with advanced-stage disease and more frequently accompanied by adjuvant chemotherapy—suggesting a more aggressive treatment strategy in the EC cohort. Even after matching, EC remained associated with higher rates of adequate lymph node retrieval (>12 nodes), likely due to the wider resection field inherent to the procedure.

Despite this, OS did not differ significantly between the groups. Interestingly, CSS was modestly but significantly better in the SC cohort. This may reflect favorable tumor biology, earlier stage, and lower perioperative risk in SC patients. These results challenge the assumption that more extensive resections inherently yield better oncologic outcomes, supporting the notion that, for selected patients, SC may offer equivalent or even superior long-term disease control.

The preference for EC in clinical practice may be driven by the anatomical complexity of the transverse colon and its proximity to major vascular structures. However, accumulating evidence—including the present study—supports the oncologic safety of SC when adequate lymphadenectomy is achieved, especially in cases with favorable biological features (7,11). The dual embryologic origin and variable lymphatic drainage of the transverse colon further complicate efforts to standardize surgical management. Thus, a uniform surgical strategy is unlikely to be appropriate in all cases. Surgical planning should instead be individualized, considering tumor location, anatomical complexity, and surgeon experience.

Our findings are consistent with previous analyses from the National Cancer Database and international cohorts, several of which have questioned the superiority of EC. Notably, poorer outcomes have been reported in some studies for EC, particularly in mid-transverse tumors and stage III disease (6,12), reinforcing the importance of tailored, biology-driven surgical approaches.

Anatomical variability—especially regarding the middle colic vessels and drainage patterns involving the right and left colic arteries—poses further challenges to standardization (13-16). Additionally, real-world clinical factors such as emergency presentation, patient frailty, and anesthetic risk often influence surgical decision-making and may appropriately lead to the selection of SC in certain contexts (16,17).

Although the absolute 5-year CSS difference between SC and EC was approximately 2.6%, this finding should be interpreted in both clinical and population-level contexts. At the individual patient level, the difference may appear modest; however, when extrapolated to large populations, even small absolute gains in survival can translate into a considerable number of lives saved over time. Furthermore, SC is generally a less extensive procedure than EC and may be associated with reduced operative time, lower perioperative morbidity, and faster recovery, making even a modest improvement in CSS clinically meaningful. The observed difference, combined with the procedural advantages of SC, supports the consideration of this approach in appropriately selected patients. It is also important to note that this effect persisted after multivariable adjustment for known prognostic factors, suggesting that the survival benefit is not solely attributable to baseline differences between patient groups.

While PSM was applied to balance stage and other measured covariates, the observed superior CSS in the SC group may be influenced by unmeasured factors not recorded in the SEER

database. In real-world surgical practice, extended resections are often chosen for tumors with more aggressive biological behavior, technically demanding locations, or advanced stage, whereas SC is typically performed for smaller, less aggressive tumors. Such underlying differences could contribute to residual confounding and may partially explain the apparent survival advantage of SC. As this is an observational study, the findings should be interpreted with caution, and prospective studies incorporating detailed clinicopathological and operative data are needed to confirm these results.

Study Limitations

A major strength of this study is the use of PSM, which minimized baseline imbalances and improved comparability between treatment groups. This statistical approach enhances the internal validity of retrospective registry analyses. Nonetheless, several limitations must be acknowledged. This study is subject to several inherent limitations associated with the SEER database. Important clinical variables, including margin status, urgency of surgery (emergency vs. elective), and the presence of lymphovascular or perineural invasion, are not captured. The absence of these data may influence the interpretation of oncological outcomes, as they are recognized prognostic factors in colorectal cancer. In addition, the PSM model in our analysis incorporated only age, sex, stage, grade, and chemotherapy status. The omission of other clinicopathological parameters, such as tumor size and additional histopathological features, may introduce residual confounding and selection bias. Furthermore, the SEER database does not provide information on surgical intent, detailed tumor location, or molecular tumor characteristics, which could also influence surgical decision-making. These unmeasured factors may partially account for the observed differences in CSS between the EC and SC groups, and their absence underscores the need for cautious interpretation. These limitations should be considered when interpreting the results, and future prospective studies with more comprehensive datasets are warranted to validate our findings.

CONCLUSION

In this comprehensive population-based analysis of patients with transverse colon adenocarcinoma, EC was more frequently employed, particularly in cases with advanced disease. However, SC provided comparable—and in certain subgroups, superior—CSS outcomes. These findings highlight the importance of personalized surgical decision-making that incorporates tumor biology, anatomical considerations, and patient-specific risk factors. Prospective, multi-institutional studies are needed to refine selection criteria and confirm the oncologic safety of SC for this anatomically and embryologically distinct region of the colon. In this population-based analysis, SC was associated with a modest CSS advantage compared to extended colectomy. However, given the observational design and the potential influence of unmeasured confounding factors, these results should not be interpreted as definitive evidence of the oncological superiority of SC. Further prospective, well-controlled studies are required to clarify the impact of surgical extent on long-term outcomes in transverse colon cancer.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Ethics Committee of Acıbadem University (approval number: 2025-09/352, date: 12.06.2025).

Informed Consent: Informed consent was obtained from patients.

Footnotes

Author Contributions

Concept - Ç.B., A.A., E.G.; Design - Ç.B., A.A., E.G.; Data Collection or Processing - Ç.B., M.E., E.G., D.A., B.B.; Analysis or Interpretation - Ç.B., A.A., V.Ö., D.A.; Literature Search - Ç.B., M.E., A.A., E.G., D.A., B.B.; Writing - Ç.B., M.E., A.A., V.Ö., D.A., B.B.

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

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ORIGINAL ARTICLE
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Transfusion requirements as a surrogate marker of mortality and morbidity in adults with severe burns: A retrospective cohort study

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ABSTRACT

Objective: Although blood transfusion is necessary for addressing anemia, coagulopathy, and systemic inflammation, transfusions also carry risks that may influence morbidity and mortality. This study, of patients with burns treated at a tertiary care centre, was conducted from October 2024 to May 2025. It aimed to investigate the association between blood and blood product transfusion requirements and clinical outcomes in adult patients with severe burns. Additionally, the study identified other predictors of mortality, and examined the prognostic role of common biochemical markers and complications in determining patient outcomes.

Material and Methods: This retrospective cohort study analyzed 82 eligible adult patients with burns. Patients were considered eligible if they were 18 years of age or older, were admitted for acute burn injury and had complete clinical and laboratory data. Demographic, clinical, laboratory, and transfusion data were retrieved from electronic medical records. Cox proportional hazards regression was used to identify independent predictors of mortality, while Kaplan-Meier analysis assessed survival trends.

Results: Participants were grouped into survivors (n=33) and non-survivors (n=49). Non-survivors required higher total volume of red blood cells (11 vs. 6 units), fresh frozen plasma (11 vs. 5 units), and platelets (4 vs. 0 units), particularly in the intensive care unit (ICU) setting. Compared to survivors, non-survivors also had elevated creatinine levels, lower platelet counts, and higher rates of complications such as pneumonia and dialysis. Cox regression confirmed total body surface area burned as the strongest independent predictor of mortality.

Conclusion: High transfusion requirements in the ICU are associated with increased mortality in patients with severe burns and may serve as a surrogate marker for disease severity. These findings support the need for restrictive, individualized transfusion strategies and underscore the importance of integrating transfusion parameters into early risk assessment and prognostic models in burn care.

Keywords: Burns, blood transfusion, blood product transfusion, burns management

INTRODUCTION

Burn injuries remain a significant global public health issue, contributing significantly to morbidity, mortality, and long-term disability, particularly in low and middle-income countries (1). According to the World Health Organization, approximately 180,000 deaths annually are attributed to burns, with the vast majority occurring in resource-limited settings (2). Despite advancements in resuscitation, wound care, surgical techniques, and critical care, the prognosis in patients with severe burns continues to be influenced by a range of clinical and biochemical factors.

Early and accurate prognostication is essential for guiding treatment intensity, triage decisions, and allocation of healthcare resources, particularly in intensive care settings. Various scoring systems have been developed to predict mortality and outcomes in patients with burns, incorporating factors such as age, total body surface area (TBSA), inhalation injury, and comorbidities (3). However, recent studies have increasingly focused on the prognostic utility of routine clinical and laboratory parameters, such as serum creatinine, platelet count, and coagulation markers (4,5). These parameters, which are readily available in most settings, may serve as early indicators of systemic deterioration and risk of poorer outcomes.

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Blood transfusion practices in patients with burns are typically guided by clinical and laboratory indicators of physiological need, particularly the assessment of end-organ perfusion. Although transfusion therapy carries well-established risks and complications, approximately 25% of patients in intensive care unit (ICU) receive transfusions, often to address anemia-related complications (6). Patients with major burn injuries present with substantial transfusion requirements due to multiple factors, including intraoperative blood loss, hemodilution from fluid resuscitation, suppressed erythropoiesis, increased hemolysis, and iatrogenic blood loss associated with frequent laboratory testing (7,8).

We conducted a comprehensive analysis of patients with burns admitted to a tertiary care burn unit, comparing survivors and non-survivors across demographic, clinical, laboratory, and treatment variables. The primary objective was to evaluate the impact of blood and blood product transfusion on survival outcomes. Secondary objectives included identifying other key predictors of mortality and examining the prognostic role of common biochemical markers and complications in determining patient outcomes. These findings aim to inform clinical decision-making and contribute to the refinement of prognostic models in burn care.

MATERIAL and METHODS

Ethical Consideration

The Institutional Ethics Committee approval for this study (2025/010.99/13/29) was provided by the Scientific Research Ethics Committee of University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital on 26 February, 2025. Data handling complied with applicable data protection regulations. This study has been conducted in accordance with the principles set forth in the Helsinki Declaration.

Study Design and Setting

This retrospective cohort study, conducted from October, 2024 to May, 2025, used data from the medical records of eligible patients with burns treated at a tertiary care centre between 1st of January 2008 and 1st of December 2020. This centre serves as a regional referral unit for patients with moderate to severe burn injuries.

Study Population and Eligibility Criteria

A total of 82 adult patients with burns who were admitted to the tertiary care centre between 1st of January 2008 and 1st of December 2020 and met the eligibility criteria were included. Inclusion criteria were age ≥18 years, admission for acute burn injury, and availability of complete clinical and laboratory data. Patients were excluded if they were <18 years, had incomplete records, or were admitted for non-burn-related conditions. Patients were categorized into two groups based on in-hospital survival status: Survivors (n=33) and non-survivors (n=49).

Data Collection and Variables

Clinical and demographic data were retrieved from electronic medical records and included age, sex, body weight, and American Society of Anesthesiologists (ASA) physical status classification. Burn characteristics were recorded according to burn type, degree of burn, and TBSA burned. TBSA was estimated at the time of initial presentation to the burn center, prior to fluid resuscitation, using the Lund and Browder chart which is a standardized and widely accepted method for burn size estimation (9,10). All assessments were performed by experienced burn care physicians who had undergone formal training in TBSA estimation. To minimize interobserver variability, the same physician team conducted the assessments throughout the study period. Data on interventions and complications included the need for mechanical ventilation, dialysis, development of pneumonia, sepsis, wound infections, and requirement for surgical procedures e.g., debridement, grafting, fasciotomy/escharotomy. Comorbidities and pre-existing conditions were systematically recorded for all patients at the time of admission using standardized medical history forms. These data included, but were not limited to, cardiovascular disease, diabetes mellitus, chronic respiratory conditions, and renal impairment. Hospital metrics were evaluated as ICU and total hospital length of stay, number of dressing changes, and total operation hours. Laboratory investigations at admission and the final time point prior to death or discharge included serum creatinine, hemoglobin, hematocrit, platelet count, international normalised ratio (INR), and troponin levels. Transfusion data included the total number of units administered for red blood cells (RBCs), fresh frozen plasma (FFP), platelets, and albumin. Transfusion details were recorded across different clinical settings (operating theatre, ICU, and general ward).

Statistical Analysis

Continuous variables were summarized as medians with interquartile ranges or means with standard deviations. Normality was checked visually using histograms. Categorical variables were presented as counts and percentages. Comparisons between survivors and non-survivors were performed using the Mann-Whitney U test for non-normally distributed continuous variables or Student's t-test for normally distributed continuous variables, and the chi-square or Fisher's exact test for categorical variables. A p-value of <0.05 was considered statistically significant.

Survival analysis was conducted using the Kaplan-Meier method, with survival curves compared using log-rank test. Associations between risk factors and mortality were assessed using a multivariable Cox proportional hazards regression model that included all selected variables in a single model. Hazard ratios (HR) with 95% confidence intervals were reported. Variables

included in the Cox model were selected based on clinical relevance and univariate analysis results. All statistical analyses were performed using STATA 17 (College Station, TX).

RESULTS

Baseline Characteristics of the Participants

Table 1 outlines the baseline characteristics of 82 eligible patients with burns who were admitted to the tertiary care center between 1st of January 2008 and 1st of December 2020. The cohort included 17 females (20.7%) and 65 males (79.3%). Of these, 33 patients survived (4 females and 29 males) while 49 were deceased (13 females and 36 males). The median age of survivors was 29 years compared to 75 years in the deceased group. In terms of ASA classification, 82% of survivors were classified as ASA I, whereas 47% of the deceased were calssified as ASA III.

Five individuals amongst the survivors sustained first-degree burns, while none of the deceased had first-degree burns. Among the non-survivors, 43% sustained second- to third-degree burns, and 16% sustained third-degree burns. In contrast, 9% of survivors had second- to third-degree burns, and 15% sustained third-degree burns. The median TBSA affected was statistically significantly higher in the deceased group [54.0 (45.0, 65.0)] compared to the alive group [38.0 (31.0, 40.0)]. Additionally, the predominant burn mechanism differed between the two groups: Most survivors sustained electrical burns, whereas flame burns were the most common among the non-survivors group.

Laboratory Investigations and Transfusion Requirements

Table 2 summarizes the laboratory values at admission and final measurement prior to death or discharge, comparing survivors and non-survivors. On admission, survivors had a lower median creatinine level (0.72 mg/dL) compared to non-survivors (1.10 mg/dL). This difference persisted at the final measurement, with survivors having a median creatinine of 0.62 mg/dL versus 1.65 mg/dL in non-survivors (p<0.001). Hemoglobin levels were similar between groups, both at admission (16.34 g/dL in survivors vs. 15.18 g/dL in non-survivors) and at last reading (10.26 g/dL in survivors vs. 10.03 g/dL in non-survivors). On admission, both groups had a median INR of 1.21, but by the final measurement, non-survivors had a higher INR of 1.54 compared to survivors (INR 1.18). Survivors had significantly higher platelet counts on admission (median 270 $x10^3$/µL) compared to non-survivors (172$x10^3$/µL), and this trend continued at the final measurement (311$x10^3$/µL vs. 144$x10^3$/µL).

Regarding transfusion requirements, the number of RBC and FFP units administered in the operating theatre and the ward was similar between groups. However, non-survivors required significantly higher number of RBC and FFP units in the ICU compared to survivors. The total median RBC transfused were 6 in survivors and 11 in non-survivors, while the total median FFP units were 5 in survivors and 11 in non-survivors (Table 3).

Interventions and Complications

Table 4 presents the interventions and complications observed among surviors and non-survivors. In the survivor group, 23 individuals (70%) required mechanical ventilation for a median

Table 1. Baseline characteristics of the participants

Factor	Level	Survivors	Non-survivors	p-value
n		33	49	
Age, median (IQR)		29.0 (25.0, 47.0)	75.0 (48.0, 84.0)	<0.001
Gender	Female	4 (12%)	13 (27%)	0.11
	Male	29 (88%)	36 (73%)	
Weight, mean (SD)		77.3 (5.5)	75.9 (5.8)	0.28
ASA	1	27 (82%)	14 (29%)	<0.001
	2	3 (9%)	12 (24%)	
	3	3 (9%)	23 (47%)	
Burn degree	1	5 (15%)	0 (0%)	<0.001
	2	20 (61%)	20 (41%)	
	2-3	3 (9%)	21 (43%)	
	3	5 (15%)	8 (16%)	
TBSA, median (IQR)		38.0 (31.0, 40.0)	54.0 (45.0, 65.0)	<0.001
Burn type	Electric	28 (85%)	18 (37%)	<0.001
	Flame	5 (15%)	31 (63%)	

ASA: American Society of Anesthesiologists, TBSA: Total body surface area, IQR: Interquartile range, SD: Standard deviation.

duration of 3 days, compared to all 49 individuals (100%) in the deceased group, who required mechanical ventilation for a median duration of 11 days. Additionally, dialysis was needed in 14 individuals in the deceased group compared to 3 individuals in the survivor group. Pneumonia was reported in 33% of survivors and 78% of non-survivors. Sepsis occurred in all individuals from both groups.

Notably, all survivors developed wound infections, whereas 47 out of 49 non-survivors experienced wound infections. Furthermore, all patients with flame burns in both groups underwent fasciotomy/esharotomy. The median number of debridement grafts was higher among survivors than non-survivors.

Regarding hospital stay metrics, the median hospital length of stay was 46 days in the survivor group and 11 days in the non-survivor group. The median ICU length of stay was 27 days for survivors and 11 days for non-survivors.

Cox Proportional Hazard Regression Analysis

Table 5 summarizes the Cox proportional HRs for various variables independently associated with mortality. Individuals with flame burns had a 1.11 times higher hazard of mortality compared to those with electrical burns, though this was not statistically significant (p=0.913). Males had a 1.48 times higher hazard of mortality compared to females. Third-degree burns were associated with nearly a threefold higher hazard of mortality compared to first- and second-degree burns, but this can be attributed due to small sample size, as only 5 survivors and 8 non-survivors had third degree burns. Patients with TBSA burns of 39-43%, 44-55%, and 56-100% had hazard ratios of 9.07 (p=0.008), 14.76 (p=0.001), and 46.00 (p<0.001), respectively,

Table 2. Admission and final time point laboratory investigations

Factor	Survivors	Non-survivors	p-value
N	33	49	
Troponin level, median (IQR)	0.04 (0.03, 0.05)	0.07 (0.07, 0.08)	<0.001
Admission creatinine, median (IQR)	0.72 (0.66, 0.90)	1.10 (0.78, 1.46)	<0.001
Admission INR, median (IQR)	1.21 (1.10, 1.33)	1.21 (1.10, 1.34)	0.96
Admission haematocrit, mean (SD)	49.45 (6.27)	46.04 (9.72)	0.087
Admission hemoglobin, mean (SD)	16.34 (2.00)	15.18 (3.16)	0.071
Admission platelet, median (IQR)	270.00 (226.00, 340.00)	172.00 (139.50, 256.50)	<0.001
Last creatinine, median (IQR)	0.62 (0.55, 0.83)	1.65 (1.04, 2.32)	<0.001
Last INR, median (IQR)	1.18 (1.10, 1.26)	1.54 (1.23, 1.98)	<0.001
Last hematocrit, mean (SD)	30.66 (3.93)	30.58 (4.74)	0.94
Last hemoglobin, mean (SD)	10.26 (1.28)	10.03 (1.59)	0.50
Last platelet, median (IQR)	311.00 (214.00, 380.00)	144.00 (107.00, 192.00)	<0.001

IQR: Interquartile range, SD: Standard deviation, INR: International normalised ratio.

Table 3. Comparison of total transfusion rate in OR and ICU

Factor	Survivors	Non-survivors	p-value
N	33	49	
OR RBC, median (IQR)	3.0 (2.0, 4.0)	4.0 (1.0, 6.0)	0.74
OR FFP, median (IQR)	2.0 (2.0, 4.0)	2.5 (1.0, 6.0)	0.74
ICU RBC, median (IQR)	2.0 (2.0, 3.0)	8.0 (6.0, 12.0)	<0.001
ICU FFP, median (IQR)	2.0 (2.0, 3.0)	8.0 (5.0, 10.0)	<0.001
ICU platelet, median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 10.0)	0.014
Ward RBC, median (IQR)	1.0 (0.0, 1.0)	1.0 (1.0, 2.0)	0.053
ICU albumin, median (IQR)	8.0 (4.0, 12.0)	8.0 (3.0, 8.0)	0.18
Total RBC, median (IQR)	6.0 (4.0, 7.0)	11.0 (8.0, 19.0)	<0.001
Total FFP, median (IQR)	5.0 (4.0, 7.0)	11.0 (6.0, 14.0)	<0.001
Total platelet, median (IQR)	0.0 (0.0, 5.0)	4.0 (1.0, 11.0)	0.003

OR: Operating room, RBC: Red blood cells, FFP: Fresh frozen plasma, ICU: Intensive care unit, IQR: Interquartile range; SD: Standard deviation.

compared to those with burns covering 0-38% TBSA. Lastly, patients with elevated creatinine levels at admission had a 1.58 times higher hazard of mortality compared to those with normal creatinine levels.

Kaplan-Meier Curves

Figure 1 illustrates the Kaplan-Meier survival function for the overall study population, showing a steady decline in survival probability over time. A sharp drop in survival probability is observed early on, indicating higher mortality rates during this initial period. The curve eventually stabilizes at approximately 0.25, signifying that 25% of individuals remain event-free (i.e., alive) by the end of the observation period.

When stratified by burn grade (Figure 2), survival curves demonstrate clear differences between the groups. Patients with first-degree burns exhibited the highest survival probability at 1.0, indicating that no events (deaths) occurred in this group throughout the observation period. In contrast, patients with second degree burns showed a steeper decline, though survival probabilities remained better compared to patients with third-degree burns. The third-degree burn group experienced the

Table 4. Interventions and complications

Factor	Level	Survivors	Non-survivors	p-value
n		33	49	
Mechanical ventilation	No	10 (30%)	0 (0%)	<0.001
	Yes	23 (70%)	49 (100%)	
Mechanical ventilation duration, median (IQR)		3.0 (0.0, 12.0)	11.0 (7.0, 19.0)	<0.001
Pneumonia	No	22 (67%)	11 (22%)	<0.001
	Yes	11 (33%)	38 (78%)	
Sepsis		33 (100%)	49 (100%)	
Dialysis	No	30 (91%)	14 (29%)	<0.001
	Yes	3 (9%)	35 (71%)	
Wound infection	No	0 (0%)	2 (4%)	0.51
	Yes	33 (100%)	47 (96%)	
Fasciotomy/escharotomy		28 (100%)	18 (100%)	
Debridement graft, median (IQR)		5.0 (4.0, 6.0)	2.0 (0.0, 3.0)	<0.001
Number of dressing, median (IQR)		13.0 (9.5, 20.0)	4.5 (3.0, 7.0)	<0.001
Total operation hours, median (IQR)		6.0 (5.0, 7.0)	5.5 (3.0, 7.0)	0.32
Hospital length of stay, median (IQR)		46.0 (36.0, 65.0)	11.0 (7.0, 19.0)	<0.001
ICU length of stay, median (IQR)		27.0 (14.0, 30.0)	11.0 (7.0, 19.0)	0.002

ICU: Intensive care unit, IQR: Interquartile range.

Table 5. Cox proportional hazard regression

Variable	Level	Hazard ratio	LCI	UCI	p-value
Burn type	Electric	Reference	-	-	-
	Flame	1.11	0.18	6.72	0.913
Gender	Female	Reference	-	-	-
	Male	1.48	0.66	3.31	0.341
Age		1.02	0.99	1.05	0.175
Burn degree	Grades 1&2	Reference	-	-	-
	Grade 3	2.80	0.81	9.63	0.103
Total body surface area	0-38%	Reference	-	-	-
	39-43%	9.07	1.77	46.53	0.008
	44-55%	14.76	3.02	72.30	0.001
	56-100%	46.00	8.46	250.25	0
Creatinine	Normal	Reference	-	-	-
	High	1.58	0.63	3.97	0.326

most pronounced decrease in survival probability, particularly in the early phase, with a markedly shorter median survival time. The separation between the survival curves for different burn degrees remains distinct throughout the observed period, highlighting the impact of burn severity on survival outcomes.

DISCUSSION

This retrospective cohort study aimed to evaluate the impact of blood transfusion on survival outcomes and identify predictors of mortality in patients with burns. Additionally, it sought to examine the prognostic role of biochemical markers and complications in influencing outcomes. This study analysed the characteristics, complications, and survival outcomes of 82 individuals with burn injuries treated in a tertiary care setting.

The management and outcomes of burn injuries remain a critical area of study due to the significant morbidity and mortality associated with such trauma. In our study, non-survivors required higher volumes of RBCs, FFP, and platelets in the ICU, underscoring the resource-intensive nature of managing severe burn injuries. These findings support the adoption of a restrictive RBC transfusion strategy in patients with severe burns. A multicentre study conducted by Du et al. (9), involving 474 patients across three institutions, identified a threshold of six units for extraoperative RBC transfusion. Their analysis demonstrated that each additional RBC unit was associated with an approximate 2.96-fold reduction in mortality risk; however, this survival benefit plateaued once transfusion volumes exceeded six units. In our study cohort, the median RBC transfusion volume in the ICU was eight units in the non-survivors group, compared to two units in the survivor group. This disparity may have contributed to the elevated mortality rate observed in our cohort and reinforces the concept that RBC transfusion beyond six units offers limited survival benefit.

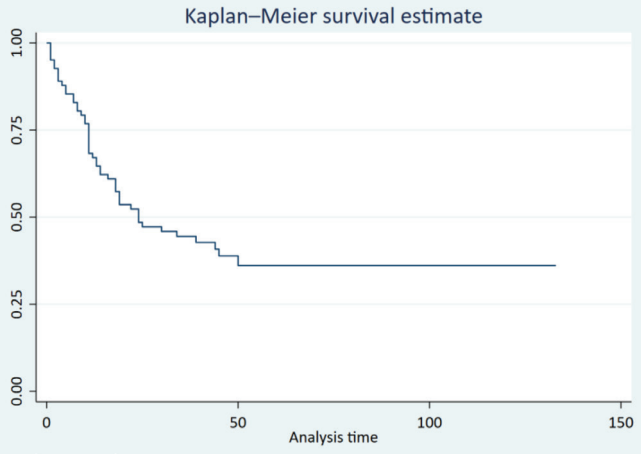

Figure 1. Kaplan-Meier curve for survival.

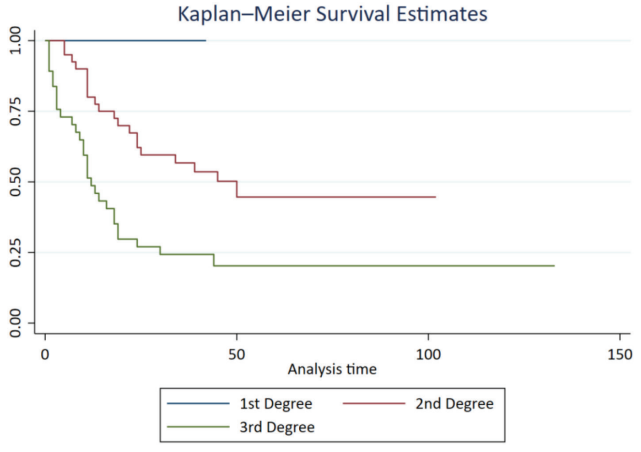

Figure 2. Kaplan-Meier curve for survival by burn degree.

In our study, non-survivors admitted to the ICU required a median platelet transfusion volume of 8 units, compared to 2 units in the survivors group. Thrombocytopenia is a common complication in patients with burns, often resulting from sepsis, coagulopathy, systemic inflammation, and various medical interventions, necessitating platelet transfusions. Notably, all patients in both groups-survivors and non-survivors- developed sepsis. While platelet transfusion is often a clinical necessity, it is not without risks. Platelet activation and subsequent release of pro-inflammatory mediators play a key role in initiating and amplifying systemic inflammation and contributing to atherosclerotic processes (11). Consequently, platelet transfusions may exacerbate a hypercoagulable state, thereby increasing the risk of thrombotic events, infections, and ultimately, a poorer overall prognosis (12,13). In our cohort, non-survivors also demonstrated higher rates of complications i.e., pneumonia and a greater need for interventions, including mechanical ventilation and dialysis. Interestingly, survivors underwent more frequent surgical interventions, suggesting that aggressive surgical management may be beneficial in selected patients, even those with severe burns (14).

Our findings align with and expand on existing evidence that older age, greater TBSA burned, higher burn severity, and systemic complications are strongly associated with increased mortality in patients with burns. Prior studies have demonstrated a sharp increase in mortality risk as TBSA increases, particulary beyond 44% (15). Consistent with these findings, our study showed that most survivors were younger and had a smaller TBSA compared to non-survivors. Additionally, cox proportional hazard analyses identified TBSA as a strong predictor of mortality, with HRs increasing substantially as burn severity escalated. This highlights the critical need for early and accurate assessment of burn extent to effectively prioritize care and predict outcomes. Moreover, both age and TBSA are key risk factors for sepsis in

severely burn patients (16), highlighting the importance of vigilant clinical observation to improve recovery and reduce sepsis-related fatalities. Furthermore, survival analysis using Kaplan-Meier curves illustrated the impact of burn severity on outcomes, with first-degree burns associated with the highest survival probability and third-degree burns showing the steepest decline in survival, particularly in the early post-injury period. Deeper burns are more likely to lead to infection, delayed healing, and systemic inflammation (17). These findings emphasize the importance of early intervention and tailored management strategies for burn patients, particularly those with extensive or high-grade injuries.

In our study, electrical burns were more common among survivors, while flame burns predominated in non-survivors. Although flame burns and male sex were associated with higher mortality risks, these findings were not statistically significant. In a review of 101 patients with electrical burns, renal injury requiring hemofiltration was associated with an approximately 12-fold higher risk of death. Consistent with these findings, our study demonstrated that renal function markers (e.g., creatinine) and coagulation markers (e.g., INR) were strongly associated with poor outcomes. These observations highlight the importance of early recognition and aggressive management of systemic complications, particularly renal dysfunction and coagulopathy in improving survival in patients with severe burns.

Study Limitations

While this study provides valuable insights, it has several limitations. The retrospective design is inherently susceptible to incomplete or missing data, and the single-centre setting and small sample size limit the external validity and generalizability of the findings. No power analysis was performed due to the retrospective nature of the study, and all eligible participants were included. Although important confounders such as comorbidities were not incorporated into the analysis, this was due to an insufficient number of outcome events, as a minimum of six events per predictor variable is generally recommended to maintain model stability. Future research should focus on prospective, multicentre studies to validate these findings and examine additional variables not assessed in this study, such as inhalation injury and time to surgical intervention.

Moreover, there is a critical need for prospective research to define optimal transfusion strategies that carefully balance the benefits of correcting physiological deficits with the risks of transfusion-related complications in critically ill burn patients. The timing of FFP administration is a critical factor in interpreting transfusion practices and clinical outcomes. In this retrospective study, the total amount of FFP administered was recorded over the entire course of the ICU stay; however, the day-specific breakdown was not consistently documented across all cases and was therefore not analyzed separately. We believe that prospective data collection with precise timing of transfusions would enhance future research on this topic.

While our findings highlight an association between transfusion volume and mortality, we did not comprehensively investigate the determinants of transfusion requirements. Although we collected relevant clinical and laboratory data—including weight, INR, RBC, platelet count, hemoglobin, and hematocrit—our primary aim, given the limitations of the dataset, was to assess prognostic associations rather than model predictors of transfusion need. Future prospective studies should use multivariable approaches to identify predictors of transfusion volume and define optimal transfusion strategies that balance the benefits of correcting physiological deficits with the risks of transfusion-related complications in critically ill burn patients.

CONCLUSION

The observed association between higher transfusion volumes and increased mortality highlights the need to refine transfusion thresholds in burn care. Over-transfusion may contribute to adverse outcomes such as infection, thrombotic complications, and organ dysfunction, particularly in patients with pre-existing risk factors such as elevated creatinine or thrombocytopenia. TBSA remains the strongest independent predictor of mortality, however transfusion requirements may serve as a dynamic and modifiable indicator of clinical trajectory. Integrating transfusion volume with other predictors including burn depth, renal function, and coagulation parameters can enhance early risk stratification and support individualized treatment strategies.

Ethics

Ethics Committee Approval: The Institutional Ethics Committee approval for this study (2025/010.99/13/29) was provided by the Scientific Research Ethics Committee of University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital on 26 February, 2025.

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Surgical and Medical Practices - A.S., S.Y., E.H.Ü.; Concept - A.S., S.Y., M.A., E.H.Ü., N.E.T., A.M.E., T.Ş., G.F., K.T.S.; Design - A.S., M.A., E.H.Ü., N.E.T., A.M.E., T.Ş., G.F., K.T.S.; Data Collection or Processing - S.Y., M.A., E.H.Ü., N.E.T., A.M.E., T.Ş., G.F. ; Analysis or Interpretation - A.S., S.Y., M.A., N.E.T., K.T.S.; Literature Search - A.S., S.Y., M.A., E.H.Ü., N.E.T., A.M.E., T.Ş., G.F., K.T.S.; Writing - A.S., S.Y., M.A., E.H.Ü., N.E.T., A.M.E., T.Ş., G.F., K.T.S.

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Risk factors for bowel resection and postoperative complications in incarcerated abdominal wall hernia

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ABSTRACT

Objective: Timely identification of the risk of bowel resection is crucial for improving surgical outcomes in incarcerated hernias. Preoperative recognition of risk factors can improve postoperative recovery and patient safety. This study aims to investigate the predictors of bowel resection and postoperative complications in patients undergoing surgery for incarcerated abdominal wall hernias.

Material and Methods: A single-center retrospective analysis was performed on patients who underwent surgery for incarcerated abdominal wall hernia between January 2017 and January 2022. Multivariate logistic regression was performed to determine risk factors for bowel resection, postoperative complications, and mortality. A p-value of <0.05 was considered statistically significant.

Results: A total of ninety-two patients were detected. Mean age was 66.1±14.5 years and the 76 (82.6%) of the patients were male. Bowel resection was associated with symptom duration, higher platelet count, higher neutrophil to lymphocyte and platelet to lymphocyte ratio (p=0.014, p=0.040, p=0.042, p=0.015). Postoperative hospital stay was longer and postoperative mortality was higher in patients who underwent bowel resection (p<0.001, p=0.013). No risk factors for bowel resection or mortality were identified. Symptom duration and bowel resection were found to be risk factors for postoperative complications [odds ratio (OR): 1.713, 95% confidence interval (CI): 1.093-2.686; p=0.019] (OR: 4.655, 95% CI: 1.230-17.613; p=0.023).

Conclusion: Although no specific risk factors for bowel resection or mortality have been identified, symptom duration and bowel resection may be considered risk factors for postoperative complications in these patients. Furthermore, hernia sac fluid is not a risk factor for bowel resection.

Keywords: Abominal wall hernia, incarceration, bowel resection, fluid in hernia sac

INTRODUCTION

Abdominal wall hernia (AWH) repairs are among the most frequently performed elective and emergency surgical procedures worldwide. Incarceration occurs in 5-15% of cases, and 15% require bowel resection due to strangulation (1). Emergency surgical interventions for incarceration can reveal incarceration or perforation, necessitating bowel resection and increasing the risks of morbidity and mortality. Early intervention and risk stratification are critical for improving outcomes. Some of the reported risk factors include female gender, advanced age, serious comorbidities, delayed hospitalization and femoral hernia (2,3). Identifying risk factors before surgery can help predict postoperative complications and facilitate safer recovery. In light of these circumstances, we designed a study to identify preoperative predictors of bowel resection and postoperative complications of incarcerated AWH to guide clinical decision-making.

MATERIAL and METHODS

This single-center retrospective cohort study analyzed patients who underwent surgery for incarcerated AWH between January 2017 and January 2022. After ethical approvals were obtained, patients presenting to the emergency department were identified from the hospital electronic database. This study was conducted retrospectively and approved by the Local Ethics Committee of University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital (approval number: 2022/06-35, date: 15.06.2022). Inclusion criteria included adults (>18 years of age) with complete medical records, while exclusion criteria were incomplete data, ascites-related comorbidities (e.g., cirrhosis, congestive heart failure), and pediatric cases. Data collection included descriptive parameters (age, gender), laboratory findings [complete blood count (CBC), C-reactive protein, albumin, lactate levels],

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preoperative findings of the hernia [hernia type, size, hernia sac fluid (HSF), symptom duration], perioperative findings (bowel resection, mesh application), and postoperative findings (hospital stay, complications and mortality). During the preoperative evaluation, the time from the onset of the patient's pain to the operation was recorded as symptom duration. Other vital signs could not be obtained retrospectively. On physical examination, all patients had pain in the area of the incarcerated hernia. Only polypropylene mesh, which had to be shaped and fixed by the surgeon, was used. The use of mesh was left to the surgeon's experience and discretion during the operation. Postoperative complications were categorized as surgery-related complications (e.g., wound infection, hematoma, seroma, ileus, anastomotic leak) and systemic complications (e.g., pneumonia, urinary tract infection, thromboembolic events). Mortality was defined as death between surgery and hospital discharge. HSF was defined as any measurable fluid detected on computed tomography (CT) scans. After descriptive statistics, patients were divided into groups according to the presence of HSF and bowel resection. The associations of parameters with these two findings were examined. Additionally, multivariate analysis was performed to investigate risk factors for bowel resection, postoperative complications, and mortality.

Statistical Analysis

SPSS version 25.0 software was used for statistical analysis. Kolmogorov-Smirnov/Shapiro-Wilk tests were used for the conformity of the variables to the normal distribution. While mean ± standard deviation was given for normally distributed variables, median (Q1-Q3) was stated for non-normally distributed variables. For comparing the continuous data in binary group, t-test was used for independent and normally distributed, and the Mann-Whitney U for not normally distributed values. Categorical data analysis were done with using Pearson's chi-square or Fisher's exact chi-square test. Independent factors were detected by using multivariate logistic regression analysis. In determination of parameters for multivariate analysis, modeling was performed considering clinical relevance and relationships of univariate parameters. To reduce concerns about overfitting, auxiliary variables were reduced using backward elimination. Model calibration was tested with the Hosmer-Lemeshow goodness-of-fit test. Furthermore, model performance was evaluated using ROC curves, and the area under the curve (AUC) was calculated based on predicted probabilities obtained from the logistic regression model. Odds ratio (OR) and 95% confidence intervals (CIs) were also given for each variable in multivariate analysis. $p<0.05$ was considered statistically significant.

RESULTS

A total of ninety-two patients were detected. The mean age was 66.1±14.5 years and the 76 (82.6%) of the patients were male. Among the incarcerated AWH, inguinal hernia was detected in 77 (83.7%) patients, incisional hernia in 7 (7.6%) patients, femoral hernia in 7 (7.6%) patients and umbilical hernia in 1 (1.1%) patient. The median duration of symptom onset until hospitalization was 1.5 (1-2.8) days. All surgeries were performed using the open surgical approach. Preoperative imaging revealed HSF in 32 (34.8%) patients. Intestinal resection was performed in 18 (19.6%) patients, and omentectomy was performed in 12 (13%) patients. A polypropylene mesh of the required size was applied to 69 (75%) patients. The median postoperative hospital stay was 3 (2-5) days. Postoperative complications were detected in 18 (19.6%) patients, and postoperative mortality was observed in 9 (9.8%) patients. Postoperative surgery-related complications included surgical site infection in 5 patients, hematuria in 2 patients, evisceration in 2 patients and ileus in 1 patient. Systemic complications included pneumonia in 2 patients, acute renal failure in 3 patients, sepsis in 1 patient and myocardial infarction in 2 patients. Other CBC results are detailed in Table 1.

Although the age was higher in patients with HSF and those who underwent bowel resection, the difference was not statistically significant. HSF was associated only with preoperative platelet count ($p=0.037$) (Table 1). The presence of bowel resection was associated with longer symptom duration, higher platelet count, higher neutrophil/lymphocyte ratio (NLR) and higher platelet/lymphocyte ratio (PLR) ($p=0.014$, $p=0.040$, $p=0.042$, $p=0.015$). Additionally, mesh placement was not preferred and the postoperative complication rate was higher in patients who underwent bowel resection ($p<0.001$, $p=0.001$). Patients who underwent bowel resection had a longer postoperative hospital stay and a higher postoperative mortality rate ($p<0.001$, $p=0.013$) (Table 2).

After crosstabs, multivariate analysis was performed to observe risk factors for bowel resection, postoperative complications and mortality. The performance of the models was evaluated using both ROC analysis and the Hosmer-Lemeshow test. None of the parameters were detected as a risk factor for bowel resection and postoperative mortality (Tables 3, 4). For the bowel resection model, ROC analysis showed an AUC of 0.736 (95% CI: 0.611-0.862) ($p=0.002$), the Hosmer-Lemeshow test showed $\chi^2=11.07$, $df=8$, $p=0.198$. For the mortality model, ROC analysis showed an AUC of 0.854 (95% CI: 0.712-0.997) ($p=0.001$), the Hosmer-Lemeshow test showed $\chi^2=8.99$, $df=8$, $p=0.343$. Among the parameters related to postoperative complications, duration of symptoms and bowel resection were found to be risk factors (OR 1.713, 95% CI 1.093-2.686; $p=0.019$) (OR 4.655, 95% CI 1.230-17.613; $p=0.023$) (Table 5). For postoperative complications model, the ROC analysis showed an AUC of 0.793 (95% CI: 0.659-0.926) ($p<0.001$), the Hosmer-Lemeshow test showed $\chi^2=3.14$, $df=8$, $p=0.926$.

Table 1. Factors associated with hernia sac fluid in incarcerated abdominal wall hernia

	All patients n=92	Without fluid in hernia sac n=60	With fluid in hernia sac n=32	p-value
Age, mean ± SD	66.1±14.5	65.1±15.2	68.2±13.1	0.332
Sex, n (%)				0.802
Male	76 (82.6)	50 (83.3)	26 (81.3)	
Female	16 (17.4)	10 (16.7)	6 (18.8)	
Type of hernia, n (%)				0.549
Inguinal	77 (83.7)	49 (81.7)	28 (87.5)	
Incisional	7 (7.6)	6 (10)	1 (3.1)	
Umbilical	1 (1.1)	1 (1.7)	0	
Femoral	7 (7.6)	4 (6.7)	3 (9.4)	
Duration of symptom, day, median (Q1-Q3)	1.5 (1-2.8)	1.5 (1-3)	1.5 (1-2)	0.797
WBC, median (Q1-Q3)	11000 (7400-14600)	10500 (7475-14225)	12050 (6525-17125)	0.354
Neutrophil, median (Q1-Q3)	8300 (5525-11500)	8300 (5650-10900)	8600 (4525-12900)	0.752
Lymphocyte, median (Q1-Q3)	1400 (900-2100)	1200 (825-2100)	1500 (950-2150)	0.319
Platelet, median (Q1-Q3)	251500 (205750-328500)	270000 (208750-362000)	237000 (190750-275250)	**0.037**
NLR, median (Q1-Q3)	6.83 (3.01-10.84)	6.83 (3.69-10.73)	6.83 (2.39-12.28)	0.544
PLR, median (Q1-Q3)	177.8 (116.1-363.1)	224.7 (125.6-397.4)	161.1 (103.3-269.3)	0.060
Fluid in hernia sac, n (%)	32 (34.8)			
Bowel resection, n (%)	18 (19.6)	10 (16.7)	8 (25)	0.337
Omentectomy, n (%)	12 (13)	8 (13.3)	4 (12.5)	1.000*
Mesh use, n (%)				0.312
Yes	69 (75)	47 (78.3)	22 (68.8)	
No	23 (25)	13 (21.7)	10 (31.3)	
Postoperative hospital stay, day, median (Q1-Q3)	3 (2-5)	3 (2-5)	3.5 (2-5.8)	0.463
Surgery-related complications, n (%)	10 (10.9)	7 (11.7)	3 (9.4)	1.000*
Systemic complications, n (%)	8 (8.7)	4 (6.7)	4 (12.5)	0.442*
Postoperative mortality, n (%)	9 (9.8)	4 (6.7)	5 (15.6)	0.268*

*: Fisher's exact test was used, SD: Standard deviation, WBC: White blood cell, NLR: Meutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio.

DISCUSSION

Incarcerated AWH remains a critical surgical emergency with high morbidity and mortality rates. Obstruction or strangulation may occur as a result of incarceration and these patients may require bowel resection. It is important to identify patients who can undergo bowel resection due to longer hospital stays and higher postoperative complications (4,5). A meta-analysis by Chen et al. (6) reported that female gender, older age, bowel obstruction, duration of incarceration, white blood cell count and neutrophilic leukocyte count were risk factors for bowel resection. Another study by Ge et al. (3) identified femoral hernia, peritonitis and lack of health insurance as risk factors in patients undergoing bowel resection for incarcerated inguinal hernia. Furthermore, some studies have reported a relationship between NLR and PLR values and bowel resection in incarcerated hernias (7). In our study, 18 patients (19.6%) underwent bowel resection due to strangulation or perforation. Although we found symptom duration, platelet count, NLR and PLR to be associated with bowel resection in patients undergoing surgery for incarcerated AWH, none of these parameters were found to be a risk factor for bowel resection in multivariate analysis. However, similar to the literature, bowel resection was associated with longer hospital stay, postoperative complications and mortality. Furthermore, consistent with the literature, femoral hernias were the hernia subgroup requiring the highest rate of bowel resection. Although femoral hernias represent a smaller proportion of cases, their clinical significance is considerable because of the higher risk of strangulation. Many studies have shown that femoral hernia is associated with bowel resection in patients. Although Ge et al. (3) identified femoral hernia as a

Table 2. Factors associated with bowel resection in incarcerated abdominal wall hernia

	All patients n=92	Without bowel resection n=74	With bowel resection n=18	p-value
Age, mean ± SD	66.1±14.5	66.1±13.6	73.3±13.4	0.051
Sex, n (%)				0.077*
Male	76 (82.6)	64 (86.5)	12 (66.7)	
Female	16 (17.4)	10 (13.5)	6 (33.3)	
Type of hernia, n (%)				0.072
Inguinal	77 (83.7)	64 (86.5)	13 (72.2)	
Incisional	7 (7.6)	6 (8.1)	1 (5.6)	
Umbilical	1 (1.1)	1 (1.4)	0	
Femoral	7 (7.6)	3 (4.1)	4 (22.2)	
Duration of symptom, day, median (Q1-Q3)	1.5 (1-2.8)	1 (1-2)	2 (1-3.3)	**0.014**
WBC, median (Q1-Q3)	11000 (7400-14600)	10550 (7175-14400)	11500 (9275-16100)	0.376
Neutrophil, median (Q1-Q3)	8300 (5525-11500)	7850 (5200-11100)	9500 (6950-12675)	0.202
Lymphocyte, median (Q1-Q3)	1400 (900-2100)	1400 (900-2225)	1400 (475-1800)	0.207
Platelet, median (Q1-Q3)	251500 (205750-328500)	247500 (201750-321750)	286000 (241500-480750)	**0.040**
NLR, median (Q1-Q3)	6.83 (3.01-10.84)	6.19 (2.66-10.66)	8.63 (5.64-20.17)	**0.042**
PLR, median (Q1-Q3)	177.8 (116.1-363.1)	171 (108.6-325)	291.3 (139.9-706.7)	**0.015**
Fluid in hernia sac, n (%)	32 (34.8)	24 (32.4)	8 (44.4)	0.337
Mesh use, n (%)				**<0.001***
Yes	69 (75)	63 (85.1)	6 (33.3)	
No	23 (25)	11 (14.9)	12 (66.7)	
Postoperative hospital stay, day, median (Q1-Q3)	3 (2-5)	3 (2-4)	7 (5-11.3)	**<0.001**
Surgery-related complications, n (%)	10 (10.9)	4 (5.4)	6 (33.3)	**0.003***
Systemic complications, n (%)	8 (8.7)	5 (6.8)	3 (16.7)	0.186
Postoperative mortality, n (%)	9 (9.8)	4 (5.4)	5 (27.8)	**0.013***

*: Fisher's exact test was used, SD: Standard deviation, WBC: White blood cell, NLR: Meutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio.

Table 3. Risk factors for bowel resection

	Univariate analysis		Multivariate analysis	
Variables for resection	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Age	**1.051 (1.007-1.096)**	**0.023**	1.030 (0.983-1.080)	0.207
Female sex	3.200 (0.978-10.468)	0.054	-	-
Inguinal hernia	0.406 (0.119-1.387)	0.151	-	-
Duration of symptom	**1.380 (1.011-1.884)**	**0.043**	1.149 (0.816-1.616)	0.427
NLR	1.038 (0.997-1.081)	0.067	-	-
PLR	**1.003 (1.001-1.005)**	**0.008**	1.002 (1.000-1.004)	0.094
Fluid in hernia sac	1.667 (0.584-4.760)	0.340	-	-

NLR: Meutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, CI: Confidence interval.

Table 4. Risk factors for postoperative mortality

	Univariate analysis		Multivariate analysis	
Variables for mortality	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Age	1.061 (0.999-1.127)	0.053	-	-
Female sex	**4.733 (1.110-20.181)**	**0.036**	2.847 (0.371-21.857)	0.314
Inguinal hernia	0.650 (0.121-3.485)	0.615	-	-
Duration of symptom	**1.467 (1.040-2.070)**	**0.029**	1.201 (0.743-1.943)	0.454
NLR	**1.071 (1.016-1.129)**	**0.010**	1.035 (0.985-1.089)	0.175
PLR	**1.004 (1.001-1.006)**	**0.004**	1.002 (0.999-1.005)	0.225
Fluid in hernia sac	2.593 (0.644-10.437)	0.180	-	-
Bowel resection	**6.731 (1.592-28.462)**	**0.010**	1.194 (0.123-11.598)	0.879
Omentectomy	0.000 (0.000-.)	0.999	-	-
Mesh use	**0.222 (0.054-0.912)**	**0.037**	0.395 (0.052-3.008)	0.370

NLR: Meutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, CI: Confidence interval.

Table 5. Risk factors for postoperative complications

	Univariate analysis		Multivariate analysis	
Variables for complication	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Age	1.019 (0.982-1.058)	0.323	-	-
Female sex	3.200 (0.978-10.468)	0.054	-	-
Inguinal hernia	0.406 (0.119-1.387)	0.151	-	-
Duration of symptom	**2.000 (1.305-3.065)**	**0.001**	**1.713 (1.093-2.686)**	**0.019**
NLR	1.027 (0.990-1.066)	0.157	-	-
PLR	**1.003 (1.001-1.005)**	**0.013**	1.001 (0.999-1.003)	0.403
Fluid in hernia sac	1.247 (0.431-3.611)	0.684	-	-
Bowel resection	**7.222 (2.270-22.979)**	**0.001**	**4.655 (1.230-17.613)**	**0.023**
Omentectomy	0.337 (0.041-2.796)	0.314	-	-
Mesh use	0.433 (0.145-1.299)	0.135	-	-

NLR: Meutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, CI: Confidence interval.

risk factor, many of the remaining studies have found only an association (1,2,6). Femoral hernias are generally considered less common and, therefore, it is difficult to detect a statistical difference. However, considering the anatomy of femoral hernia, it may be associated with bowel resection. Our findings are consistent with previous reports emphasizing early surgical intervention in this subgroup. However, the small number of femoral hernias in our series precludes definitive conclusions, and we consider this a limitation. Patients who underwent bowel resection were older, but this was not statistically significant. HSF, previously associated with surgical site infections (8), did not predict resection in our study.

Mortality and morbidity rates in incarcerated AWH have been reported to be approximately 5% and 20-30%, respectively. In our study, postoperative complication and mortality rates were 19.6% and 9.8%, respectively. Symptom duration and bowel resection were found to be risk factors for postoperative complications, but no risk factor was found for mortality. The logistic regression model demonstrated acceptable calibration and good discriminative ability. These findings support the robustness of our multivariate analysis despite the limited number of events.

Another issue in these patients is the use of mesh during hernia repair. While some advocate avoiding the use of mesh in contaminated cases (9), others support its safety in emergency situations (10,11). Furthermore, Loftus et al. (8) reported HSF as a predictive factor for surgical site infection in patients undergoing mesh repair for acutely incarcerated ventral and inguinal hernias. In our study, surgeons appeared to prefer mesh use more in patients undergoing bowel resection and HSF, but no statistical difference was found. Furthermore, mesh use was not identified as a risk factor for postoperative mortality or postoperative complications.

Study Limitations

This study has several limitations. First, the retrospective and single-center nature of the study limits its generalizability to other populations and may have affected the power to detect statistically significant risk factors. Second, our study lacked more specific parameters such as the amount or density of HSF. However, the presence or absence of fluid on CT findings was consistently reported by all patients.

CONCLUSION

Our study did not identify any risk factors for bowel resection. However, symptom duration, platelet count, NLR, and PLR may be associated with bowel resection. HSF was not identified as a risk factor. Furthermore, bowel resection prolongs the length of hospital stay and increases postoperative complications and mortality in patients undergoing surgery for incarcerated AWH. Duration of symptoms and bowel resection should be considered risk factors for postoperative complications. Randomized controlled trials in larger populations are needed to identify risk factors for bowel resection.

Ethics

Ethics Committee Approval: This study was conducted retrospectively and approved by the Local Ethics Committee of University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital (approval number: 2022/06-35, date: 15.06.2022).

Informed Consent: Informed consent was not provided by the patients as this was a retrospective study.

Footnotes

Author Contributions

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

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ORIGINAL ARTICLE
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De novo malignancy development following kidney transplantation: Managing risks and outcomes in clinical practice

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ABSTRACT

Objective: *De novo* malignancy is a significant complication following kidney transplantation, attributed to prolonged immunosuppression. This study evaluates the incidence, risk factors, and clinical outcomes of *de novo* malignancies in kidney transplant recipients.

Material and Methods: A retrospective cohort analysis was conducted on 1200 kidney transplant recipients between 2016 and 2023. Patients were categorized based on the presence or absence of *de novo* malignancies. Statistical analyses were performed to identify risk factors, including age, sex, comorbidities, and immunosuppressive regimens. Patient and graft survival were assessed using Kaplan-Meier analysis and the log-rank test.

Results: Among the study population, 43 patients (3.6%) developed *de novo* malignancies. The most frequent malignancy types were non-melanoma skin cancers (27.9%) and post-transplant lymphoproliferative disorders (18.6%). Patients with malignancies exhibited a lower three-year survival rate (83.7%) compared to those without malignancies (91.4%), though the difference was not statistically significant (p=0.067). Graft survival at three years was slightly lower in the malignancy group (84.0% vs. 88.7%, p=0.146). Older recipient age was identified as a significant risk factor (hazard ratio=1.03 per year, p=0.025).

Conclusion: *De novo* malignancy remains a concern in kidney transplant recipients, particularly among older patients. Regular screening protocols, lifestyle interventions, and individualized immunosuppressive regimens are essential to mitigate risk and improve outcomes.

Keywords: Cancer, general surgery, incision

INTRODUCTION

Kidney transplantation continues to be the optimal therapeutic approach for patients with end-stage renal disease (ESRD), providing significant survival benefits and enhanced standard of living (1). However, the use of lifelong immunosuppressive therapy to prevent allograft rejection also increases the risk of *de novo* malignancies, which has become a growing concern as recipient and transplant success rates improve (2). Post-transplant malignancies may result in significant illness and death in this population, emphasizing the significance of preventive strategies, prompt identification, and effective management (3). The etiology of such malignancies is multifactorial, involving complex interactions between immunosuppression, viral oncogenesis, and genetic predispositions (4). Despite advances in immunosuppressive protocols, optimizing long-term outcomes requires a delicate balance between controlling rejection and minimizing cancer risk (5).

In this study, we aim to assess the frequency, risk factors, and medical results of *de novo* malignancy after kidney transplant surgery, thereby shedding light on potential strategies to improve both recipient and transplant viability. By elucidating the challenges faced in clinical practice, our findings may contribute to the development of individualized management approaches that enhance patient prognosis and reduce the burden of cancer in kidney transplant recipients.

MATERIAL and METHODS

This a retrospective cohort analysis was performed at a single tertiary care facility from January 2016 and December 2023. An overall count of 1200 individuals who underwent kidney transplantation within the stated timeframe were incorporated

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into the analysis. Of these patients, 43 (3.6%) were diagnosed with *de novo* malignancies. All patients were followed until December 2023 or until the date of death, whichever occurred first.

Data Collection

Patient demographic, clinical, and laboratory information was obtained retrospectively from electronic medical records and the hospital's transplant database. Collected variables included age, sex, underlying renal disease etiology, immunosuppressive regimens, comorbidities, and post-transplant follow-up time. Malignancy diagnoses were confirmed by pathology reports, radiological findings, and clinical assessment.

Definitions and Endpoints

***De novo* malignancy:** Any malignancy diagnosed for the first time following kidney transplantation.

Follow-up duration: The period from the date of transplantation to the last outpatient clinic visit or the date of death.

Primary endpoints included patient survival, graft survival, and malignancy-related morbidity. Table 1 summarizes the baseline characteristics of the study population.

Statistical Analysis

All statistical analyses were performed utilizing SPSS software (version 25.0). The Kolmogorov-Smirnov test was employed to assess whether continuous variables conformed to a normal distribution. For variables exhibiting a normal distribution, results were r presented as mean ± standard deviation, while not following a normal distribution variables were described using median (range: minimum-maximum) values. Group comparisons were carried out conducted using the independent samples t-test for variables with a normal distribution variables and the Mann-Whitney U test for variables that did not meet normality criteria. When analyzing categorical variables, the chi-square test or Fisher's exact test (in instances of low expected frequencies) was utilized.

Table 1. Baseline characteristics of the study population (n=1200)

Characteristic	Value
Age (years), mean ± SD	48.2±11.3
Male, n (%)	693 (57.8)
Female, n (%)	507 (42.2)
***De novo* malignancy, n (%)**	43 (3.6)
Primary renal disease (e.g., diabetic nephropathy), n (%)	310 (25.8)
Comorbidities (e.g., hypertension), n (%)	640 (53.3)
Follow-up (months), median (range)	36 (1-96)

SD: Standard deviation.

Patient and graft survival estimates were obtained via the Kaplan-Meier approach, and variations in survival curves were evaluated were analyzed using the log-rank test. To determine potential predictive factors for *de novo* malignancy and overall survival, a Cox proportional hazards regression analysis was employed, adjusting adjusted for age, gender, immunosuppressive regimen, and comorbid conditions. A p-value of 0.05 was regarded as statistically significant.

Ethical Considerations

The research protocol was approved by the Biruni University Institutional Review Board at the participating center (approval no: 2024-BİAEK/05-18, date: 12.12.2024). All procedures conformed to international ethical guidelines. Patient confidentiality was protected by removing identifying details and limiting data access strictly for research purposes.

RESULTS

An aggregate of 1200 individuals who underwent kidney transplant procedures were incorporated into the analysis, with 43 (3.6%) developing *de novo* malignancies during the follow-up period. The midpoint follow-up duration for all participants was 36 months (range, 1-96 months).

Individuals who experienced *de novo* malignancies were more likely to be older during transplantation (mean age 52.1±10.3 years) compared to those without malignancies (47.9±11.4 years, p=0.032). No notable variations were observed regarding sex distribution, although there was a marginally greater percentage of males in the malignancy group (60.5% vs. 57.6%, p=0.684). Comorbidities, particularly hypertension, were more prevalent in the malignancy group (62.8% vs. 52.9%, p=0.144), however, this variation was not statistically significant (Table 2).

Among the 43 individuals who experienced *de novo* malignancies, the most common types were non-melanoma skin cancers (n=12), followed by post-transplant lymphoproliferative disorders (PTLD) (n=8), renal cell carcinoma (n=6), and various solid tumors (n=17) (Figure 1). The median time to malignancy diagnosis was 18 months (range, 3-54 months) after transplantation (Table 3).

During the duration of the study, the total patient survival proportion was 90.8%. Patients who developed *de novo* malignancies exhibited a reduced three-year survival rate (83.7%) in comparison with those without malignancies (91.4%), although this difference was not statistically significant (p=0.067) by log-rank test. Transplant viability at three years was 88.4% for the entire cohort, with *de novo* malignancy patients showing a slightly decreased graft survival rate (84.0% vs. 88.7%, p=0.146) (Table 4).

On Cox proportional hazards regression analysis, older recipient age at transplantation (hazard ratio= 1.03 per year, 95%

confidence interval: 1.01-1.05, p=0.025) was associated with an increased risk of *de novo* malignancy. Other variables, such as sex, hypertension, and the specific immunosuppressive regimen, did not show statistically significant associations in this study (Figure 2).

All patients diagnosed with *de novo* malignancies received individualized treatment according to tumor type, including surgical resection, chemotherapy, or immunotherapy. Immunosuppressive regimens were modified (reduced or switched) in 65.1% of these patients to balance oncologic control with the risk of allograft rejection. Of the 43 patients, 5 (11.6%) experienced graft loss and 4 (9.3%) died due to cancer-related complications during the follow-up.

In addition, a subgroup analysis revealed that patients who received induction therapy with anti-thymocyte globulin (ATG) had a higher cumulative incidence of PTLD compared with those who received basiliximab (18.9% vs. 6.7%, p=0.041). Furthermore, the median time to presentation differed by cancer type: Non-melanoma skin cancer presented at 12 months, whereas solid organ malignancies manifested later, at a median of 30 months. Kaplan-Meier curves demonstrated that the presence of multiple comorbidities (≥3) was associated with inferior graft survival (logrank p=0.038).

DISCUSSION

Kidney transplantation is broadly acknowledged as the foremost therapeutic option for ESRD. However, long-term immunosuppressive therapy increases the risk of developing *de novo* malignancies (6,7). In this study, 3.6% of our kidney transplant patients developed malignancies, with older age at transplantation emerging as a significant risk factor. Similar findings have been reported in multicenter studies, underscoring the contributions of age, as well as the type and dose of immunosuppression, to malignancy risk (8).

The incidence we observed aligns with the lower end of the 2-10% range reported in contemporary European registries, likely reflecting both regional variations in cancer screening

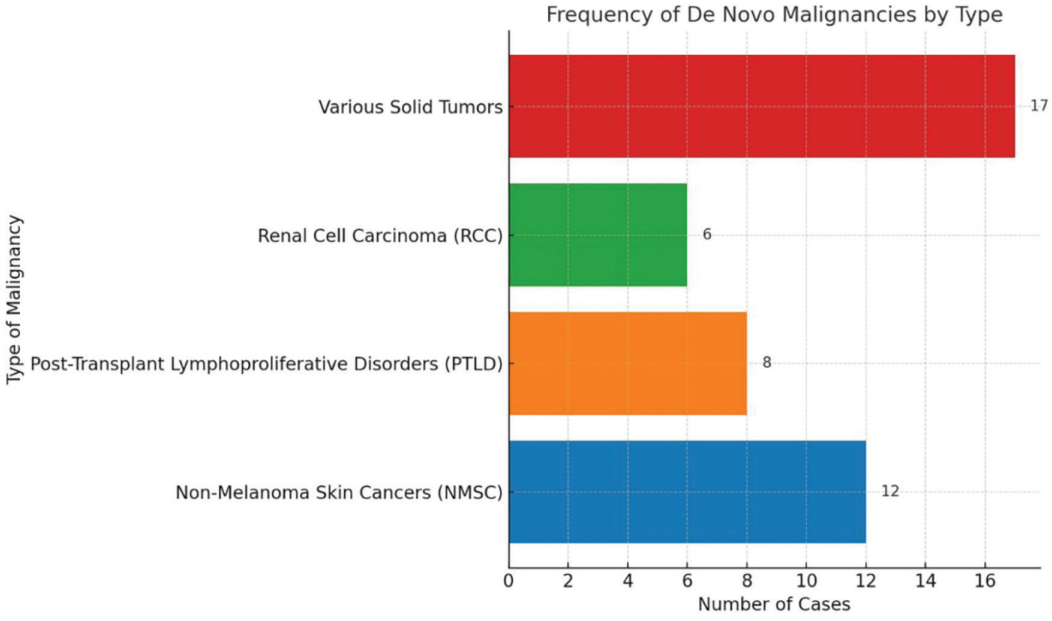

Figure 1. The frequency of *de novo* malignancies by type.

Table 2. Comparison of selected baseline characteristics between patients with and without *de novo* malignancies

Variable	Malignancy (n=43)	No malignancy (n=1157)	p-value
Age (years), mean ± SD	52.1±10.3	47.9±11.4	0.032*
Male, n (%)	26 (60.5)	667 (57.6)	0.684
Female, n (%)	17 (39.5)	490 (42.4)	0.684
Hypertension, n (%)	27 (62.8)	613 (52.9)	0.144
Diabetes mellitus, n (%)	12 (27.9)	298 (25.7)	0.735
Follow-up (months), median (range)	38 (2-96)	36 (1-96)	0.607

*: Statistically significant (p<0.05), SD: Standard deviation.

practices and the relatively younger age of our cohort. Importantly, our data expand on previous work by quantifying the relative contribution of induction therapy choice: ATG exposure conferred a twofold higher risk of PTLD after adjusting for Epstein-Barr virus (EBV) serostatus. This corroborates mechanistic studies suggesting profound and durable B-cell depletion as a driver of oncogenic viral reactivation.

Effective strategies for preventing or delaying *de novo* malignancies include implementing regular screening protocols and individualizing immunosuppressive therapy (9). For example, non-melanoma skin cancers can be detected and treated at earlier stages through regular dermatological examinations. Additionally, sun protection measures (such as wearing protective clothing, using broad-spectrum sunscreen, and avoiding intense sun exposure) are critical in reducing the incidence of these cancers (10). In the context of PTLD, EBV monitoring is particularly emphasized during the initial period following transplantation to minimize lymphoma risk (11).

Furthermore, careful decrease or adjustment in immunosuppressive treatment is an increasingly adopted strategy aimed at balancing graft survival with cancer risk reduction (12). Nevertheless, if immunosuppression is insufficient, the risk of allograft rejection may increase considerably; thus, each patient requires an individualized approach (13). Lifestyle interventions also play a vital role in mitigating post-transplant cancer risk. Specifically, smoking cessation, sustaining a healthy body mass index and participating in consistent physical exercise have been associated with lower overall cancer risk (10,12). Some studies further suggest considering vaccination against oncogenic viruses, such as HPV, for appropriate age and risk groups among transplant candidates (14).

Another emerging preventive avenue involves the use of mTOR inhibitors (e.g., sirolimus or everolimus) either *de novo* or as a conversion strategy in patients at heightened oncologic risk. Meta-analyses demonstrate a 40-60% reduction in skincancer incidence among recipients switched from calcineurin inhibitors

Table 3. Patterns and types of *de novo* malignancies (n=43)

Type of malignancy	n (%)
Non-melanoma skin cancers	12 (27.9)
Post-transplant lymphoproliferative disorder	8 (18.6)
Renal cell carcinoma	6 (14.0)
Various solid tumors	17 (39.5)
Total	43 (100)

Table 4. Clinical outcomes and survival rates

Outcome	Malignancy (n=43)	No malignancy (n=1157)	p-value
3-year patient survival (%)	83.7	91.4	0.067
3-year graft survival (%)	84.0	88.7	0.146
Median time to malignancy (months)	18 (3-54)	-	-

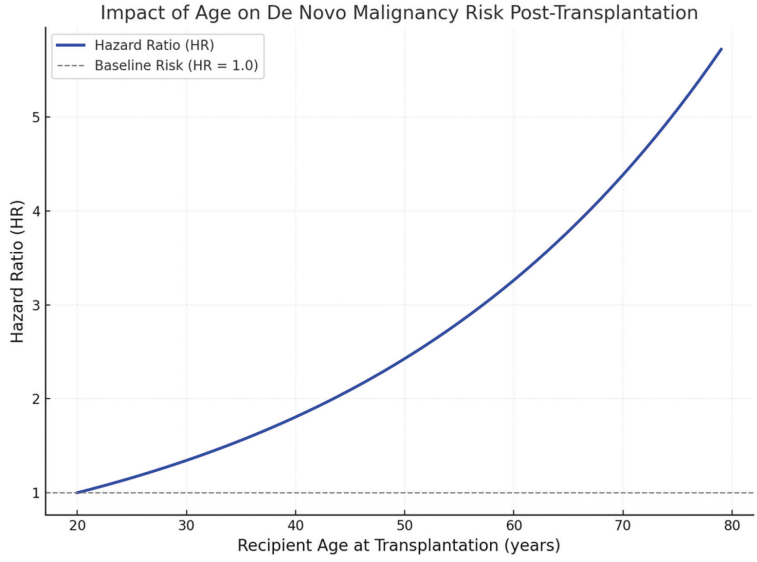

Figure 2. The graph above illustrates the relationship between recipient age at transplantation and the HR for developing *de novo* malignancies, derived from the Cox proportional hazards regression analysis. The HR increases progressively with age, reflecting the elevated risk associated with older recipients. The dashed line indicates the baseline risk (HR=1.0).

to mTOR based regimens, albeit at the expense of dyslipidemia and delayed wound healing. Prospective randomized trials are warranted to define the optimal timing and patient selection for such conversions.

Our findings should be interpreted in light of several limitations. First, the retrospective nature of data collection raises the possibility of ascertainment bias, particularly for cutaneous malignancies that may be under reported. Second, molecular profiling of tumors was not systematically performed; thus, the impact of donor derived versus recipient origin neoplasms could not be delineated. Third, the single-center design limits external validity, although transplant protocols during the study period mirrored national guidelines.

A key strength of this research is the inclusion involving a substantial cohort (n=1200) with a considerable follow-up period (1-96 months), which enhances the reliability of the findings. Additionally, the thorough retrospective review of multifaceted data (demographic, clinical, laboratory, pathological) improves the validity of the results. However, this single-center design could restrict the applicability of the results to broader populations. Moreover, the study's retrospective design introduces the possibility of incomplete or inaccurate records.

Future work should focus on multi-center prospective registries integrating granular immunosuppression pharmacokinetics, viral surveillance data, and tumor genomics to facilitate precision medicine strategies aimed at simultaneously safeguarding grafts and minimizing oncologic sequelae.

CONCLUSION

De novo malignancy constitutes a significant consideration for extended-term survival and overall well-being among kidney transplant recipients. The present research highlights older age as a particularly notable risk factor. Identifying risk factors and optimizing immunosuppressive management, coupled with effective screening protocols and multidisciplinary collaboration, can help improve both recipient and graft survival rates in this vulnerable population.

Ethics

Ethics Committee Approval: The research protocol was approved by the Biruni University Institutional Review Board at the participating center (approval no: 2024-BİAEK/05-18, date: 12.12.2024).

Informed Consent: As this was a retrospective study, informed consent was not required and therefore was not obtained from the patients.

Footnotes

Author Contributions

Concept - A.H., S.N.K.Ç.; Design - A.H., S.N.K.Ç.; Data Collection or Processing - A.H., S.N.K.Ç.; Analysis or Interpretation - A.H.; Literature Search - A.H.; Writing - A.H., S.N.K.Ç.

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

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ORIGINAL ARTICLE
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Proactive fat grafting from the breast area in gynecomastia surgery: Impact on the prevention of contour irregularities and patient satisfaction

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ABSTRACT

Objective: Contour irregularities are among the most significant complications that may occur after gynecomastia surgery and they can adversely affect aesthetic outcomes. This study evaluated the use of proactively harvested autologous fat grafts from the same surgical field prior to gynecomastia surgery for the treatment of intraoperative contour deformities, as well as the impact of this approach on patient satisfaction.

Material and Methods: A retrospective evaluation was conducted on 24 male patients who were diagnosed with gynecomastia between April 2023 and March 2025 through physical examination, endocrinology consultation, and breast ultrasonography, who subsequently underwent surgical treatment. Prior to surgery, autologous fat grafts were harvested from the breast area in all patients. Intraoperatively identified contour irregularities were treated with same-session fat injection using the previously harvested grafts. All patients were followed up with ultrasonography and digital photography. Additionally, patient satisfaction was assessed using BODY-Q chest module and the chest satisfaction questionnaire.

Results: Of the 24 patients, 83% (n=20) presented with pseudogynecomastia and were treated with liposuction alone, while 17% (n=4) had gynecomastia and underwent liposuction combined with gland excision. Intraoperative contour irregularities were detected in 9 patients (37.5%), in whom an average of 8 cc (interquartile range 7-10) of fat was injected. Over a mean follow-up of 12.4 months, no statistically significant difference in aesthetic satisfaction was observed between patients with and without fat grafting ($p>0.05$). Both groups reported high satisfaction, and intraoperative contour deformities were successfully corrected.

Conclusion: Proactively harvesting autologous fat from the breast tissue during gynecomastia surgery may be a safe and practical method for immediate correction of intraoperative contour irregularities. This approach avoids additional donor site morbidity and provides a readily available graft source. While satisfaction outcomes were high in all patients, larger prospective studies are needed to confirm the long-term efficacy and broader applicability of this technique.

Keywords: Fat grafting, gynecomastia, liposuction, patient satisfaction, pseudogynecomastia

INTRODUCTION

The term gynecomastia, derived from the Greek words gynec (woman) and mastos (breast), has been used since antiquity to describe male breast enlargement. Gynecomastia is characterized by benign proliferation of the glandular component of the male breast tissue. It typically arises from an imbalance between estrogen and androgen levels, resulting in a feminized breast appearance (1).

Pseudogynecomastia, also known as fatty gynecomastia, is characterized by an increase in adipose tissue in the male breast without fibroglandular proliferation. Although it is most commonly observed in obese individuals, it may also be associated with certain conditions such as neurofibromatosis Type 1 (2).

Differentiating between pseudogynecomastia and gynecomastia is critical for appropriate treatment planning. In cases of isolated adipose tissue enlargement (pseudogynecomastia), liposuction alone is usually sufficient. However, in gynecomastia where glandular tissue is also present, satisfactory outcomes often require periareolar gland excision (adenectomy) in addition to liposuction (3).

One of the most frequently encountered complications following gynecomastia surgery is contour irregularities and depressions due to excessive tissue removal. These issues can negatively affect aesthetic outcomes and reduce patient satisfaction. Autologous fat injection, with its potential to correct contour deformities, serves as a valuable tool in managing these complications (4).

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This study aims to describe the use of proactively harvested autologous fat grafts from the same surgical field prior to gynecomastia surgery for the treatment of intraoperative contour irregularities, and to evaluate the impact of this approach on patient satisfaction.

MATERIAL and METHODS

Study Design and Patient Population

This retrospective study was conducted on 24 male patients who were diagnosed with either gynecomastia or pseudogynecomastia and underwent surgical treatment between April 2023 and January 2025 at Yeditepe University Kozyatağı Hospital, İstanbul/Türkiye. Diagnoses were based on physical examination, endocrinology consultation, and breast ultrasonography. The study was approved by the Yeditepe University Ethics Committee under the approval number: 202310Y0668, date: 15.11.2024 and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants. Figure 1 shows the breast ultrasonography image of a patient who presented with the complaint of feminine breast enlargement and was diagnosed with gynecomastia.

The inclusion criteria were as follows: Being between 18 and 65 years of age, having a complaint of feminine breast enlargement in both breasts for at least one year, no pharmacological or pathological cause identified during endocrinology consultation, and ultrasonographic findings consistent with gynecomastia. Patients were excluded if they had undergone previous gynecomastia surgery, had serious systemic diseases, had incomplete data, or failed to complete the follow-up period.

Surgical Technique

All surgical procedures were performed under endotracheal general anesthesia. Patients were placed in the supine position, the skin was aseptically prepared using an appropriate antiseptic solution, and sterile draping was applied. In patients diagnosed with pseudogynecomastia, bilateral liposuction was planned, while in those with gynecomastia, liposuction was combined with periareolar gland excision (adenectomy).

In all cases, two 5 mm incisions were made at the intersection of the anterior axillary line and the inframammary fold on each breast. A tumescent solution (500 mL Ringer's lactate, 40 mg of 2% lidocaine, 0.5 mL of 1:1000 epinephrine) was infiltrated through these incisions and allowed to take effect for 10 minutes.

Before initiating gynecomastia surgery, breast tissue was proactively utilized as the donor site in all patients. Autologous fat grafts were harvested using 20 mL Luer-Lock BD Plastipak syringes (Becton Dickinson, Ireland) with manual negative pressure (Figure 2). The collected adipose tissue was decanted and centrifuged at 3000 rpm for 3 minutes, then stored under sterile conditions for potential intraoperative use following gynecomastia surgery (liposuction ± adenectomy) to correct contour irregularities, if needed (5,6).

In pseudogynecomastia cases, liposuction was performed using Mercedes-type (4 mm, blunt-tip, three-hole at 120° intervals) and multi-holed basket-type (3-4 mm) cannulas. In gynecomastia cases, the procedure began with liposuction and proceeded to adenectomy. A periareolar incision was made between the 3 and 9 o'clock positions below the nipple to access the glandular tissue. Excess glandular tissue was grasped with an Allis clamp (Aesculap, Germany) and excised using electrocautery. After hemostasis was achieved, the glandular bed was approximated with 3-0 polyglactin 910 sutures, and the periareolar incision was closed intradermally using 6-0 polypropylene sutures.

Following excision, all patients were evaluated both in the supine and seated positions for symmetry, surface irregularities, and depressions (Figure 3). In cases requiring correction, the pre-harvested autologous fat grafts were injected radially using 18G

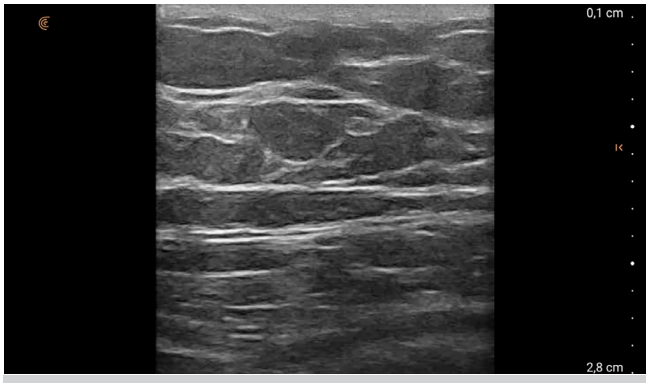

Figure 1. Breast ultrasonography of a patient presenting with complaints of female-type breast enlargement and diagnosed with gynecomastia.

Figure 2. Harvesting of fat grafts using 20 cc Luer-Lock syringes (BD Plastipak™, Becton Dickinson, Ireland).

Coleman cannulas (Tulip Medical, USA) to restore contour and ensure symmetry (Figures 4 and 5) (7,8).

Patients who underwent only liposuction did not receive surgical drains; however, those who also underwent adenectomy had one 10 French Jackson-Pratt drain (Ethicon, Johnson & Johnson, USA) placed per breast. The incisions at the anterior axillary line were closed primarily with 5-0 polypropylene sutures. Subsequently, a polyurethane compressive foam dressing (Epifoam, 3M, USA) and a three-strap compression vest were applied, marking the end of the procedure.

Postoperative Follow-up and Imaging

Patients were evaluated for hematoma on postoperative day 1. Drains were removed once the drainage volume dropped below 25 mL. All patients were discharged with prescriptions for antibiotics and anti-inflammatory medications.

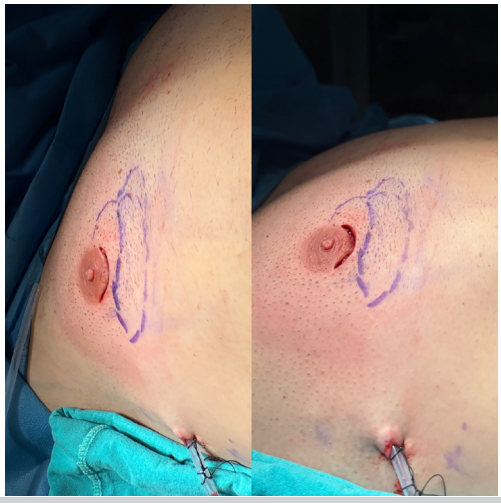

Figure 3. Marking of intraoperatively detected contour irregularity with a surgical marker in a patient who underwent liposuction and periareolar gland excision.

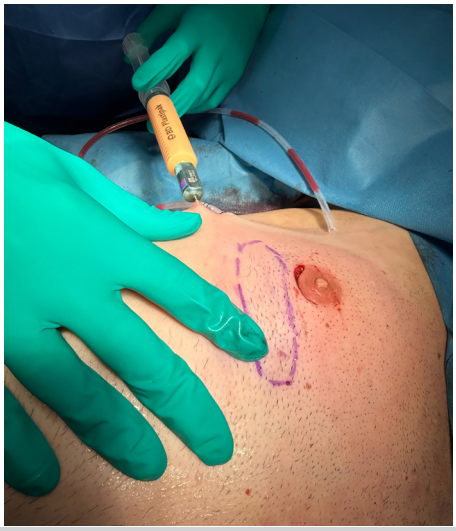

Figure 4. Radial injection of autologous fat grafts harvested at the beginning of the operation into contour irregularities using 18G Coleman cannulas (Tulip Medical, USA).

At the first-week follow-up, the polyurethane compressive foam materials were removed, sutures at the incision sites were taken out, and patients were given wound care instructions. They were advised to continue wearing the three-strap chest compression garment until the fourth postoperative week.

During the follow-up visits at 1 week, 1 month, 3 months, 6 months, and 12 months, all patients underwent imaging with a portable high-frequency ultrasound device (Clarius L20, Clarius Mobile Health, Canada) and were photographed using a digital camera (Canon EOS 5D Mark II, Canon Inc., Tokyo, Japan).

Patient Satisfaction Assessment

Patient satisfaction was assessed between 6 months and 1 year postoperatively using the BODY-Q chest module and the chest satisfaction questionnaire (9).

Surveys were supplemented with questions about perceived contour irregularities or depressions. Participants rated their satisfaction with chest contour, symmetry, chest fullness, contour smoothness, social confidence, and overall aesthetic results on a scale from 0 (not satisfied) to 5 (very satisfied).

Statistical Analysis

Patients who did not develop intraoperative contour irregularities (and thus did not receive fat grafts) were compared with those who did (and received autologous fat grafting). Patient satisfaction survey scores between the two groups were statistically analyzed.

Data were evaluated using SPSS 29.0 (IBM, New York, USA). As satisfaction scores were obtained through ordinal scales, values were expressed as median [interquartile range (IQR)]. The Mann-Whitney U test was used for comparisons between the

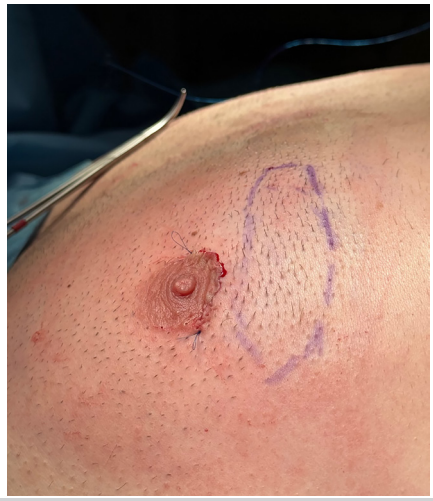

Figure 5. Post-injection view of the operative field following fat grafting.

two independent groups, while Fisher's exact test was applied for categorical variables. A $p<0.05$ was considered statistically significant.

A post hoc power analysis was performed to check whether our sample size was sufficient. With 24 patients (9 in the fat grafting group and 15 in the control group), the study had enough power to detect only large differences between groups. Smaller or more subtle differences might not have been detected with this sample size.

RESULTS

Demographic and Surgical Data

No anesthesia- or surgery-related complications were observed in any of the 24 patients included in the study. The mean age of the participants was 38.34.3± years, and the mean body mass index (BMI) was calculated as 27.312.6± kg/m^2. The mean follow-up period was 12.4 months (range: 8-24 months), According to the Rohrich classification, 20% (n=5) of the patients were classified as Grade 1, 50% (n=12) as Grade 2, 25% (n=6) as Grade 3, and 5% (n=1) as Grade 4 (5).

A total of 83% (n=20) of the patients were treated with liposuction alone for pseudogynecomastia, while 17% (n=4) underwent liposuction combined with gland excision for gynecomastia.

Before the surgical procedures began, an average of 50 cc (IQR 40-60) of autologous fat graft was harvested from each patient. This proactive harvesting ensured that sufficient graft material was readily available in case contour irregularities occurred. However, only nine patients (37.5%) required intraoperative correction, and in these cases an average of 8 cc (IQR 7-10) of fat was injected into the affected areas. In the remaining patients, the harvested grafts were discarded at the end of the procedure. This explains the discrepancy between the mean harvested and injected volumes, reflecting the selective use of grafting rather than technical inefficiency.

Follow-up of the nine patients who received fat injections revealed no contour irregularities on physical examination or handheld ultrasonography (Figure 6). No volume loss or fat necrosis was detected in the injected areas (Figure 7). Furthermore, none of the patients required a second fat injection. Video 1 and Video 2 present sagittal and transverse ultrasound images, respectively, obtained at the postoperative 6-month follow-up of a patient diagnosed with gynecomastia who underwent autologous fat grafting due to intraoperative contour irregularity and received periareolar gland excision in addition to liposuction.

Satisfaction Survey Results

In the patient satisfaction survey conducted between those who received fat grafting (n=9) and those who did not (n=15), no statistically significant difference was observed between the groups ($p>0.05$). Both groups reported similarly positive feedback in terms of overall satisfaction with chest contour, perception of symmetry, chest fullness, sense of social confidence, and overall satisfaction with aesthetic outcomes. Satisfaction regarding contour smoothness was also similar between the two groups (Table 1). Figure 8A-J presents the preoperative and postoperative 1-year photographs of a patient diagnosed with pseudogynecomastia who underwent liposuction alone and received intraoperative autologous fat grafting due to contour irregularity.

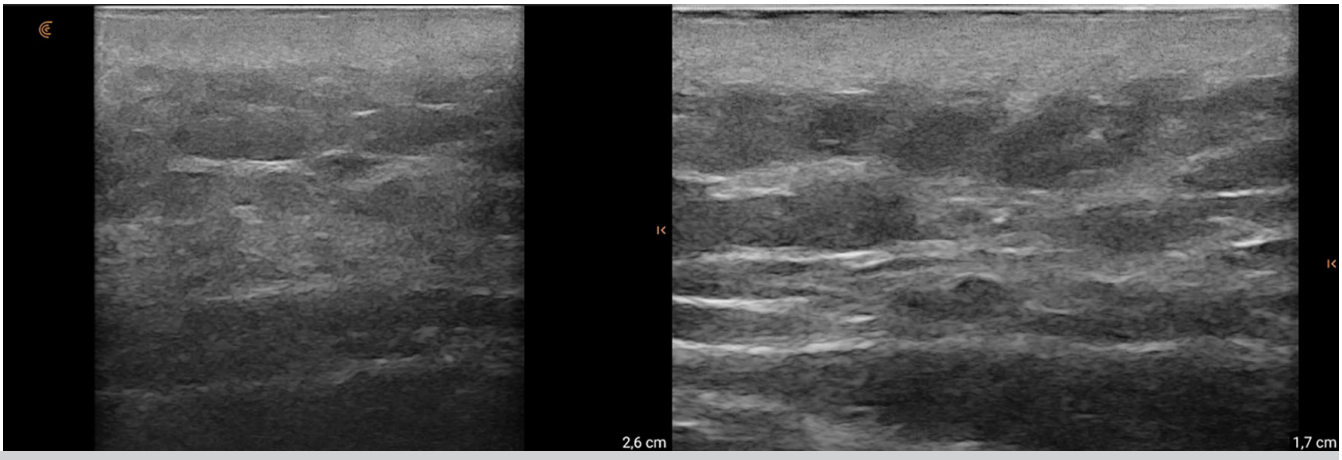

Figure 6. Postoperative ultrasonographic images of the patient at the 1st week and 1st month, obtained using a portable high-frequency ultrasound device (Clarius L20, Clarius Mobile Health, Canada). No irregularities were detected in the imaging.

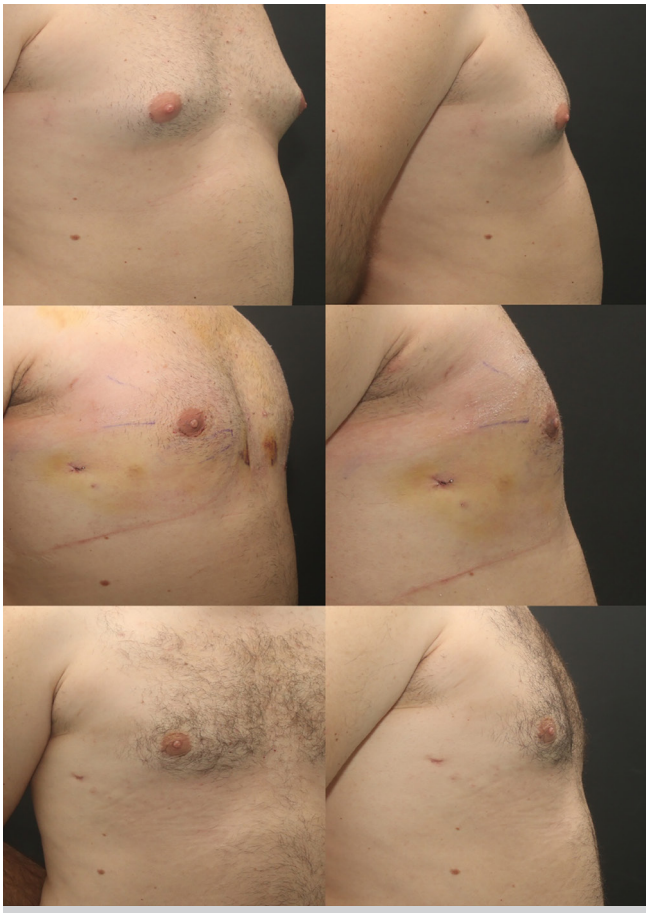

Figure 7. Clinical photographs of a patient diagnosed with gynecomastia who underwent autologous fat grafting due to intraoperative contour irregularity in addition to liposuction and periareolar gland excision.

Top row, left to right: Preoperative right oblique and right lateral views.

Middle row, left to right: Postoperative 1st week right oblique and right lateral views.

Bottom row, left to right: Postoperative 1st month right oblique and right lateral views.

The area of contour irregularity marked intraoperatively with a surgical marker is visible in the 1st-week photographs. No irregularities were observed in these areas during the 1st-week and 1st-month follow-ups.

DISCUSSION

Gynecomastia is a benign proliferation of glandular breast tissue in males, typically resulting from an imbalance between estrogen and androgen levels, and leads to a feminized breast appearance. In contrast, pseudogynecomastia is characterized by localized fat accumulation in the breast region without glandular proliferation (1,4). The reported prevalence of gynecomastia ranges between 32% and 65% (10). Autopsy data suggest a prevalence of approximately 40%, which can increase up to 80% in individuals with a BMI over 25 kg/m^2 (11,12). Bilateral involvement is observed in about 75% of cases (13).

Gynecomastia may result from physiological, pharmacological, or pathological causes. However, in approximately 25% of cases, no specific cause can be identified, and these are classified as idiopathic gynecomastia (5,14).

A systematic and comprehensive approach is essential for accurate diagnosis. The diagnostic process begins with a detailed medical history including age, onset and duration of symptoms, associated complaints, regular medications, and underlying diseases. Physical examination focuses on evaluating the breast tissue for glandular or adipose predominance, ptosis, skin excess, and any palpable masses, which aids in differentiating gynecomastia from pseudogynecomastia and detecting possible malignancy.

Ultrasonography plays a critical role in confirming the diagnosis and ruling out other conditions. In gynecomastia, ultrasound typically reveals a well-defined, hyperechoic or hypoechoic glandular tissue in the retroareolar area, while pseudogynecomastia shows only an increase in adipose tissue without glandular proliferation (15). In cases with suspicious or atypical findings, advanced imaging or biopsy may be required to exclude malignancy. Evaluation of hormonal imbalances should include endocrinology consultation and relevant laboratory testing. An accurate and reliable diagnosis of gynecomastia is achieved through the integration of clinical, radiological, and laboratory data (14,16).

Table 1. Postoperative patient satisfaction survey results

Survey item	Patients with intraoperative contour correction via fat grafting (n=9)	Control group (no fat grafting applied) (n=15)	p-value
Overall satisfaction with chest contour	4 (4-5)	5 (4-5)	0.478
Perception of symmetry	4 (4-5)	4 (4-5)	0.612
Chest fullness	4 (3-5)	4 (4-5)	0.775
Contour smoothness	4 (4-5)	5 (4-5)	0.518
Sense of social confidence	4 (4-5)	5 (4-5)	0.689
Overall satisfaction with aesthetic outcome	4 (4-5)	5 (4-5)	0.317

Figure 8A-J. Preoperative and postoperative 1-year photographs of a patient diagnosed with pseudogynecomastia who underwent only liposuction and received autologous fat grafts due to intraoperative contour irregularity. No contour irregularities are noticeable in the postoperative photographs.

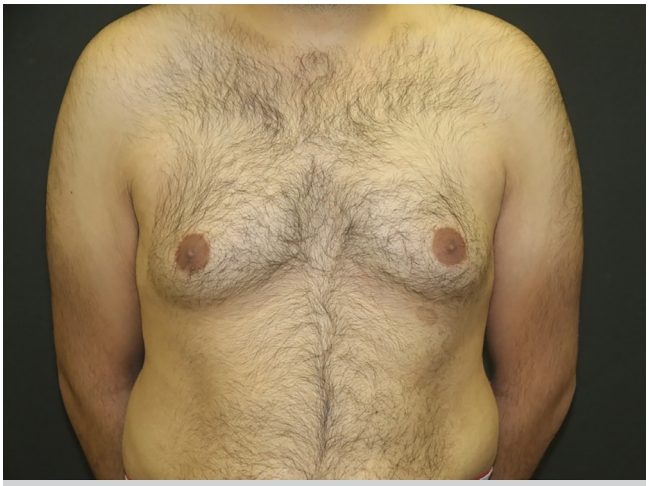

Figure 8A. Preoperative frontal view.

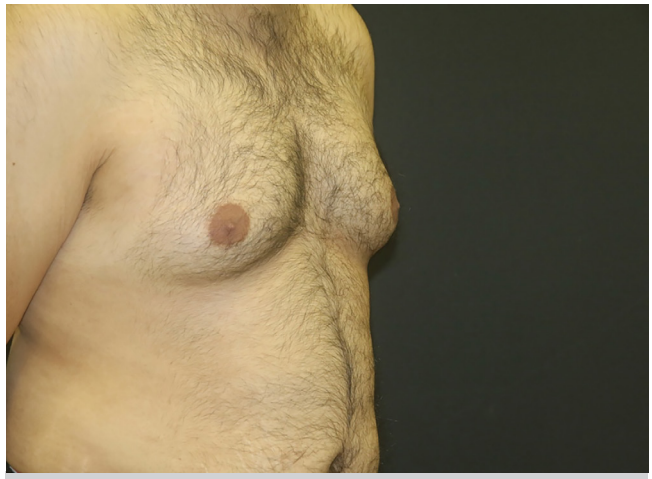

Figure 8B. Preoperative right oblique view.

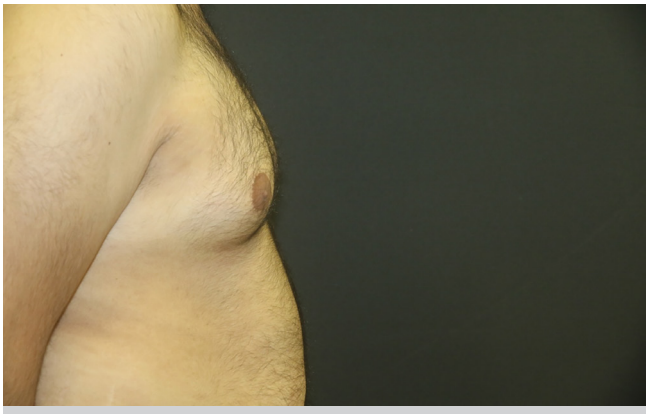

Figure 8C. Preoperative right lateral view.

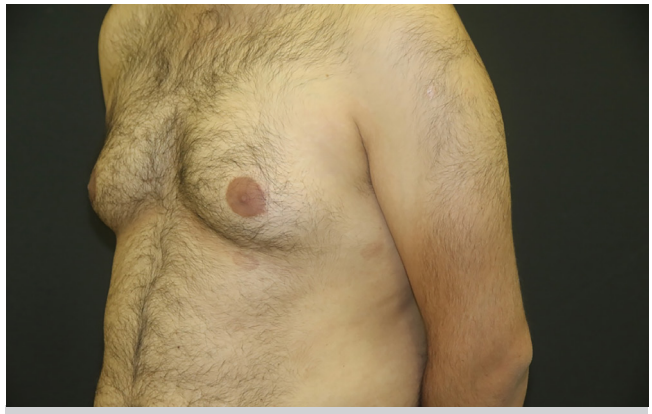

Figure 8D. Preoperative left oblique view.

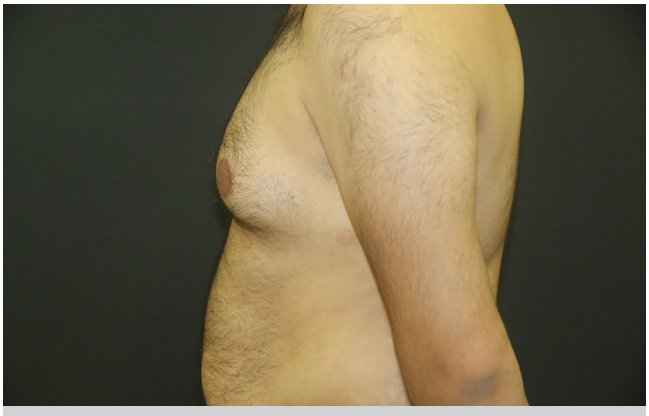

Figure 8E. Preoperative left lateral view.

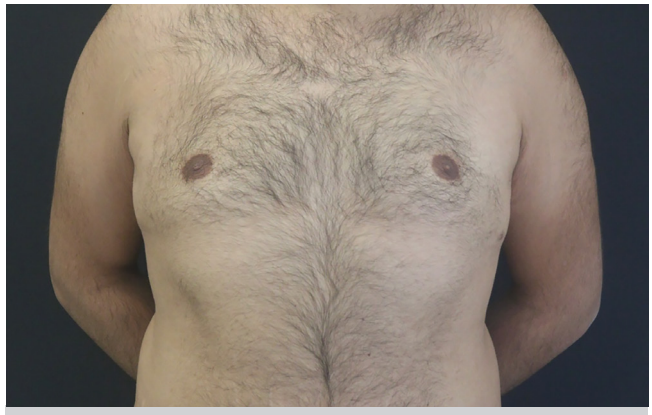

Figure 8F. Postoperative 1-year frontal view.

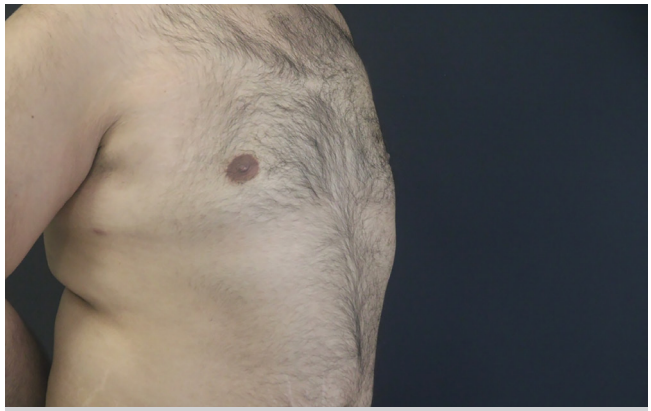

Figure 8G. Postoperative 1-year right oblique view.

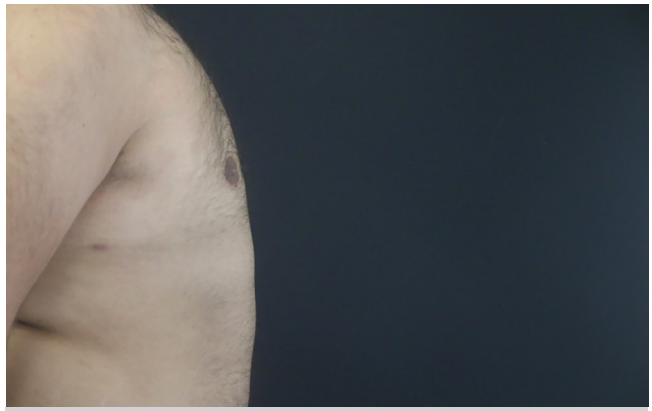

Figure 8H. Postoperative 1-year right lateral view.

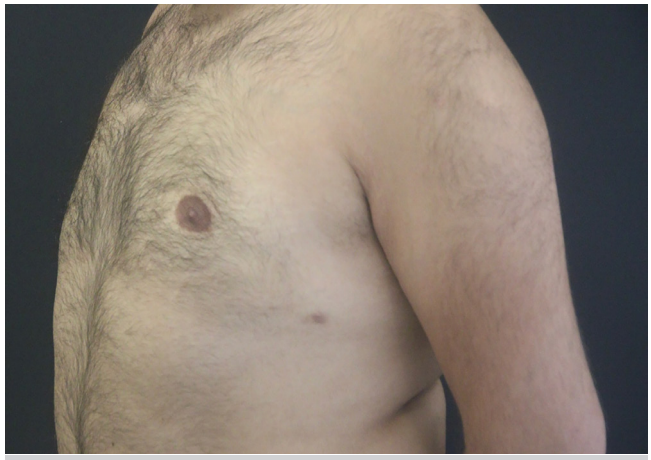

Figure 8I. Postoperative 1-year left oblique view.

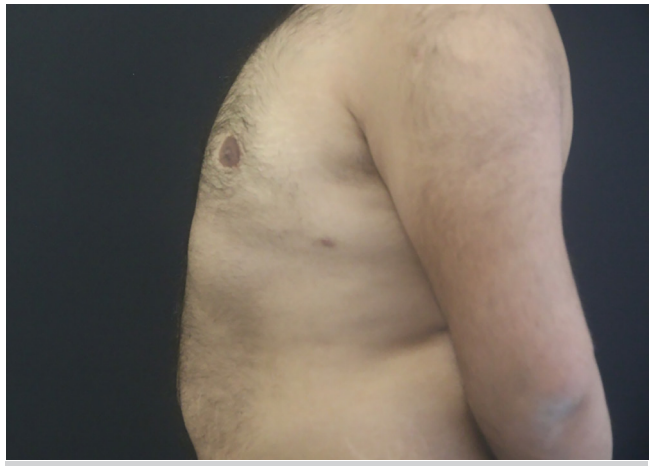

Figure 8J. Postoperative 1-year left lateral view.

The Rohrich classification, which serves as a guiding framework in determining the surgical approach to gynecomastia treatment, evaluates patients in four stages based on breast volume and the degree of ptosis. In Grade 1, breast enlargement is less than 250 grams, with no excess skin or ptosis. In Grade 2, the breast tissue ranges between 250 and 500 grams, accompanied by minimal ptosis. Grade 3 is characterized by a breast volume that may exceed 500 grams, along with mild to moderate excess skin and ptosis. In Grade 4, the condition typically involves more than 750 grams of breast tissue, significant skin redundancy, and advanced ptosis (6). This classification provides valuable guidance for the surgeon in determining the need for additional procedures, such as skin excision.

The approach to gynecomastia treatment is determined based on the underlying cause. Physiological gynecomastia typically resolves spontaneously and therefore does not require treatment; regular follow-up is usually sufficient. In cases of pharmacological gynecomastia, discontinuation of the causative medication often leads to regression of the condition (17). Pathological gynecomastia, on the other hand, necessitates treatment of the underlying disease or disorder (17,18). For idiopathic gynecomastia, initial management may involve observation and weight loss. However, if glandular proliferation persists for more than 12 months and causes aesthetic or psychosocial distress, surgical treatment is recommended, as irreversible fibrotic changes are likely to occur beyond this period (18).

The surgical treatment approach for gynecomastia is planned based on several factors, including the amount of glandular tissue, predominance of adipose tissue, and the presence of excess skin. Treatment typically involves liposuction, glandular excision, and, when necessary, skin excision. In cases of pseudogynecomastia or when glandular proliferation is minimal, liposuction alone may be sufficient (3). Classic suction-assisted liposuction is one of the most commonly used techniques. In addition, energy-assisted modalities such as ultrasound-assisted liposuction or power-assisted liposuction may be preferred in patients with dense or fibrous tissue (16,17).

In patients with a significant glandular component, liposuction alone is inadequate, and periareolar excision is performed (16). In this technique, an inferior hemiperiareolar

incision is made to access the glandular tissue through the skin and subcutaneous layers. The glandular tissue is dissected down to the pectoral fascia and excised in a manner that preserves the natural chest contour (17). Surgical treatment may be carried out in a single session combining both liposuction and gland excision. Alternatively, in selected patients, a two-stage approach may be planned: liposuction is performed in the first session, followed by excision of residual glandular tissue in a second procedure.

Postoperative complications following gynecomastia surgery include over-resection, under-resection, hematoma, seroma, infection, hypertrophic scarring, and areolar hypoesthesia (17,18). The main causes of over-resection are preoperative asymmetry of the chest anatomy, differing proportions of glandular and adipose tissue between the two breasts, and the inability to achieve perfectly symmetrical tissue removal during surgery. Over-resection may lead to crater deformities, contour irregularities, and subcutaneous adhesions, all of which can negatively affect patient satisfaction (4).

The findings of our study suggest that contour irregularities that may arise during gynecomastia surgery may be corrected with autologous fat grafting. The proactive harvest does not involve deliberately creating deformities; instead, it ensures that a sterile and readily available graft source is on hand to address irregularities if they occur, thereby preventing a decrease in patient satisfaction. Despite a minimum follow-up period of eight months, none of the patients required a second fat grafting procedure or surgical revision, further supporting the efficacy of this approach.

Several prior studies have supported the use of autologous fat grafting for correcting contour deformities after gynecomastia or breast surgery (19,20). Pilanci et al. (21) described abdominal fat harvesting during gynecomastia procedures but noted the drawback of additional donor-site morbidity. More recent research has focused on improving graft survival and donor-site efficiency. Yu et al. (22) emphasized the influence of recipient-site factors on graft viability, while Friedhofer et al. (23) compared syringe-based and device-assisted harvesting techniques, demonstrating differences in adipocyte integrity.

Meta-analyses and systematic reviews by Trotzier et al. (24) and Canizares et al. (25) identified processing and handling as critical determinants of long-term graft retention. Vyas et al. (26) analyzed biological enrichment strategies such as platelet-rich plasma and adipose-derived stem cells, while Tsekouras et al. (27) compared donor-site adipocyte viability across anatomical regions. Hoyos et al. (28) further demonstrated the role of high-definition liposculpture with autologous fat grafting for chest contouring in male patients, underscoring the aesthetic versatility of this approach. Small et al. (29) examined the influence of donor-site selection on adipocyte quality, highlighting that regional variations may affect graft longevity. Complementing these findings, Tripathy et al. (16) and Innocenti et al. (17) provided contemporary evidence on technical refinements and complication profiles in gynecomastia correction.

In contrast to these approaches, the technique described in this study may reduce the need for an additional donor site by using breast tissue itself as a graft source. This proactive, intraoperative strategy could represent a simple and cost-effective adjunct, though further controlled studies are required to evaluate long-term graft survival and donor-site reliability.

Study Limitations

This study has several limitations. The retrospective, single-center design inherently restricts the strength of the evidence, and the relatively small sample size (n=24), with only nine patients receiving fat grafting, limits the statistical power of the analysis. A post hoc power analysis indicated that the current sample size provided adequate power only to detect large differences between groups; smaller or more subtle differences in satisfaction may have gone undetected. Therefore, the lack of statistically significant differences should be interpreted with caution. In addition, the average follow-up period of 12.4 months, while sufficient to assess early outcomes, may not fully reflect long-term graft survival or contour stability. Finally, although ultrasonography was used to monitor contour and detect fat necrosis, no objective volumetric measurements were performed. Future prospective, multicenter studies with larger cohorts and longer follow-up are needed to validate the clinical utility of proactive intraoperative fat grafting in gynecomastia surgery.

In this context, our study aims to contribute to the existing gap in literature by providing evidence on the feasibility of using breast tissue as a donor site and to serve as a foundation for future research. Furthermore, in this study, fat injections performed in patients who underwent gland excision for gland-dominant gynecomastia were not evaluated as a separate subgroup from those with pseudogynecomastia treated with liposuction alone. Future studies that take these parameters into account may offer clearer insights into optimal donor site selection and the effectiveness of fat grafting strategies across different gynecomastia subtypes.

CONCLUSION

This study suggests that proactively harvesting autologous fat from the breast region during gynecomastia surgery may be a feasible and safe technique for immediate correction of intraoperative contour irregularities. Using tissue from the same operative field may reduce donor-site morbidity and provide a readily available graft source when needed. However, given the retrospective design, small sample size, and limited follow-up, these findings should be regarded as preliminary rather than

definitive. Larger prospective studies are needed to confirm long-term outcomes and further evaluate the clinical value of this approach. Within these limitations, the described technique could represent a practical adjunct to standard gynecomastia surgery.

Videos link:

Video 1: Sagittal plane breast ultrasound imaging at postoperative 6 months of a patient who underwent autologous fat grafting due to intraoperative contour irregularity.

https://youtube.com/shorts/KU8Nh6FGxkk

Video 2: Transverse plane breast ultrasound imaging at postoperative 6 months of a patient who underwent autologous fat grafting due to intraoperative contour irregularity. https://youtube.com/shorts/KjvzqCRXhXE

Ethics

Ethics Committee Approval: The study was approved by the Yeditepe University Ethics Committee under the approval number: 202310Y0668, date: 15.11.2024 and was conducted in accordance with the principles of the Declaration of Helsinki.

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

Footnotes

Author Contributions

Concept - M.E.; Design - M.E.; Data Collection or Processing - M.E., E.Y.; Analysis or Interpretation - M.E., E.Y.; Literature Search - M.E., E.Y.; Writing - M.E., E.Y.

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

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ORIGINAL ARTICLE
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Perioperative airway events in pediatric patients with obesity undergoing bariatric surgery: A retrospective cohort

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ABSTRACT

Objective: Obesity presents challenges in airway management due to physiological and anatomical changes, increasing the risk of difficult mask ventilation and tracheal intubation. This study aimed to determine the frequency and types of airway complications and identify risk factors for difficult intubation and extubation in pediatric patients undergoing bariatric surgery.

Material and Methods: This retrospective cohort included 269 patients aged 12-17 years with body mass index ≥30 undergoing bariatric surgery under general anesthesia in Hamad Medical Corporation operating rooms between January 1, 2014, and January 1, 2024. We collected demographic data, preoperative airway assessment values; postoperative airway complications, and vital parameters. Multivariable logistic regressions were performed to assess variables associated with difficult intubation or extubation.

Results: Of the 269 patients, one developed cardiovascular instability post-operatively and one experienced bronchospasm after intubation. None of the patients experienced laryngospasm, vomiting, or airway edema. Desaturation occurred in 10 (3.6%) patients during intubation and 14 (5.1%) during extubation. Male sex was associated with a higher odd of difficult intubation [odds ratio (OR) 2.28, 95% confidence interval (CI): 0.95-5.49, p=0.065] and extubation (OR 3.83, 95% CI: 0.85-17.35, p=0.082). More than one intubation attempt increased the odds of difficult extubation 15.52- fold (95% CI: 1.83-131.37, p=0.012).

Conclusion: Male pediatric patients with obesity, especially with a history of snoring, are at higher risk for difficult intubation. Multiple intubations attempts strongly predict difficult extubation.

Keywords: Obesity, airway management, difficult intubation, difficult extubation, pediatric surgery, bariatric surgery

INTRODUCTION

Bariatric surgery in the pediatric population has become an increasingly utilized intervention for the management of severe obesity and its associated comorbidities, particularly when lifestyle modifications and medical therapy prove insufficient. This approach is especially pertinent for individuals with a body mass index (BMI) of 40 or higher, categorized as Class 3 or severe obesity, who face an increased risk of serious complications including type 2 diabetes, hypertension, obstructive sleep apnea (OSA), and diminished quality of life (1). Recent guidelines, including those from the Swedish National Board for Health and Welfare and the American Academy of Pediatrics, now recommend bariatric surgery for patients aged ≥15 years and ≥13 years, respectively, with severe obesity (1). While numerous studies have documented reductions in BMI, weight loss, adverse surgical outcomes, and the overall efficacy and safety of bariatric surgery in children and adolescents, the perioperative management of these patients—particularly regarding airway management and anesthesia—remains an underexplored area (2).

Airway management poses significant challenges in the perioperative care of pediatric bariatric patients due to anatomical and physiological factors, including reduced airway patency, increased neck circumference, and comorbid conditions

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such as OSA (3). Moreover, the challenges extend beyond the intraoperative period to include complications during extubation, such as hypoxia, laryngospasm, and airway trauma, which may result in prolonged recovery times and increased morbidity (4).

Despite the recognized risks, there is a paucity of comprehensive studies exploring the incidence and predictors of difficult airway management in pediatric populations undergoing bariatric surgery. Existing research on airway management in bariatric pediatric patients is often extrapolated from adult data or limited pediatric cohorts, which may not fully capture the unique considerations in this subgroup (5). This study aims to fill this gap by analyzing the frequency and types of complications related to tracheal intubation and extubation in pediatric patients undergoing bariatric surgery. Additionally, this study seeks to identify risk factors associated with the development of difficult intubation and extubation.

MATERIAL and METHODS

Ethical Considerations

The Institutional Review Board approval for this study (MRC-01-24-445) was provided by the Medical Research Center at Hamad Medical Corporation (HMC) Doha, Qatar (Chairperson Prof. Jassim Mohd. Al Suwaidi) on 17th September, 2024. Written informed consent was obtained for the surgery from parents of the pediatric patients. This study has been conducted in accordance with the principles set forth in the Helsinki Declaration.

Study Design, Population, and Eligibility Criteria

This study was designed as a retrospective cohort study and was conducted at HMC in Qatar. The study population consisted of pediatric patients with obesity aged 12 to 17 years, with a BMI of 30 or higher, who underwent bariatric surgery under general anesthesia in HMC operating rooms between January 1, 2014, and January 1, 2024. Patients were excluded if they were over 18 years of age, had a BMI below 30, underwent surgeries other than bariatric procedures, or received only sedation, local, or regional anesthesia.

Data Collection and Variables

Data was collected from the electronic medical records after approval from the institutional review board. Key variables included, 1) Demographic information (age, gender, nationality, BMI, and type of surgery); 2) Preoperative assessment parameters such as American Society of Anesthesiologists (ASA) score, Mallampati score, neck movement, neck circumference, mouth opening, thyromental distance, and comorbidities (e.g., OSA, asthma, and diabetes mellitus); 3) Intraoperative data captured Cormack-Lehane score, anesthetic agents used, laryngoscope type and size, endotracheal tube type and size, cuff pressure, laryngeal mask airway size, number of intubation attempts, any intubation or ventilation difficulties, and the use of stylet or bougie. Additionally, any need for airway rescue techniques such as supraglottic airway device, videolaryngoscope, or cricothyroidotomy was noted. Postoperative complications such as desaturation, airway trauma or edema, laryngospasm, bronchospasm, cardiovascular instability and technical complications were documented. Postoperative vital signs, as well as duration of post-anesthesia care unit (PACU) stay, intensive care unit (ICU) stay, and hospital stay, were also recorded.

Outcomes of Interest

The primary outcome of interest was the frequency and types of complications during tracheal intubation and extubation in pediatric patients undergoing bariatric surgery. Preoperative difficult airways were defined by the 1) Occurrence of desaturation (SpO_2 ≤94% for ≥10 seconds) during intubation, 2) Use of assisted intubation devices, and 3) The need for rescue airway techniques. Postoperative difficult extubation was identified by desaturation (SpO_2 ≤94% for ≥10 seconds) during extubation; as other potential complications, such as airway trauma, airway edema, laryngospasm, did not occur in this population. The secondary outcome was to assess preoperative factors associated with difficult intubation, as well as preoperative and intraoperative variables associated with difficult extubation.

Statistical Analysis

All statistical analyses were conducted using Stata 17 (College Station, TX, USA). Continuous variables were assessed for normality using histograms; normally distributed variables were reported as means and standard deviations (SD), while non-normally distributed variables were presented as medians and interquartile ranges (IQR). For comparisons between difficult intubation or extubation groups, t-tests were used for normally distributed continuous variables, and the Wilcoxon rank-sum test was applied for non-normally distributed variables. Categorical data were compared using the chi-squared test, or Fisher's exact test when appropriate. To evaluate factors associated with difficult intubation and extubation, logistic regression analyses were conducted. Association models were used and was adjusted for age and gender. Exact p-values were reported and were interpreted as evidence against the null hypothesis. For the logistic regression, odds ratios (OR) with 95% confidence intervals (95% CI) were reported to two decimal places.

RESULTS

Baseline Characteristics

Table 1 reports the baseline characteristics of 269 participants who were included in the study, of whom 64.3% (n=173) were males. The median age was 16 years (IQR 15.0 to 17.0). The

median BMI in the cohort was 47.7 kgm^{-2}, and the majority of the patients included had Class III obesity (63.2%, n=170). In terms of comorbidities, 45.7% (n=123) of participants had at least one comorbidity, with the most common being asthma (22.7%, n=61), followed by OSA (11.2%, n=30), hypothyroidism (7.1%, n=19), diabetes mellitus (4.8%, n=13), glucose-6-phosphate dehydrogenase (G6PD) deficiency (4.5%, n=12), and hypertension (3.7%, n=10). The remaining 54.3% (n=146) had no documented comorbid conditions. Majority of participants underwent laparoscopic sleeve gastrectomy, accounting for 89.6% (n=241) of the cohort. The median length of hospital stay was 2.0 days (IQR 2.0 to 3.0), and the median ICU stay was 2.0 days (IQR 1.0 to 2.0).

Preoperative Assessment

Preoperative assessments are outlined in Table 2, which demonstrates that 63.6% (n=171) of participants were classified as ASA 2, while 36.4% (n=98) were classified as ASA 3. For the Mallampati score, 63.9% (n=172) of patients were in Class II, 11.5% (n=31) in Class I, 16.0% (n=43) in Class III, and 3.0% (n=8) in Class IV. Cormack-Lehane scores were distributed as follows: 27.9% (n=75) in Class I, 28.3% (n=76) in Class II, 21.9% (n=59) in Class IIa, 9.3% (n=25) in Class IIb, and 0.4% (n=1) in Class III. A short neck was noted in 4.1% (n=11) of participants. The mean thyromental distance was 5.7 cm (SD=0.9), with 28.3% (n=76) measuring less than 6 cm, 45.7% (n=123) between 6 and 6.5 cm, and 8.6% (n=23) over 6.5 cm. Tracheal tube sizes of 7.0 and 7.5

Table 1. Baseline characteristics of the patients

Variable	Level	Value
N		269
Age (years), median (IQR)		16.0 (15.0, 17.0)
Sex	Female	96 (35.7%)
	Male	173 (64.3%)
BMI (kgm^{-2}), median (IQR)		47.7 (44.4, 52.5)
BMI categories	Class 3 obesity	170 (63.2%)
	Class 4 obesity	85 (31.6%)
	Class 5 obesity	14 (5.2%)
Comorbidities	No	146 (54.3%)
	Yes	123 (45.7%)
Type of comorbidities		
	Hypertension	10 (3.7%)
	Diabetes mellitus	13 (4.8%)
	G6PD deficiency	12 (4.5%)
	Hypothyroidism	19 (7.1%)
	Asthma	61 (22.7%)
	Obstructive sleep apnea	30 (11.2%)
Type of procedure	Robotic single gastric anastomosis	1 (0.4%)
	Endoscopic intragastric balloon insertion	5 (1.9%)
	Endoscopic intragastric balloon removal	13 (4.8%)
	LRYGB	4 (1.5%)
	LSG	241 (89.6%)
	Lap perigastric LN biopsy (spindle cell)	1 (0.4%)
	MGB	3 (1.1%)
	RRGB	1 (0.4%)
Duration of anesthesia (mins), mean (SD)		66.5 (22.5)
Duration of surgery (hrs), median (IQR)		1.0 (1.0, 1.0)
PACU stay (days), median (IQR)		70.0 (45.0, 100.0)
Hospital stay (days), median (IQR)		2.0 (2.0, 3.0)
ICU stay (days), median (IQR)		2.0 (1.0, 2.0)

BMI: Body mass index, SD: Standard deviation, G6PD: Glucose-6-phosphate dehydrogenase, PACU: Post-anesthesia care unit, ICU: Intensive care unit, IQR: Interquartile range, LRYGB: Laparoscopic roux-en-Y gastric bypass, LSG: Laparoscopic sleeve gastrectomy, LN: Lymph node, MGB: Mini gastric bypass, RRGB: Roux-en Y gastric bypass.

Table 2. Preoperative assessment and intubation data

Variable	Level	Value
N		269
ASA physical status classification	2	171 (63.6%)
	3	98 (36.4%)
Mallampati score	Not reported	15 (5.6%)
	I	31 (11.5%)
	II	172 (63.9%)
	III	43 (16.0%)
	IV	8 (3.0%)
Cormack-Lehane score	Not reported	33 (12.3%)
	I	75 (27.9%)
	II	76 (28.3%)
	IIa	59 (21.9%)
	IIb	25 (9.3%)
	III	1 (0.4%)
Short neck	No	258 (95.9%)
	Yes	11 (4.1%)
Thyromental distance (cm), mean (SD)		5.7 (0.9)
Thyromental distance categories (cm)	<6	76 (28.3%)
	6 to 6.5	123 (45.7%)
	>6.5	23 (8.6%)
	Not reported	47 (17.5%)
Tracheal tube size	6	1 (0.4%)
	6.5	9 (3.3%)
	7	157 (58.4%)
	7.5	86 (32.0%)
	8	8 (3.0%)
	Not reported	8 (3.0%)
Laryngoscope blade number	3	44 (16.4%)
	3.5	6 (2.2%)
	4	193 (71.7%)
	Not reported	26 (9.7%)

ASA: American Society of Anesthesiologists, SD: Standard deviation.

were most commonly used, at 58.4% (n=157) and 32.0% (n=86), respectively. Lastly, a laryngoscope blade size of 4 was used in 71.7% (n=193) of cases, followed by size 3 in 16.4% (n=44) and size 3.5 in 2.2% (n=6).

Characteristics of Difficult Intubation or Extubation

Table 3 summarizes the difficult airway management and outcomes during intubation and extubation. Amongst the 269 patients, 1 patient developed cardiovascular instability post-operatively in the PACU and 1 patient developed bronchospasm after intubation. None of the patients experienced laryngospasm, vomiting, airway edema, or airway injury. Fifteen patients

Table 3. Difficult intubation and extubation data

Variable	Level	Value
N		269
Use of video laryngoscope	No	254 (94.4%)
	Yes	15 (5.6%)
Intubation through supraglottic airway device	No	267 (99.3%)
	Yes	2 (0.7%)
Requirement of stylet/bougie	Bougie	1 (0.4%)
	Stylet	8 (3.0%)
	None	260 (96.7%)
Cardiovascular instability	No	268 (99.6%)
	Yes	1 (0.37%)
Bronchospasm	No	268 (99.6%)
	Yes	1 (0.37%)
Desaturation during intubation <94%	No	259 (96.3%)
	Yes	10 (3.7%)
Desaturation during extubation <94%	No	255 (94.8%)
	Yes	14 (5.2%)
Number of intubation attempts	1	259 (96.3%)
	>1	4 (1.5%)
	Not reported	6 (2.2%)

required the use of a videolaryngoscope, while the majority (94.4%, n=254) did not. Intubation through a supraglottic airway was used in two patients (0.7%). A stylet or bougie was required for intubation in 3.4% (n=9) of cases, with 3.0% (n=8) using a stylet and 0.4% (n=1) using a bougie. Desaturation events (SpO_2 <94% for ≥10 seconds) were observed in 10 participants during intubation and 14 participants during extubation. Most intubations (96.3%, n=259) were successful on the first attempt, with more than one attempt required in 1.5% (n=4) of cases.

Logistic Regression Analysis for Difficult Intubation

Table 4 presents the logistic regression analysis for factors associated with difficult intubation. Male sex was associated with increased odds of difficult intubation, with an adjusted OR of 2.28 (95% CI: 0.95-5.49; p=0.065), compared to females. Patients aged 16 years and older had decreased odds of difficult intubation (OR=0.68, 95% CI: 0.32-1.45; p=0.322) compared to those under 16, though this was with limited evidence against the null hypothesis. Notably, history of snoring was associated with difficult intubation, with an OR of 2.66 (95% CI: 1.20-5.90; p=0.016) with strong evidence against the null hypothesis at this sample size. For ASA score, patients classified as ASA 3 had slightly higher odds of difficult intubation (OR=1.38, 95% CI: 0.65-2.92; p=0.404) compared to those with an ASA score of 2, again with weak evidence against the model hypothesis. BMI was also analyzed, with patients in BMI Class 4 obesity demonstrating

higher odds of difficult intubation (OR=1.20, 95% CI: 0.55-2.62; p=0.645) compared to Class 3 obesity. OSA was associated with an increased odds of difficult intubation (OR=1.73, 95% CI: 0.63-4.71; p=0.286), though this result had weak evidence against the null hypothesis.

Logistic Regression Analysis for Difficult Extubation

Table 5 presents the logistic regression analysis for factors associated with difficult extubation. Male patients showed an increased likelihood of difficult extubation, with an OR of 3.83 (95% CI: 0.85-17.35; p=0.082) compared to females. Additionally, those in BMI Class 4 obesity had increased odds of difficult extubation (OR=1.33, 95% CI: 0.45-3.90; p=0.605) relative to BMI Class 3 obesity, however with weak evidence against the null hypothesis. Among the variables, a notable association was observed with the number of intubation attempts; whereby patients requiring more than one intubation attempt had significantly higher odds of desaturation during extubation (OR=15.52, 95% CI: 1.83-131.37; p=0.012). OSA was associated with an increased odds of difficult extubation (OR=1.92, 95% CI: 0.49-7.47; p=0.384), though this result also had weak evidence against the null hypothesis. Duration of anesthesia for ≥60 minutes was associated with higher odds of desaturation during extubation (OR=2.53, 95% CI: 0.69-9.27; p=0.161) compared to a duration of <60 minutes.

DISCUSSION

Obesity presents a significant challenge in perioperative airway management, particularly in pediatric patients undergoing bariatric surgery. This study aimed to identify the frequency and types of complications related to tracheal intubation and extubation, as well as to investigate factors associated with difficult intubation and extubation in pediatric patients with severe obesity.

Our findings show that male sex, age below 16 years, elevated BMI, and higher ASA scores were all associated with an increased likelihood of difficult intubation. Furthermore, a history of snoring and OSA further elevated these odds. The unique anatomical and physiological characteristics associated with obesity in this population—such as increased neck circumference, excess soft tissue mass around the airway, and OSA—contribute to a higher likelihood of both difficult intubation and extubation, in line with findings from prior studies in adult and limited pediatric cohorts.

Table 4. Multivariable logistic regression for difficult intubation

Variable	Level	Adjusted OR	Adjusted 95% CI	p-value	Reference
Sex	Male	2.28	0.95-5.49	0.065	Female
Age	≥16	0.68	0.32-1.45	0.322	<16
ASA score	3	1.38	0.65-2.92	0.404	2
Body mass index	Class 4	1.20	0.55-2.62	0.645	Class 3
	Class 5	0.51	0.06-4.16	0.530	Class 3
Comorbidity	Yes	1.41	0.67-2.95	0.362	No
Asthma	Yes	1.53	0.67-3.45	0.311	No
Hypertension	Yes	0.71	0.09-5.85	0.747	No
Hypothyroidism	Yes	0.43	0.05-3.39	0.423	No
Obstructive sleep apnea	Yes	1.73	0.63-4.71	0.286	No
G6PD deficiency	Yes	2.20	0.55-8.73	0.262	No
Mallampati score	II	1.10	0.34-3.56	0.870	I
	III	0.98	0.23-4.06	0.974	I
	IV	2.43	0.35-17.11	0.372	I
Cormack-Lehane score	II	0.71	0.26-1.93	0.505	I
	IIa	0.89	0.31-2.55	0.832	I
	IIb	0.91	0.23-3.70	0.900	I
Snoring	Yes	2.66	1.20-5.90	0.016	No
Thyromental distance	6 cm to 6.5 cm	0.78	0.32-1.88	0.577	<6
	>6.5 cm	1.09	0.30-4.01	0.898	<6
Tracheal tube type	Straight	1.14	0.53-2.45	0.730	Regular
Tracheal tube size	7.5	1.41	0.63-3.18	0.406	7
Laryngoscope blade number	4	1.28	0.27-6.14	0.762	3

ASA: American Society of Anesthesiologists, OR: Odds ratio, CI: Confidence interval, G6PD: Glucose-6-phosphate dehydrogenase.

Table 5. Multivariable logistic regression for difficult extubation

Variable	Level	Adjusted OR	Adjusted 95% CI	p-value	Reference
Sex	Male	3.83	0.85-17.35	0.082	Female
Age	≥16 years	0.92	0.30-2.80	0.884	<16
ASA score	3	0.51	0.16-1.67	0.264	2
Body mass index	Class 4 obesity	1.33	0.45-3.90	0.605	Class 3
Comorbidity	Yes	1.28	0.45-3.68	0.643	No
Asthma	Yes	1.62	0.53-5.00	0.401	No
Hypothyroidism	Yes	1.23	0.15-10.28	0.850	No
Obstructive sleep apnea	Yes	1.92	0.49-7.47	0.348	No
Mallampati score	II	2.07	0.25-17.44	0.503	I
	III	1.62	0.14-19.25	0.700	I
Cormack-Lehane	II	0.74	0.21-2.58	0.641	I
	IIa	0.39	0.08-2.07	0.272	I
Short neck	Yes	1.75	0.20-15.14	0.609	No
Snoring	Yes	1.41	0.43-4.66	0.576	No
Thyromental distance	6 cm to 6.5 cm	0.65	0.16-2.57	0.537	<6
	>6.5	1.37	0.22-8.45	0.734	<6
Number of intubation attempts	>1	15.52	1.83-131.37	0.012	1
Tracheal tube type	Straight	1.60	0.52-4.87	0.412	Regular
Tracheal tube size	7.5	0.89	0.29-2.70	0.838	7
Laryngoscope blade number	4	2.51	0.31-20.12	0.387	3
Duration of anesthesia	≥60 minutes	2.53	0.69-9.27	0.161	<60 minutes
Difficult intubation	Yes	0.93	0.20-4.40	0.929	No

ASA: American Society of Anesthesiologists, OR: Odds ratio, CI: Confidence interval.

Obesity also induces physiological changes in the respiratory system, leading to a shortened time to desaturation during anesthesia induction and airway management (6). The Pediatric Difficult Intubation Collaborative has highlighted that multiple intubation attempts and continued use of direct laryngoscopy are significant risk factors for complications in children with difficult airways (7). In response, they launched initiatives to minimize repeated attempts and reliance on direct laryngoscopy. Our study found that patients requiring multiple intubation attempts had statistically significant greater odds of desaturation during extubation, likely due to airway trauma or edema incurred during these repeated attempts, though this finding was limited by the small sample size (n=4). More than one intubation attempt was related with 15.5 fold higher odds of desaturation at extubation. Desaturation during Extubation occurred in 5.2% of patients overall. Using this as a baseline to illustrate the magnitude of effect, a 15.5 fold increase in odds translated into an estimated 46% risk of desaturation if a patient has required more than one intubation attempt. Clinically, this means that failure to achieve first-pass success was not only an intraoperative challenge but also carried forward into extubation and recovery, underscoring the critical importance of a first-pass success strategy in pediatric bariatric cases.

Male sex was associated with higher risks of both extubation desaturation and difficult intubation. Snoring increased the odds of difficult intubation by 2.66-fold. These markers identify children who warrant automatic escalation in airway planning including the involvement of a senior operator, VL as first-line, apneic oxygenation, and a formalized extubation plan. In addition, anesthesia lasting longer than 60 minutes was associated with a 2.53 fold higher odds of desaturation during extubation. This emphasizes the importance of planning for an earlier, controlled, "no-drift" emergence in longer cases. We recommend to minimize residual anesthetic or opioid load, use PEEP or CPAP support, and extubate fully awake with two-person jaw support.

Moreover, in our study, video laryngoscopy was only used in 15 patients while majority did not require it. Nonetheless, it is vital to minimize intubation attempts through advanced techniques, such as videolaryngoscopy, and pre-emptively addressing difficult airway predictors. Simulation-based training

offers a structured approach to improve performance in this domain. High-fidelity scenarios allow anesthesia teams to practice advanced techniques of video laryngoscopy, bougie-first intubation, ramped positioning or apneic oxygenation in a safe environment, while reinforcing crisis resource management skills. By repeatedly rehearsing anticipated difficult airway cases including extubation failure and re-intubation drills, trainees internalize decision algorithms and develop muscle memory for rarely used but life-saving maneuvers (8). We are of the opinion that, if implemented systematically, such simulation curricula can reduce the incidence of multiple intubation attempts, thereby attenuating the increased risk of extubation desaturation identified in our analysis. In this way, simulation training directly addresses the mechanism underlying the ORs we report, translating statistical risk into modifiable practice change.

Additionally, many children with obesity present with comorbidities such as bronchial asthma (8). In our study, the odds of difficult intubation were increased in patients with bronchial asthma and G6PD deficiency. Difficulties with extubation were primarily linked to factors such as previous intubation attempts. The higher incidence of desaturation during extubation emphasizes the need for meticulous planning and monitoring during the transition from mechanical ventilation, particularly in patients with anatomical or functional airway compromise (9).

This study emphasizes the critical need for tailored preoperative assessment, including the use of predictive scoring systems. Routine screening for OSA and snoring history, alongside careful evaluation of neck circumference and thyromental distance, should guide the choice of airway management strategies. Our findings also support the routine availability of advanced airway devices and personnel trained in pediatric airway management in bariatric centers (10).

Study Limitations

While this study provides valuable insights, its retrospective design is prone to incomplete data therefore limiting the ability to control all relevant variables. The single center design and relatively sample size, though substantial for a pediatric cohort, may restrict the diversity of patient demographics and institutional practices, thereby limiting the external validity and generalizability of findings. Moreover, potential confounders, such as anesthesiologist experience and variation in institutional airway management protocols, which could have affected the choice of airway technique and the occurrence of complications were not accounted for. Future research should include prospective multicenter studies to validate these findings and explore interventions to mitigate airway management risks in this population.

CONCLUSION

The perioperative airway management of pediatric patients with obesity undergoing bariatric surgery is challenging but manageable with appropriate preparation and vigilance. Male patients, those with a history of snoring, and requiring multiple intubation attempts are at higher risk for complications. Early identification of these risk factors and the strategic use of advanced airway devices are crucial for improving outcomes.

Ethics

Ethics Committee Approval: The Institutional Review Board approval for this study (MRC-01-24-445) was provided by the Medical Research Center at Hamad Medical Corporation (HMC) Doha, Qatar (Chairperson Prof. Jassim Mohd. Al Suwaidi) on 17th September, 2024.

Informed Consent: Written informed consent was obtained for the surgery from parents of the pediatric patients.

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Footnotes

Author Contributions

Surgical and Medical Practices - A.S., A.R.R.V., M.K., M.R., M.M.B., Y.O.O.M.E., M.W.J., K.T.S.; Concept - A.S., A.R.R.V., B.M.A., A.M.E., M.A., A.M.O.A.I., M.K., M.R., M.M.B., Y.O.O.M.E., M.W.J., K.T.S.; Design - A.S., B.M.A., A.M.E., A.M.O.A.I., M.K., M.R., M.M.B., Y.O.O.M.E.; Data Collection or Processing - B.M.A., A.M.E., A.M.O.A.I., M.K., M.R., M.M.B., Y.O.O.M.E.; Analysis or Interpretation - A.S., A.R.R.V., B.M.A., A.M.E., M.A., K.T.S.; Literature Search - A.S., A.R.R.V., B.M.A., A.M.E., M.A., A.M.O.A.I., M.K., M.R., M.M.B., Y.O.O.M.E., M.W.J., K.T.S.; Writing - A.S., A.R.R.V., B.M.A., A.M.E., M.A., A.M.O.A.I., M.K., M.R., M.M.B., Y.O.O.M.E., M.W.J., K.T.S.

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ORIGINAL ARTICLE
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The impact of the COVID-19 pandemic on the diagnosis and surgical treatment processes of gastric cancer

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ABSTRACT

Objective: This study aimed to evaluate the effects of the coronavirus disease-2019 (COVID-19) pandemic on the diagnostic and surgical treatment processes of gastric cancer. Three-year periods before and after the pandemic were compared to examine differences in the diagnostic process, disease stage, surgical extent, and survival.

Material and Methods: A retrospective analysis was conducted on 395 patients who underwent resection surgery for gastric cancer between March 11, 2017, and March 11, 2023. Patients with incomplete data regarding the diagnostic and treatment processes, those deemed inoperable following exploratory surgery and subsequently referred for alternative treatment, and patients operated on at external centers were excluded. A total of 197 patients were analyzed and divided into two groups: pre-pandemic (PP, n=137) and post-pandemic (PS, n=60).

Results: A significant decrease in the number of surgeries was observed in the PS group compared to the PP group. Significant differences were found between the two groups regarding locally advanced disease at diagnosis (T4/N+), the application rate of cytoreductive surgery+hyperthermic intraperitoneal chemotherapy, and follow-up mortality (p=0.031, p=0.028, and p=0.005). The overall mean survival was 50.02±2.78 months in the PP group and 32.52±2.24 months in the PS group (p=0.765). No significant differences were observed between the groups regarding the diagnostic process and pathological stages.

Conclusion: The COVID-19 pandemic may have reduced both the referral rates for surgery and the extent of surgical interventions for advanced-stage gastric cancer. It is believed that both surgeons and patients adopted more conservative approaches during the pandemic.

Keywords: Gastric adenocarcinoma, gastric cancer surgery, COVID-19, pandemic

INTRODUCTION

Gastric cancer continues to represent a major global health concern due to its high incidence and cancer-related mortality rates. Based on data from the Global Cancer Observatory, nearly 1 million new cases of gastric cancer were recorded in 2020, resulting in over 770,000 deaths attributed to the disease (1). While the prevalence is particularly high in East Asian countries, gastric cancer remains a leading cause of morbidity and mortality in many developing regions as well. The disease typically progresses insidiously, and the absence of prominent clinical symptoms in the early stages often leads to delayed diagnosis. Consequently, a significant proportion of patients are identified at either locally advanced or metastatic stages (2).

The contemporary management of gastric cancer typically incorporates a multimodal strategy, combining surgical intervention with systemic therapies based on the tumour stage. For early-stage disease, therapeutic options may include endoscopic resection or minimally invasive laparoscopic surgery. In contrast, patients with locally advanced tumors generally undergo extensive resections following neoadjuvant chemotherapy, which serves as the foundation of curative treatment (3). Total or subtotal gastrectomy accompanied by D2 lymphadenectomy is widely accepted as the surgical standard in oncologic practice. In more complex cases, such as those involving peritoneal dissemination or adjacent organ invasion, advanced procedures like cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have been adopted as potential treatment modalities (4). Nevertheless, due to the elevated risk of postoperative complications, meticulous patient selection remains crucial.

The coronavirus disease-2019 (COVID-19) pandemic, which was officially recognised on March 11, 2020, has had a profound and widespread influence on global

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healthcare delivery (5). With health systems primarily directed toward managing acute respiratory infections, there was a substantial disruption in routine medical services, including delays in elective surgeries, limitations in diagnostic workflows, and interruptions in oncologic care (6). Particularly concerning was the restriction of aerosol-generating procedures such as upper gastrointestinal endoscopy, which hindered the timely diagnosis of cancers like gastric cancer that often present with subtle or non-specific symptoms. As a result, many patients presented at more advanced disease stages, limiting opportunities for curative interventions (7).

Beyond diagnostic delays, the pandemic also led to significant modifications in surgical decision-making and treatment planning. Due to constraints such as limited availability of intensive care resources, surgical teams and multidisciplinary cancer boards increasingly adopted conservative treatment strategies, reserving high-risk procedures for select cases. In this context, neoadjuvant treatment protocols gained traction for locally advanced gastric cancer, while definitive surgeries were frequently delayed or omitted (7). Additionally, the use of high-morbidity procedures such as CRS and HIPEC for peritoneal carcinomatosis became more selective, highlighting a shift in clinical decision-making that accounted not only for oncological criteria but also for health system limitations.

Although comprehensive data remain scarce, early reports indicate a trend toward more advanced disease presentation at diagnosis, reduced surgical intervention rates, and compromised oncological outcomes in gastric cancer patients during the pandemic period (8). The magnitude of these effects, however, has varied depending on regional healthcare capacities and pandemic management strategies. Institutions with resilient infrastructure were generally able to sustain oncologic services, whereas facilities with limited resources experienced considerable disruptions in both diagnostic and therapeutic pathways (9).

This retrospective study was conducted to assess the effects of the COVID-19 pandemic on the diagnostic and therapeutic pathways of patients undergoing surgical resection for gastric cancer at our institution. We systematically compared several parameters between the pre-pandemic (PP) and pandemic periods, including stage at diagnosis, time from diagnosis to treatment, surgical extent, frequency of neoadjuvant therapy, and survival outcomes. The objective was to clarify how the pandemic influenced surgical care in gastric cancer and to inform future planning and response strategies in the face of comparable global health emergencies.

MATERIAL and METHODS

This retrospective analysis included patients diagnosed with gastric cancer who underwent surgical resection within the Department of General Surgery at Ege University Faculty of Medicine Hospital. Ethical approval for the study was obtained by the Ege University Local Medical Research Ethics Committee on May 9, 2024 (approval no: 24-5T/11).

Patients who were diagnosed with gastric cancer and underwent resection surgery at our institution between March 11, 2017, and March 11, 2023, were evaluated for inclusion in the study. Eligible cases included those with a confirmed histopathological diagnosis of gastric adenocarcinoma, established through endoscopic biopsy or exploratory surgery, with clearly identifiable dates of diagnosis and, where applicable, initiation of neoadjuvant therapy. Only patients who received definitive surgical treatment in our department, including appropriate lymphadenectomy and, when indicated, additional resective procedures such as adjacent organ resection, CRS, or HIPEC, were considered for analysis.

Patients with incomplete information regarding diagnostic or treatment procedures, those deemed inoperable during exploratory surgery and subsequently referred for non-surgical treatment, individuals who underwent definitive surgery at external centers and were referred to our institution only for additional procedures, or patients receiving solely palliative care were excluded from the analysis. Finally, 197 out of 395 patients were included in the final cohort.

All clinical and pathological data were retrospectively collected from the hospital's electronic medical records, including patient history, discharge summaries, endoscopic and radiologic reports, operative notes, and pathology findings.

The study cohort was stratified into two groups based on the timeline relative to the onset of the COVID-19 pandemic: The PP and post-pandemic (PS) periods. Patients treated between March 11, 2017 and March 10, 2020 were categorized as the PP group, while those managed between March 11, 2020 and March 11, 2023 comprised the PS group. The groups were compared across multiple parameters, including demographic characteristics (age, sex), the time interval from symptom onset to diagnosis (in months), the interval between diagnosis and initiation of first-line therapy (neoadjuvant treatment or surgery, in days), radiological evidence of locally advanced disease (cT4, cN+) or peritoneal spread, intraoperative findings such as adjacent organ invasion (cT4B) or peritoneal carcinomatosis, type of gastric resection performed, implementation of CRS and HIPEC, and postoperative pathological staging (pTNM classification and prognostic stage).

Statistical Analysis

Categorical variables were presented as frequencies and percentages, while continuous variables were reported as means with standard deviations. The normality of continuous data was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov

tests. Group comparisons were conducted using the chi-square test for categorical variables, the Student's t-test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed variables. It could be better to add the place labeled yellow in statistical analysis "Survival analyses utilized the Kaplan-Meier method to generate and compare the survival curves between the pre-pandemic and post-pandemic groups. Furthermore, Cox Regression Analysis was performed to identify independent prognostic factors affecting mortality". A p-value less than 0.05 was considered statistically significant, and all analyses were performed using SPSS version 23.0 (IBM Corp., Chicago, IL, USA).

RESULTS

A total of 197 patients who fulfilled the inclusion criteria and had complete data regarding diagnostic and therapeutic processes were enrolled in the study. Of these, 136 (69.0%) were male and 61 (31.0%) were female, with a mean age of 62.53±11.39 years. An overview of the patients' demographic characteristics and clinical parameters is provided in Table 1.

Of the 197 patients included in the study, 137 (69.5%) were treated during the PP period, while 60 (30.5%) received treatment during the PS period. There were no statistically significant differences between the two groups regarding baseline demographic variables such as gender and age, or temporal metrics including symptom duration and time to initiation of treatment (p>0.05).

However, the proportion of patients diagnosed with locally advanced disease (cT4 and/or cN+) was significantly higher in the PP group compared to the PS group (48.2% vs. 31.7%; p=0.031). Similarly, the use of CRS combined with HIPEC significantly declined during the pandemic period (PP: 10.9% vs. PS: 1.7%; p=0.028). Follow-up data also revealed a higher mortality rate in the PP group (53.3%) compared to the PS group (31.7%), a difference that reached statistical significance (p=0.005). Further details are presented in Table 2.

The mean overall survival for the entire cohort was calculated as 50.36±2.45 months. The 1-year and 3-year survival rates were 63.6% and 57.7%, respectively. When analyzed by pandemic period, the mean overall survival was 50.02±2.78 months for the PP group and 32.52±2.24 months for the PS group; however, this difference was not statistically significant (p=0.765) (Figures 1, 2).

In the multivariate analysis conducted using Cox regression, the only factor found to have a significant impact on mortality was the pathological stage (p<0.001). No significant effects of other variables on mortality were observed (p>0.05) (Table 3).

Table 1. Descriptive and clinical statistics

Descriptive statistics	
Age	64.97±11.59
Gender male/female	136 (69.0%)/61 (31.0%)
Symptom onset (month)	5.08±9.16
Interval between diagnosis and treatment (day)	45.31±52.73
Peritoneal carcinomatosis findings at diagnosis	16 (8.1%)
Locally advanced disease findings at diagnosis	85 (43.1%)
Neoadjuvant therapy	53 (26.9%)
Resection type-total	100 (50.8%)
Resection type-subtotal	73 (37.1%)
Resection type-proksimal	24 (12.2%)
Peritoneal carcinomatosis findings at the operation	11 (5.6%)
Adjacent organ invasion findings at the operation	19 (9.6%)
CRS + HIPEC	16 (8.1%)
pT grade-T0	8 (4.1%)
pT grade-T1	28 (14.2%)
pT grade-T2	22 (11.2%)
pT grade-T3	44 (22.3%)
pT grade-T4a	80 (40.6%)
pT grade-T4b	13 (6.6%)
pN grade-N0	67 (34.0%)
pN grade-N1	36 (18.3%)
pN grade-N2	29 (14.7%)
pN grade-N3a	41 (20.8%)
pN grade-N3b	24 (12.2%)
pM grade-M0	187 (94.9%)
pM grade-M1	10 (5.1%)
Grade-0	10 (5.1%)
Grade-1A	25 (12.7%)
Grade-1B	15 (7.6%)
Grade-2A	17 (8.6%)
Grade-2B	25 (12.7%)
Grade-3A	34 (17.3%)
Grade-3B	37 (18.8%)
Grade-3C	24 (12.2%)
Grade-4	10 (5.1%)
Overall survival	50.36±2.45 year
1-year overall survival	63.6%
3-year overall survival	57.7%

HIPEC: Hyperthermic intraperitoneal chemotherapy, CRS: Cytoreductive surgery.

DISCUSSION

This study aimed to investigate the effects of the COVID-19 pandemic on the diagnostic and surgical treatment processes of gastric cancer by retrospectively analyzing patients who

Table 2. Comparison of parameters between the PP and PS groups

	PP	PS	p
Age	64.27±12.44	66.56±9.25	0.385
Gender (male/female)	92 (67.2%)/45 (32.8%)	44 (73.3%)/16 (26.7%)	
Symptom onset (month)	5.28±8.83	4.66±9.91	0.098
Interval between diagnosis and treatment (day)	43.93±56.08	48.71±47.02	0.305
Peritoneal carcinomatosis findings at diagnosis	12 (8.8%)	4 (6.7%)	0.623
Locally advanced disease findings at diagnosis	66 (48.2%)	19 (31.7%)	0.031
Neoadjuvant therapy	34 (24.8%)	19 (31.7%)	0.318
Resection type-total	65 (47.4%)	35 (58.3%)	
Resection type-subtotal	53 (38.7%)	20 (33.3%)	
Resection type-proksimal	19 (13.9%)	5 (8.3%)	
Peritoneal carcinomatosis findings at the operation	8 (5.8%)	3 (5.0%)	0.814
Adjacent organ invasion findings at the operation	13 (9.5%)	6 (10.0%)	0.911
CRS + HIPEC	15 (10.9%)	1 (1.7%)	0.028
pT grade-Tis	2 (1.5%)	0 (%)	
pT grade-T0	6 (4.4%)	2 (3.3%)	
pT grade-T1	21 (15.3%)	7 (11.7%)	
pT grade-T2	12 (8.8%)	10 (16.7%)	
pT grade-T3	32 (23.4%)	12 (20.0%)	
pT grade-T4a	54 (39.4%)	26 (43.3%)	
pT grade-T4b	10 (7.3%)	3 (5.0%)	
pN grade-N0	46 (33.6%)	21 (35.0%)	
pN grade-N1	25 (18.2%)	11 (18.3%)	
pN grade-N2	16 (11.7%)	13 (21.75)	
pN grade-N3a	34 (24.8%)	7 (11.7%)	
pN grade-N3b	16 (11.7%)	8 (13.3%)	
pM grade-M0	129 (94.2%)	58 (96.7%)	0.569
pM grade-M1	8 (5.8%)	2 (3.3%)	0.463
Grade-0	8 (5.8%)	2 (3.3%)	
Grade-1A	19 (13.9%)	6 (10.0%)	
Grade-1B	8 (5.8%)	7 (11.7%)	
Grade-2A	13 (9.5%)	4 (6.7%)	
Grade-2B	13 (9.5%)	12 (20.0%)	
Grade-3A	21 (15.3%)	13 (21.7%)	
Grade-3B	21 (15.3%)	7 (11.7%)	
Grade-3C	30 (21.9%)	7 (11.7%)	
Grade-4	17 (12.4%)	2 (3.3%)	
Exitus	73 (53.3%)	19 (31.7%)	0.005
Overall survival	50.02±2.78	32.52±2.24	0.765
1-year overall survival	83.2%	84.8%	
3-year overall survival	57.5%	65.7%	

PP: Pre pandemic, PS: Post pandemic, HIPEC: Hyperthermic intraperitoneal chemotherapy, CRS: Cytoreductive surgery.

underwent surgery before and after the pandemic. Our findings indicate that during the pandemic period, there was a significant reduction in the number of patients undergoing surgery, a decline in the rate of locally advanced disease at diagnosis, and a significant decrease in the frequency of advanced surgical interventions such as CRS+HIPEC. These results not only reflect

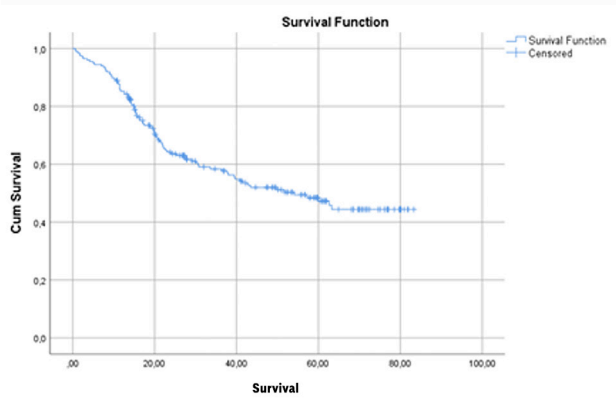

Figure 1. Overall survival curve.

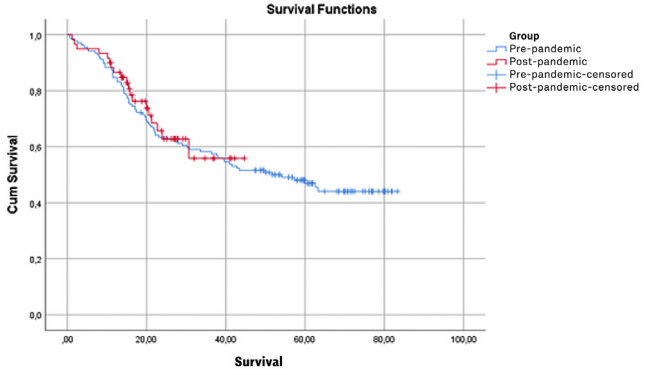

Figure 2. Survival comparison between the PP and PS groups.
PP: Pre pandemic, PS: Post pandemic

the burden placed on healthcare systems during the pandemic but also highlight its impact on surgical decision-making processes.

The reduction in surgical cases observed during the pandemic is in line with data reported from various countries. In nations such as China, Italy, Spain, and the United States, marked declines in surgical rates for gastrointestinal cancers have been documented. This trend is attributed both to a decrease in patient referrals and to the reallocation of hospital resources (e.g., intensive care beds, personnel, and equipment) to the management of COVID-19 patients (10). In our study, 30.5% fewer patients received surgical treatment during the pandemic period compared to the PP period, suggesting that the number of gastric cancer patients who were either undiagnosed or unable to access surgery may be even higher.

The lower rate of locally advanced disease at diagnosis in the PS period appears to contradict some findings in the literature. For instance, a study conducted in the United Kingdom reported an increased rate of advanced-stage disease among gastrointestinal cancer patients during the pandemic (11). However, our study included only patients eligible for surgery—a selected patient population—which may explain this discrepancy. It is possible that patients with more advanced diseases were either directed to non-surgical treatment modalities or deemed inoperable during the pandemic. Moreover, the relatively maintained access to diagnosis and treatment at our centre, owing to its robust healthcare infrastructure, might have contributed to these findings.

The marked reduction in high-morbidity procedures such as CRS+HIPEC during the pandemic aligns with current international guidelines. Authorities such as European Society For Medical Oncology and National Comprehensive Cancer Network recommended a more selective approach to these high-risk procedures during the pandemic (12). Our findings suggest that this recommendation was reflected in clinical practice, with surgeons adopting more conservative management strategies, particularly for patients with peritoneal disease driven by both clinical and logistical concerns.

Although the survival analysis revealed a lower mean overall survival for patients operated on during the pandemic, this difference was not statistically significant. This observation may be explained by the relatively short follow-up period, the selected nature of the patient population, and the exclusion of patients who did not undergo surgery during the pandemic. Additionally, the Cox regression analysis identified only the pathological stage as an independent predictor of survival, underscoring the critical role of tumour staging in treatment outcomes (13).

One of the strengths of this study is the use of patient data covering six years from a single centre, where patients were treated by a homogeneous surgical team. This minimizes heterogeneity in surgical techniques and follow-up protocols. Furthermore, by including data from a three-year pandemic period, our study allows for an evaluation of both the immediate and longer-term effects of the COVID-19 crisis.

Study Limitations

Nonetheless, our study has several limitations. As a retrospective analysis, it is subject to methodological constraints such as selection bias and potential inaccuracies in record-keeping. Patients who were directed to non-surgical treatment modalities or who succumbed to their disease without accessing surgery were not included, which may lead to an underestimation of the true impact of the pandemic. Moreover, the incomplete long-term survival data limits a comprehensive prognostic evaluation.

CONCLUSION

The COVID-19 pandemic has profoundly affected not only the management of infectious diseases but also the diagnostic and treatment pathways for oncological conditions. This study

Table 3. Cox regression analysis results of factors affecting survival

	B	SE	Wald	df	Sig.	Exp(B)	95% CI lower	95% CI upper
Locally advanced disease findings at diagnosis	0.121	0.262	0.213	1	0.644	0.886	0.53	1.481
HIPEC	0.076	0.614	0.015	1	0.902	0.927	0.278	3.086
Grade			33.116	8	0.0			
Grade-1A	0.764	1.025	0.556	1	0.456	0.466	0.062	3.472
Grade-1B	0.711	0.89	0.638	1	0.424	2.036	0.356	11.652
Grade-2A	1.097	0.837	1.715	1	0.19	2.994	0.381	15.455
Grade-2B	1.247	0.794	2.467	1	0.116	3.481	0.734	16.557
Grade-3A	1.317	0.792	2.761	1	0.097	3.731	0.789	17.631
Grade-3B	1.978	0.785	6.353	1	0.012	7.227	1.553	33.645
Grade-3C	2.312	0.798	8.403	1	0.004	10.096	2.114	48.203
Grade-4	3.226	0.913	12.482	1	0.0	25.185	4.206	150.816
Age	0.006	0.01	0.332	1	0.565	1.006	0.96	1.054
Gender	0.194	0.236	0.676	1	0.411	1.214	0.765	1.927
Pandemic	0.027	0.105	0.071	1	0.791	0.974	0.801	1.186
Peritoneal carcinomatosis findings at diagnosis	0.702	0.523	1.803	1	0.179	0.496	0.178	1.381
Neoadjuvant therapy	0.344	0.395	0.756	1	0.385	1.41	0.65	3.063
Total gastrectomy	1.569	0.456	11.855	2	0.456	4.804	1.726	13.366
Subtotal gastrectomy	0.317	0.256	1.533	1	0.216	0.728	0.44	1.203
Proksimal gastrectomy	0.074	0.388	0.036	1	0.849	0.929	0.434	1.987
Peritoneal carcinomatosis findings at the operation	0.313	0.487	0.412	1	0.521	1.367	0.526	3.553
Adjacent organ invasion findings at the operation	0.099	0.348	0.082	1	0.775	0.905	0.458	1.789

CI: Confidence interval, SE: Standard error, HIPEC: Hyperthermic intraperitoneal chemotherapy.

demonstrates that the pandemic resulted in a significant reduction in the number of patients referred for surgery, a hesitancy to perform advanced surgical interventions, and potential variations in tumour staging at diagnosis among gastric cancer patients. Although no statistically significant difference in overall survival was observed between the PP and PS periods, the exclusion of patients who did not undergo surgery suggests that the true impact of the pandemic may be even more substantial.

These findings underscore the necessity of enhancing the resilience of healthcare systems to ensure the continuity of oncological care during global crises. In anticipation of future health emergencies, it is imperative to develop flexible health policies and dynamic resource management strategies, particularly for high-mortality malignancies.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained by the Ege University Local Medical Research Ethics Committee on May 9, 2024 (approval no: 24-5T/11).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Surgical and Medical Practices - E.U., V.S., B.Ç., M.S.E., T.Ö.S.; Concept - E.U., V.S.; Design - E.U., Ö.F.; Data Collection or Processing - S.T., B.E.B., Ö.F.; Analysis or Interpretation - S.T., B.E.B., B.Ç.; Literature Search - E.U., V.S., Ö.F.; Writing - E.U., V.S., B.Ç.

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Health and economic outcomes of metabolic bariatric surgery: A patient perspective

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ABSTRACT

Objective: Türkiye has the highest obesity prevalence in Europe, contributing to significant health and economic burdens. Metabolic bariatric surgery (MBS) is the most effective intervention for achieving sustained weight loss and improving obesity-related conditions. This study aimed to assess short-term remission rates in six obesity-related conditions and quantify changes in direct medical costs from the patient's perspective at 3 and 6 months following MBS.

Material and Methods: This prospective multicentre cohort study included 179 patients aged 18-65 with Class II or higher obesity who underwent MBS between July 2017 and November 2018. Clinical parameters and self-reported direct medical expenditures were evaluated preoperatively and at 3 and 6 months post-operatively. Outcomes included remission or improvement in diabetes, hypercholesterolemia, hypertension, joint diseases, obstructive sleep apnea syndrome (OSAS), and depression, as well as cost reductions.

Results: Mean age was 38.8±11.7 years; 57.5% had been living with obesity for over 25 years. Preoperatively, 82.1% had obesity-related conditions. At 6 months, excess weight loss reached 68.3%. Remission rates were 89.5% for diabetes, 94.6% for hypertension, 85.7% for hypercholesterolemia, and 100% for joint diseases and OSAS. Depression remission was 95.7%. Medication/device use declined by 96%. Total direct medical costs decreased by 13.95%, and by 88.53% excluding surgery.

Conclusion: In a country with high obesity and diabetes rates, MBS offers rapid clinical improvements and substantial cost reductions. Notably, 57% of patients had used non-prescriptive supplements preoperatively, highlighting the need for better health literacy. These findings reinforce the need to prioritize early surgical intervention within national obesity care frameworks.

Keywords: Bariatric and metabolic surgery, economic evaluation, healthcare costs, obesity, treatment outcome

INTRODUCTION

The World Health Organization defines obesity as a chronic disease characterized by excessive fat accumulation that impairs health, typically classified by body mass index [(BMI) ≥30 kg/m^2]. According to this categorization, BMI 25-29.9 is overweight and BMI ≥30 is obesity for adults (1). The International Federation of Surgery of Obesity and Metabolic Disorders (IFSO) further categorizes BMI 30-35 as Class I, BMI 35-40 as Class II, BMI 40-50 as Class III (severe), BMI 50-60 as Class IV, and BMI 60-70 as Class V obesity (2). Globally, obesity is projected to rise from 14% in 2020 to 24% by 2035, affecting over 2 billion individuals, including children and adolescents (3). Contrary to conventional assumptions, the highest prevalence is seen in middle- and lower-middle-income countries (4). Türkiye had the highest obesity prevalence in Europe at 33% in 2019 (5), and is projected to reach 55% in adults by 2035 (3).

Obesity is linked to multiple serious complications and comorbidities such as diabetes, cardiovascular disease, stroke, cancer, and obstructive sleep apnea syndrome (OSAS), as well as non-lethal complications like joint disorders, infertility, depression, and reduced quality of life (1,2). The associated rise in healthcare utilization—including diagnostics, prescriptions, surgical procedures, and hospital stays—translates into a substantial economic burden. OECD countries are expected to allocate up to 8.4% of their health budgets to obesity-related diseases by 2050 (5). These economic burdens serve to highlight the pressing need for the implementation of effective interventions to address obesity-related complications and comorbidities. Such interventions are not only necessary to improve public health outcomes, but also to inform allocation decisions for healthcare managers.

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Treatment options for obesity include diet, exercise, behavioral therapy, pharmacotherapy, and metabolic bariatric surgery (MBS), with MBS shown to be most effective for Class II and above obesity. MBS provides sustainable weight loss, improved comorbidities, increased life expectancy, and better quality of life (6-8). Sleeve gastrectomy (SG), the most common MBS procedure worldwide, accounted for 53.6% of surgeries globally in 2016, rising to 55.4% in 2018 (9,10) and 60.2% in Türkiye.

According to the Turkish Social Security Institution (SGK), the number and cost of publicly reimbursed bariatric procedures in Türkiye have experienced notable changes over the five-year period between 2015 and 2019. The total number of procedures covered by SGK increased from 8.181 in 2015 to 11.594 in 2019, with a rise in expenditure from 28.69 million TL to over 52 million TL. A significant trend is the rapid expansion of SG, which accounted for 89.1% (n=10.327) of all reimbursed bariatric surgeries in 2019, compared to 7.331 procedures in 2015. By 2019, SG alone constituted 84.7% of all reimbursed bariatric operations and received the largest financial allocation 42.17 million TL out of the total 52.02 million TL in public reimbursement (11). The availability of such detailed national reimbursement data is rare in the literature, adding to the contextual and policy relevance of this study.

Existing studies on the economic impact of MBS primarily adopt a third-party payer or societal perspective in high-income countries, often overlooking direct costs to patients (12-18). Limited research from Türkiye has not comprehensively addressed these costs or from the patient's perspective (17-19). This study addresses that gap by evaluating six obesity-related conditions and five direct medical cost components from the patient's viewpoint in a low-middle-income country. This study aimed to assess short-term remission rates in six obesity-related conditions and quantify changes in direct medical costs from the patient's perspective at 3 and 6 months following MBS.

MATERIAL and METHODS

Study Design

This prospective, multicenter, cohort, and quantitative study included 190 patients aged 18-65 years who were referred to two bariatric surgery centers in Ankara between July 2017 and November 2018. Eligible participants had Class II obesity (BMI ≥35 kg/m^2) with at least one complication or comorbidity, or Class III and above obesity regardless of complications and comorbidities. All patients had previously failed to achieve optimal clinical outcomes with diet, exercise, and behavioral therapy administered for at least six months.

This study uses the term "obesity-related conditions" as an umbrella term to refer to both complications and comorbidities. In line with the 2024 IFSO Consensus (5), diabetes, hypertension, and OSAS are considered complications due to their established causal relationship with obesity, while conditions such as hypercholesterolemia, joint disorders, and depression are treated as comorbidities.

Prior to surgery, all patients were evaluated by a multidisciplinary team comprising a general surgeon specializing in MBS, an endocrinologist, an anesthesiologist, and a psychiatrist. The study aimed to enroll all eligible patients consecutively during the study period, based on voluntary participation, without applying any sampling methods. Patients were excluded if they were re-hospitalized within 30 days post-operatively or failed to attend follow-up appointments.

The study protocol was approved by the Ankara University Ethics Committee (date: May 29, 2017, number: 10/174), and conducted in accordance with the Declaration of Helsinki. All participants received a cover letter outlining the study purpose, the voluntary nature of participation, confidentiality, withdrawal rights, and signed an informed consent form.

All surgical procedures were performed by one of two experienced general surgeons specialized in MBS. The surgical technique was determined based on a comprehensive pre-op assessment and surgeon's preference. Of the 190 patients enrolled, 11 were excluded from final analysis: Three due to early rehospitalization and 8 due to loss to follow-up. The final analysis included 179 patients. No life-threatening complications or deaths occurred during the study period.

A post-hoc power analysis was conducted using G*Power, based on a medium effect size (d=0.5), α=0.05, and n=179, yielding a statistical power of 0.81. The effect size assumption was guided by the estimated prevalence of obesity in the Turkish population.

Data Collection

Upon referral to either of the two centers, patients were registered in the electronic health records system. Data were collected from these records and through a structured questionnaire administered preoperatively and at 3 and 6 months post-operatively, using a data record form developed by the researchers.

Pre-op data included sociodemographic characteristics, duration of obesity, height, weight, and BMI. Additional information was collected on blood values, blood pressure, general health status, and the duration of obesity-related conditions as well as prior obesity treatments, medication use, and work absences due to obesity. However, the question on work absences was excluded from analysis due to inadequate responses.

Post-op data at 3 and 6 months included blood values, blood pressure, BMI, and medication use, gathered through follow-up questionnaires. Height and weight were directly measured during outpatient visits.

Excess weight loss (EWL%)—a key indicator of MBS success—was calculated using the following formula (20):

EWL%= [pre-op weight-post-op weight (kg)]/[pre-op weight-ideal weight* (kg)]x100

(*) ideal weight was accepted as BMI =25 kg/m^2 for each patient.

Remission of obesity-related conditions was defined as the complete cessation of all medications and/or medical devices. Improvement was defined as a reduction in dosage or number of medications/devices (21-23). Changes in metabolic markers and blood pressure were assessed according to the diagnostic, treatment, and follow-up guidelines of the Turkish Society of Endocrinology and Metabolism (TEMD), as summarized in Table 1 (24-26). Remission of joint disorders was defined as absence of symptoms as reported by the patient and discontinuation of pain medication. For OSAS, remission was defined as absence of self-reported symptoms and discontinuation of continuous positive airway pressure (CPAP) use without clinical reassessment.

Due to the heterogeneity in the onset and duration of obesity-related conditions, preoperative cost data were treated as cumulative rather than time-bound. This reflects real-world financial trajectories experienced by patients before undergoing MBS. All direct medical expenditures were assumed to be out-of-pocket, irrespective of patients' insurance status. It was presumed that patients regularly attended medical appointments and adhered to treatments. The frequency of outpatient visits was determined using national guidelines, with expert opinion applied and where guideline data were lacking: Every 6 months for diabetes, annually for hyperlipidemia, hypertension, and joint diseases, and every 3 months for depression.

Medication costs were calculated using retail prices from the Turkish Medicines and Medical Devices Agency's Detailed Drug Price List as of 29.11.2019, based on usage period and dosage (27). Non-prescriptive supplements were excluded. Costs for treatments, visits, and medical procedures were based on 2019 HAC Annex-2 PHPL tariffs (28). The cost of medical devices (e.g., glucose meters, test strips, CPAP masks, canes, walkers, and wheelchairs) was calculated using the average prices of the three best-selling products listed by certified online retailers in November 2019. Due to missing data on CPAP device specifications, the average price of the three top-selling global models, as recommended by specialists, was used.

Statistical Analysis

Data were coded and entered a database for analysis aligned with the study's aim and hypotheses. Descriptive statistics included frequencies and percentages for categorical variables, mean ± standard deviation for normally distributed continuous variables, and median (min-max) for non-normal data. Statistical analyses were performed using SPSS v.15.0. Paired samples t-test, Wilcoxon signed-rank test, and chi-square test were applied where appropriate. A p-value of <0.05 was considered statistically significant.

RESULTS

Descriptive Findings

The study included 179 patients, of whom 66.5% were female and 33.5% male, with a mean age of 38.8011.74± years. More than half (54.2%) were under the age of 40. The average height was 1.670.09± meters, mean body weight was 126.4524.12± kg,

Table 1. Classification of metabolic parameters and blood pressure

Diabetes classification			
	Pre-diabetes	**Diabetes**	**High risk**
Fasting blood glucose (mg/dL)	100-125	≥126	-
HbA1c (%)	-	≥6.5	5.7-6.4
HbA1c: Glycated hemoglobin A1c			
Serum lipid classification			
	Optimal	**Borderline**	**High risk**
Total cholesterol (mg/dL)	<200	200-239	>240
LDL cholesterol (mg/dL)	<100	100-159	>160
HDL cholesterol (mg/dL)	≥60	40-59	<40
Triglycerides (mg/dL)	<150	150-499	>500
Blood pressure classification			
	Normal	**Pre-hypertension**	**Hypertension**
Systolic (mmHg)	<120	120-139	≥140
	and	and/or	and/or
Diastolic (mmHg)	<80	80-89	≥90

LDL: Low-density lipoprotein, HDL: High-density lipoprotein.

and the mean pre-op BMI was 45.176.90± kg/m^2. The duration of obesity exceeded 25 years in 57.5% of participants.

Regarding obesity-related conditions, 17.9% of patients had no obesity-related complications or comorbidities before surgery, while 33.0% had one, 23.5% had two, 15.6% had three, 6.1% had four, and 3.9% had five.

Before undergoing MBS, 63.7% of patients had consulted a dietitian, 70.9% had attempted a popular diet, 37.4% had tried acupuncture, and 57.0% reported using non-prescription weight-loss supplements.

Findings Related to Health Status

The mean EWL% was calculated to be 45.85±15.78% at 3 months and 68.2721.33%± at 6 months post-operatively (Figure 1).

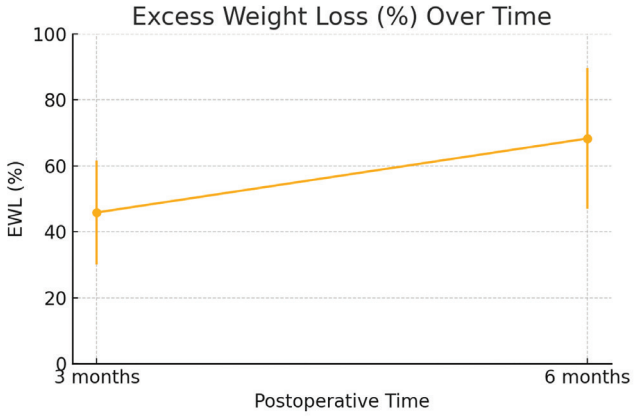

Figure 1. Excess weight loss (%) over time.
EWL: Excess weight loss

Remission rates for all six obesity-related conditions improved markedly between the third and sixth post-operative months, as illustrated in Figure 2. At the 6-month follow-up, remission and improvement rates for obesity-related conditions were as follows: For diabetes, 89.5% remission and 7.9% improvement; for hypercholesterolemia, 87.5% and 2.9%, respectively; and for hypertension, 94.6% and 3.6%. Among patients with joint disease (n=103), all reported symptom resolution at 6 months and had discontinued the use of pain medication. Similarly, among patients diagnosed with OSAS (n=27), no ongoing symptoms were reported, and all had ceased the use of CPAP devices. These figures reflect self-reported improvements supplemented by behavioral indicators and are not based on objective clinical re-evaluation. Additionally, depression showed a remission rate of 95.7% at the sixth month (Table 2).

Post-op laboratory assessments at the 3rd and 6th months demonstrated significant improvements in fasting blood glucose, lipid profile, and blood pressure compared to pre-op values ($p<0.05$), except for diastolic blood pressure between months 3 and 6, which showed no significant change ($p=0.479$) (Table 3). Fasting glucose decreased from 98 mg/dL to 88 mg/dL, HbA1c from 5.6% to 4.9%, and total cholesterol from 189 mg/dL to 162 mg/dL.

Based on TEMD guidelines, the proportion of patients with diabetes declined from 20.7% to 0.6% at six months. High-risk HbA1c profiles reduced from 25.0% to 11.5%, and high total cholesterol was reduced from 16.2% to 2.5%. The percentage of patients classified as hypertensive decreased from 45.3% preoperatively to 0%—all statistically significant—($p<0.05$) (Table 4).

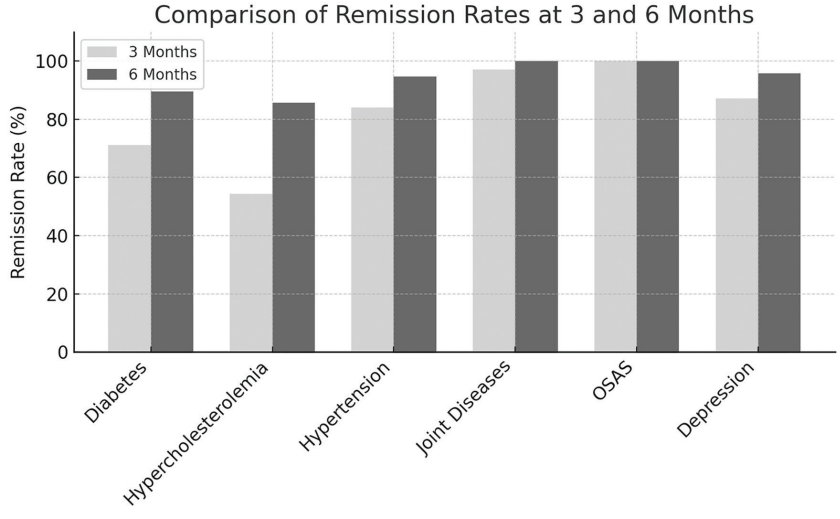

Figure 2. Remission rates at 3 and 6 months.
OSAS: Obstructive sleep apnea syndrome

Table 2. Comparison of pre-op and post-op obesity-related conditions

Obesity-related conditions (complications and comorbidities)*	T_0	ΔT_0-T_1			ΔT_0-T_2		
	n (%)	Remain n (%)	Remission n (%)	Improvement n (%)	Remain n (%)	Remission n (%)	Improvement n (%)
Diabetes	38 (21.2)	6 (15.8)	27 (71.0)	5 (13.2)	1 (2.6)	34 (89.5)	3 (7.9)
Hypercholesterol	35 (19.5)	12 (34.3)	19 (54.3)	4 (11.4)	4 (11.4)	30 (85.7)	1 (2.9)
Hypertension	56 (31.3)	2 (3.6)	47 (83.9)	7 (12.5)	1 (1.8)	53 (94.6)	2 (3.6)
Joint diseases	103 (57.5)	0 (0.0)	100 (97.1)	3 (2.9)	0(0.0)	103 (100.0)	0 (0.0)
OSAS	27 (15.1)	0 (0.0)	27 (100.0)	0 (0.0)	0 (0.0)	27 (100.0)	0 (0.0)
Depression	47 (26.2)	6 (12.8)	41 (87.2)	0 (0.0)	2 (4.3)	45 (95.7)	0 (0.0)
Total	179 (100.0)						

T_0: Pre-op, T_1: Post-op 3rd month, T_2: Post-op 6th month
ΔT_0-T_1: Change between pre-op and post-op 3rd month
ΔT_0-T_2: Change between pre-op and post-op 6th month
Remission: Discontinuation of all medications and/or medical devices.
Improvement: A reduction in the dose or number of medications and/or medical devices
*: There are patients with more than one complication or comorbidity, all comparisons yielded statistically significant results ($p<0.05$), OSAS: Obstructive sleep apnea syndrome

Table 3. Comparison of pre-op and post-op clinical parameters

	Time	Median (min-max)	Mean ± SD	Effect size (Cohen's d, 95% CI)
Fasting blood glucose (mg/dL)	T_0 T_1 T_2	98.0 (73.0-288.0) 89.0 (66.0-149.0) 88.0 (65.0-133.0)	110.7±37.7 92.0±15.0 89.0±9.8	0.8 (0.5-1.1)
	P_1<0.001; P_2<0.001; P_3=0.001			
HbA1c (%)	T_0 T_1 T_2	5.6 (4.4-11.4) 5.2 (4.2-9.5) 4.9 (4.1-6.6)	6.1±1.5 5.5±1.0 5.0±0.6	1.4 (1.07-1.73)
	P_1<0.001; P_2<0.001; P_3<0.001			
Total cholesterol (mg/dL)	T_0 T_1 T_2	189.0 (49.0-339.0) 167.0 (97.0-290.0) 162.0 (104.0-290.0)	194.5±41.4 170.4±31.5 164.6±30.3	0.71 (0.41-1.01)
	P_1<0.001; P_2<0.001; P_3<0.001			
LDL cholesterol (mg/dL)	T_0 T_1 T_2	121.0 (43.0-241.0) 110.0 (40.0-212.0) 101.0 (54.0-211.0)	126.4±35.2 110.8±27.4 106.7±28.1	0.62 (0.32-0.92)
	P_1<0.001; P_2<0.001; P_3=0.001			
HDL cholesterol (mg/dL)	T_0 T_1 T_2	35.0 (23.0-77.0) 40.3 (22.0-78.0) 47.0 (22.0-91.0)	37.5±9.5 42.3±9.5 49.9±11.5	-1.1 [(-1.41) - (-0.79)]
	P_1<0.001; P_2<0.001; P_3<0.001			
Trigliycerides (mg/dL)	T_0 T_1 T_2	139.0 (52.0-681.0) 109.0 (49.0-275.0) 98.0 (41.0-271.0)	152.5±71.5 118.5±41.1 104.0±35.2	0.88 (0.57-1.19)
	P_1<0.001; P_2<0.001; P_3<0.001			
Systolic blood pressure (mmHg)	T_0 T_1 T_2	130.0 (100.0-200.0) 110.0 (100.0-140.0) 110.0 (100.0-130.0)	132.8±21.1 115.0±7.9 112.7±6.8	2.56 (2.16-2.96)
	P_1<0.001; P_2<0.001; P_3<0.001			

Table 3. Continued

	Time	Median (min-max)	Mean ± SD	Effect size (Cohen's d, 95% CI)
Diastolic blood pressure (mmHg)	T_0 T_1 T_2	80.0 (60.0-120.0) 70.0 (60.0-90.0) 60.0 (60.0-80.0)	78.3±12.7 65.5±5.9 65.1±5.4	0.94 (0.63-1.25)
	P_1<0.001; P_2<0.001; P_3=0.479			

T_0: Pre-op, T_1: Post-op 3rd month, T_2: Post-op 6th month
P_1: T_0 vs. T_1
P_2: T_0 vs. T_2
P_3: T_1 vs. T_2
Wilcoxon Signed-Rank test used for comparisons
Effect sizes calculated using pooled standard deviation; CI based on normal approximation. CI: Confidence interval, SD: Standard deviation, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

Table 4. Comparison of pre-op and post-op diabetes, serum lipid and blood pressure classification

Diabetes classification				
	Time	**Optimal** **n (%)**	**Pre-diabetes** **n (%)**	**Diabetes** **n (%)**
Fasting blood glucose	T_0 T_1 T_2	100 (55.8) 140 (78.2) 161 (89.9)	42 (23.5) 32 (17.9) 17 (9.5)	37 (20.7) 7 (3.9) 1 (0.6)
HbA1c	Time	Low diabetes risk n (%)	Diabetes n (%)	High diabetes risk n (%)
	T_0 T_1 T_2	61 (50.8) 70 (69.3) 81 (85.3)	29 (24.2) 14 (13.9) 3 (3.2)	30 (25.0) 17 (16.8) 11 (11.5)
Serum lipid classification				
	Time	Optimal n (%)	Risky n (%)	High risk n (%)
Total cholesterol	T_0 T_1 T_2	113 (63.1) 153 (85.5) 162 (90.5)	37 (20.7) 20 (11.2) 12 (6.7)	29 (16.2) 6 (3.3) 5 (2.8)
LDL cholesterol	T_0 T_1 T_2	26 (18.1) 47 (32.6) 65 (46.1)	91 (63.2) 92 (63.9) 69 (48.9)	27 (18.8) 5 (3.5) 7 (5.0)
HDL cholesterol	T_0 T_1 T_2	7 (4.9) 6 (4.2) 24 (16.9)	37 (25.7) 73 (50.7) 98 (69.0)	100 (69.4) 65 (45.1) 20 (14.1)
Blood pressure classification				
	Time	Optimal n (%)	Pre-hypertension n (%)	Hypertension n (%)
Systolic+ diastolic	T_0 T_1 T_2	37 (20.6) 97 (54.2) 110 (61.5)	61 (34.1) 79 (44.1) 69 (38.5)	81 (45.3) 3 (1.7) 0 (0.0)

T_0: Pre-op, T_1: Post-op 3rd month, T_2: Post-op 6th month
P_1: T_0 vs. T_1
P_2: T_0 vs. T_2
P_3: T_1 vs. T_2
All comparisons yielded statistically significant results ($p<0.05$),
chi-square test used for comparisons, LDL: Low-density lipoprotein, HDL: High-density lipoprotein.

Preoperatively, patients used an average of 2.09 medications or medical devices related to obesity management. This number decreased markedly to 0.24 per patient at three months (an 88.5% reduction) and to 0.08 at six months (a 96% reduction). In contrast, the use of proton pump inhibitors and multivitamin supplements—routinely prescribed following SG—increased significantly, rising by 200% at three months and 100% at six months. These trends reflect standard post-op supplementation protocols rather than continued pharmacologic management of comorbid conditions.

Findings Related to Costs

As presented in Table 5, diabetes accounted for the highest share of pre-op costs, representing 40.06% of the total expenses. This was followed by hypertension (14.19%), joint diseases (13.27%), obesity (10.30%), OSAS (10.09%), depression (9.86%), and hypercholesterolemia (2.24%). Notably, 94% of pre-op diabetes-related expenses were attributed to medication and medical devices.

As shown in Table 6, medications and medical devices collectively accounted for 75.4% of the total pre-op costs. Following surgery, the cost distribution shifted markedly, with surgical procedures accounnting for 86.7% of total post-op expenses. Meanwhile, expenditures for diet therapy and traditional or complementary treatments, which together accounted for over 5% of pre-op costs, were completely eliminated in the post-op period (Figure 3).

At the third post-op month, the average cost per patient was 6,307.76 TL (approx. $1.098), increasing slightly to 6,706.96 TL (approx. $1.167) by the sixth month. Of this amount, 86.7% was attributed to the surgical procedure. When the operation cost was included, a 13.95% reduction in total expenses was observed at six months compared to the pre-op period. However, when surgical costs were excluded, the average cost per patient decreased from 7,794.07 TL (approx. $1.357) to 893.96 TL (approx. $156), corresponding to an 88.53% reduction (Table 7).

Table 5. Distribution of pre- and postoperative costs by diagnosis

	Pre-op		Post-op month six		
Diagnosis	**Share in total cost (%)**	**Cost TL($)[1,2]**	**Share in total cost (%)**	**Cost TL($)[2,3]**	
Diabetes		40.06	558,951.33 (97,281.68)	0.54	6,539.55 (1,138.16)
Hypertension	14.19	197,906.72 (34,444.32)	0.01	141.32 (24.59)	
Joint diseases	13.27	185,123.36 (32,219.46)	0.00	0.00 (0.00)	
Obesity	10.30	143,656.70 (25,002.47)	99.28	1,191,871.50 (207,437.13)	
OSAS	10.09	140,784.64 (24,502.61)	0.00	0.00 (0.00)	
Depression	9.86	137,518.50 (23,934.16)	0.17	1,992.73 (346.82)	
Hypercholesterol		2.24	31,197.12 (5,429.65)	0.00	0.00 (0.00)
Total cost		1,395,138.37 (242,814.34)		1,200,545.10 (208,946.71)	
Average cost per patient		7,794.07 (1,356.50)		6,706.96 (1,167.30)	

[1]: Costs include medication, medical devices (blood glucose meter, test strips), outpatient visits for diabetes; medication, outpatient visits, surgical procedures (knee prosthesis, breast reduction due to back and joint pain), medical devices (cane, walker, wheelchair) for joint diseases; traditional and complementary medicine (acupuncture, lipolysis with mesotherapy), surgical procedures (liposuction, adjustable gastric band, gastric balloon, medication, diet therapy, outpatient visits for obesity; medical devices (CPAP) and outpatient visits for OSAS; medication and outpatient visits for hypertension, depression and hypercholesterol before MBS.
[2]: According to the average exchange rate of the Central Bank of the Republic of Türkiye in November 2019 1 $=5,7457 TL
[3]: Costs include medication, medical devices (blood glucose meter, test strips), outpatient visits for diabetes; medication, outpatient visits, surgical procedures (knee prosthesis, breast reduction due to back and joint pain), medical devices (cane, walker, wheelchair) for joint diseases; traditional and complementary medicine (acupuncture, lipolysis with mesotherapy), surgical procedures (liposuction, adjustable gastric band, gastric balloon, medication, diet therapy, outpatient visits for obesity; medical devices (CPAP) and outpatient visits for OSAS; medication and outpatient visits for hypertension, depression and hypercholesterol after MBS.
CPAP: Continuous positive airway pressure, OSAS: Obstructive sleep apnea syndrome, MBS: Metabolic bariatric surgery.

Table 6. Distribution of pre- and postoperative costs by type of cost

	Pre-op		Post-op month six	
Type of cost	**Share in total cost (%)**	**Cost TL($)[1]**	**Share in total cost (%)**	**Cost TL($)[1]**
Medication[2]	53.72	749,525.24 (130,449.77)	11.61	139,478.74 (24,275.32)
Medical devices	21.75	303,476.77 (52,818,07)	0.12	1,539.36 (267.91)
Outpatient visit	13.82	192,850.00 (33,564.23)	1.58	19,000.00 (3,306.82)
Surgical procedures[3]	5.64	78,726.36 (13,701.79)	86.67	1,040,527.00 (181,096.65)
Traditional and complementary medicine therapy[4]	3.70	51,600.00 (8,980.63)	0.00	0.00 (0.00)
Diet therapy	1.36	18,960.00 (3,299.86)	0.00	0.00 (0.00)
Total cost	100.00	1,395,138.37 (242,814.34)	100.00	1,200,545.10 (208,946.71)

[1]: According to the average exchange rate of the Central Bank of the Republic of Türkiye in November 2019 1 $=5,7457 TL
[2]: Costs include prescribed oral forms and subcutan injection flacons
[3]: Costs include liposuction, adjustable gastric band, gastric balloon for pre-op; laparoscopic sleeve gastrectomy for post-op
[4]: Costs include acupuncture and lipolysis with mesotherapy.

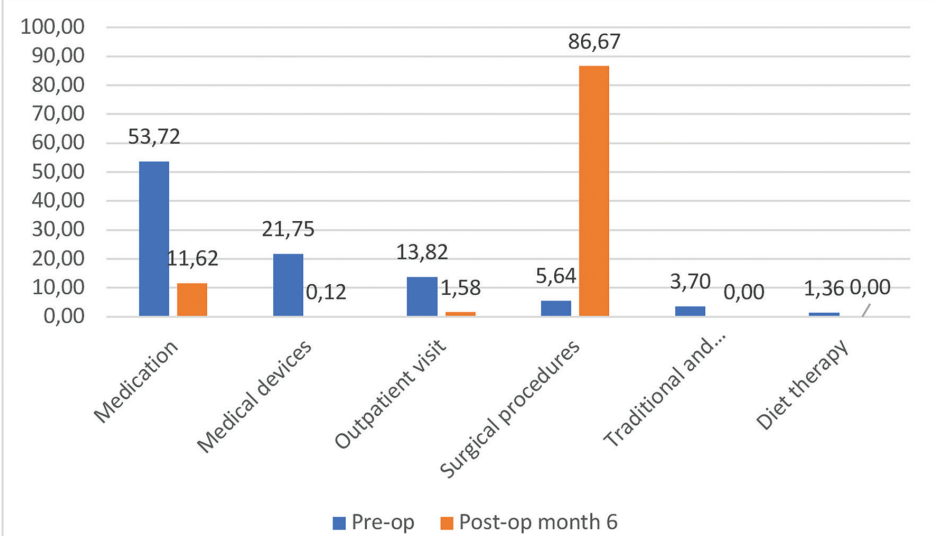

Figure 3. Comparison of pre- and post-operative cost shares by category.

Table 7. Change in average cost per patient pre- and post-operatively

	T_0 cost TL($)[1]	T_1 cost TL($)[1]	T_2 cost TL ($)[1]	ΔT_0-T_1 (%)	ΔT_0-T_2 (%)	p
Operation cost included	7,794.07 (1,356.50)	6.307,76 (1,097.82)	6.706,96 (1,167.30)	-19.07	-13.95	<0.05
Operation cost excluded	7,794.07 (1,356.50)	494.76 (86.11)	893.96 (155.59)	-93.65	-88.53	<0.05

[1]: According to the average exchange rate of the Central Bank of the Republic of Türkiye in November 2019 1 $=5,7457 TL
T_0: Pre-op, T_1: Post-op 3rd month, T_2: Post-op 6th month
ΔT_0-T_1: Change between pre-op and post-op 3rd month
ΔT_0-T_2: Change between pre-op and post-op 6th month.

DISCUSSION

The high rate of patients who had previously attempted popular diets, alternative therapies, and non-prescription supplements underscores the widespread reliance on unproven or unsupervised weight-loss methods. These findings highlight the need to improve health literacy and guide patients toward evidence-based obesity treatments. The findings presented here represent early post-operative outcomes observed within a six-month follow-up period and should be interpreted in the context of short-term recovery and adjustment.

EWL%, a key metric for evaluating surgical success, was 45.85% at 3 months and 68.27% at 6 months. These findings are consistent with systematic reviews reporting 3-month EWL% between 36.3-47.2% and 6-month values ranging from 51.7-72% (29-31). Variation in outcomes across studies may stem from differences in baseline BMI, patient age, and surgical techniques (32).

Early remission of obesity-related conditions supports the metabolic effectiveness of MBS. This study observed remission or improvement in several conditions before significant weight loss occurred, highlighting the metabolic efficacy of MBS. In particular, the 89.5% remission rate for diabetes at 6 months exceeds reported rates of 64.7-81.9% in prior LSG studies (23,33-36). This supports not only the clinical efficacy but also the economic value of early MBS, especially given diabetes' substantial burden on healthcare systems globally and in Türkiye (37). Since patients with early-stage diabetes show better outcomes, surgery should not be delayed in those diagnosed with obesity and diabetes (38).

Remission rates for hypercholesterolemia and hypertension reflect the known benefits of MBS. Hypercholesterolemia remission was 85.7%, aligning with systematic review data (64-84%) (23,39). Our findings support previous conclusions on SG's favorable impact on lipid profiles and its role in reducing long-term costs associated with cardiovascular risk (39,40).

The observed remission in joint disorders is likely driven by post-operative weight loss and reduced mechanical stress on joints. Additionally, the reduction in analgesic use, including NSAIDs, may reflect improved symptom control and decreased dependency on pharmacological pain management. As this study is based on patient-reported outcomes, these findings capture subjective improvements in joint symptoms, which are important indicators of functional recovery and patient satisfaction following MBS. Systematic reviews indicate a wide range of improvement rates (50-100%) due to varying definitions and assessment tools (23,40-44). Our high remission rate may also be influenced by behavioral changes post-operatively, such as patients' reluctance to use NSAIDs due to concerns over gastrointestinal side effects (45).

Remission of OSAS was consistent with the literature but highlights diagnostic variability. OSAS remission and improvement rates in the literature vary (78-100% and 75.8-90.77%, respectively) due to differences in BMI, disease severity, and assessment tools (23,33,40,46). Our results align with these ranges, though the absence of standardized measurement tools remains a limitation. Long-term CPAP use is associated with weight regain, reinforcing the importance of sustained post-op management.

The mental health benefits of MBS are well-documented, with significant improvements in depressive symptoms typically observed within the first two years post-operatively (47,48). However, some studies have reported a recurrence or worsening of symptoms beyond this period (48,49). In our study, a 95.7% remission rate for depression was recorded at six months, supporting the short-term psychological efficacy of MBS. Variability in outcomes may stem from differences in diagnostic criteria and definitions of remission across studies. Prior research from Türkiye has shown that psychological constructs such as self-esteem, body image dissatisfaction, and emotional eating are strongly associated with depression and anxiety in bariatric surgery candidates (50). Our findings suggest that MBS not only addresses physical comorbidities but also helps mitigate psychological burdens, particularly when supported by structured multidisciplinary care.

Significant reductions in medication and device use following MBS indicate both economic and clinical benefits. In our study, the average number of obesity-related prescriptions declined from 2.09 preoperatively to 0.24 at three months and to 0.08 at six months—a 96% reduction. This aligns with international findings; Lopes et al. (12) reported a decrease from 3.9 to 1.75 medications per patient after surgery. Beyond financial savings, this reduction also carries gastroenterological relevance and may reflect overall improvements in patient health, contributing to better adherence, fewer side effects, and enhanced quality of life (12,45,51,52).

To accurately contextualize this study's cost findings within the broader international literature, several structural factors must be considered. Reported costs of MBS and obesity-related healthcare are consistently higher in studies from other countries. This discrepancy is due primarily to Türkiye's low exchange rate and its position as the OECD country with the lowest healthcare service prices—approximately 20% of the OECD average (53). In this study, costs were calculated from the patient's perspective, considering each individual's obesity and related conditions profile. In contrast, most international studies adopt a health system or third-party payer perspective, using reimbursement data obtained from national health databases or institutional records. These structural differences

significantly limit direct monetary comparisons. Therefore, rather than comparing absolute cost values, it is more appropriate to examine the distribution and proportion of cost components (e.g., medication, outpatient visits, medical devices) to derive meaningful international insights. To enable more comprehensive and comparable analyses in future research, large-scale cost and outcomes data should be made accessible to researchers through structured health information systems and national databases.

Detailed cost distribution comparisons reinforce the long-term economic value of MBS. In our study, 53.7% of pre-op costs were attributable to medications, highlighting the dominant share of pharmaceutical expenses in patient-borne obesity-related healthcare. This distribution differs significantly from international findings. For instance, Weiner et al. (54) reported cost allocations as follows: 34% for outpatient visits, 25% for inpatient treatments, 21% for private examinations, and 20% for medications. Similarly, Cremieux et al. (55) found that 73% of total costs were due to outpatient and inpatient care, with medications accounting for 27%. Karim et al. (56) reported 58% for inpatient treatment, 33% for medications, and 9% for outpatient care. These differences emphasize not only variations in healthcare delivery systems but also in the pricing and coverage models across countries.

Despite these discrepancies, a consistent finding across the literature is that the initial cost of MBS is largely offset within 2 to 5 years (55,57,58). The Turkish Ministry of Health has also confirmed that the economic burden of MBS is typically neutralized by the end of the second year, with financial gains emerging in years three and four post-operatively (17). Keating et al. (51) further emphasized that the primary driver of cost savings post-surgery is the significant reduction in diabetes-related medication use. A systematic review concluded that MBS is cost-effective in diabetic patients, although it also noted a lack of data from broader societal perspectives, long-term cost evaluations, and methodological consistency across studies (15).

MBS provides long-term economic advantages, particularly for patients with high-cost complications such as diabetes. Several studies have highlighted that although MBS may lead to modest increases in short-term costs due to procedural expenses and reimbursement dynamics, the long-term financial benefits are substantial. Palli et al. (16) reported that while there was a slight increase in short-term costs due to MBS reimbursements, long-term savings were significant, particularly for diabetic patients. Terranova et al. (59) demonstrated that MBS not only offers clinical improvements but can also extend life expectancy at a reasonable cost, resulting in significant savings for healthcare systems—especially for individuals burdened by high-cost obesity-related complications such as diabetes. Another study further emphasized considerable impact of diabetes medication on public expenditure. Gallagher et al. (60) found that the average healthcare cost per patient decreased from 10.800 USD in the year before surgery to 2.840 USD in the first post-op year, reflecting a nearly fourfold decrease. Moreover, delaying surgical treatment for patients with severe obesity is considerably more costly for healthcare systems (61). Collectively, these findings support the position that timely MBS not only improves health outcomes but also serves as a cost-saving strategy in national healthcare planning, particularly in countries with a high prevalence of obesity and related conditions.

Study Limitations

This study has several limitations. As the primary focus of the study was on clinical and economic outcomes, biochemical parameters such as micronutrient levels were not assessed. Although some patients received care in public hospitals, the majority were treated in private hospitals where out-of-pocket payments were common. To ensure consistency in cost analysis, all expenditures were calculated using the SGK public pricing tariff and categorized as out-of-pocket, regardless of insurance status. This assumption, based on the patient-reported perspective, may limit the generalizability of cost findings to other healthcare financing models. The lack of a prospectively defined sample size calculation is acknowledged as a minor methodological limitation, however, a post-hoc power analysis confirmed sufficient statistical power. As this was a patient-centered study from a health management and health economics perspective, depression, joint disease, and OSAS status were assessed via self-report without clinical retesting or the use of standardized instruments. Additionally, the follow-up period was limited to six months, which may not capture long-term trends. Cost calculations were based on patient-reported expenditures, rather than system-level reimbursement data. Nevertheless, this approach offers valuable insight into the financial burden experienced directly by patients and provides a relevant perspective for healthcare managers and policymakers.

It should be noted that pre-op costs may accumulate over an extended period due to the chronic progression of obesity and its related conditions, while post-op costs in this study reflect only the first six months after surgery. Therefore, these figures do not represent a direct time-adjusted cost comparison, but rather demonstrate the short-term economic impact of MBS from the patient perspective. Nevertheless, the strength of this study lies in its comprehensive approach, which includes six obesity-related conditions and a detailed account of all medications, medical devices, and treatment categories used both pre- and post-operatively, offering nuanced insight into individual-level cost dynamics. Furthermore, all cost estimates were self-reported, which may introduce recall bias. The analysis also assumed adherence to national treatment guidelines, though individual compliance could not be verified. Surgical costs were standardized using a national public pricing tariff,

but granular breakdowns of cost components (e.g., hospital stay, consumables) were not available.

CONCLUSION

This study demonstrates that MBS provides substantial health and economic benefits for patients with obesity-related complications and comorbidities. In Türkiye—where obesity affects over one-third of the adult population and diabetes prevalence continues to rise—these findings are especially relevant. High remission rates for conditions such as diabetes, hypertension, hypercholesterolemia, joint disorders, sleep apnea, and depression within just six months after surgery confirm the broad therapeutic efficacy of MBS.

From an economic perspective, the procedure resulted in a dramatic reduction in the use of medications and medical devices—averaging over 95%—leading to significant cost savings. These reductions are particularly important in low- and middle-income countries, where out-of-pocket payments often create barriers to long-term disease management. The widespread pre-op use of non-prescriptive supplements (reported by 57% of participants) further highlights the need to enhance public health literacy around evidence-based treatments for obesity.

To our knowledge, this is the first study in Türkiye to integrate patient-reported economic data with detailed remission outcomes across six obesity-related conditions following MBS. These results provide compelling support for the early adoption of MBS within national obesity treatment strategies as both a clinically effective and economically advantageous intervention. In addition to short-term savings through reduced medication use, the long-term economic impact of improved disease remission may translate into fewer hospitalizations, lower disability rates, and reduced productivity losses—critical considerations for healthcare managers and policy-makers. Sustained, structured post-operative follow-up remains essential to maintain these gains and detect potential nutritional or metabolic complications.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ankara University Ethics Committee (date: May 29, 2017, number: 10/174), and conducted in accordance with the Declaration of Helsinki.

Informed Consent: All participants received a cover letter outlining the study purpose, the voluntary nature of participation, confidentiality, withdrawal rights, and signed an informed consent form.

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Footnotes

The research is based on the first author's (Y.Ö.) doctoral thesis, which was conducted at Ankara University Graduate School of Health Sciences under the supervision of the second author.

Author Contributions

Concept - Y.Ö., İ.A.; Design - Y.Ö., İ.A.; Data Collection or Processing - Y.Ö., İ.A.; Analysis or Interpretation - Y.Ö., İ.A.; Literature Search - Y.Ö.; Writing - Y.Ö.

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ORIGINAL ARTICLE
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A prospective study on the outcome of pyonephrosis and infected hydronephrosis drained by percutaneous nephrostomy – a tertiary care centre experience

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ABSTRACT

Objective: Pyonephrosis is defined as accumulation of purulent debris in the renal pelvis and urinary collecting system. Urinary diversion through percutaneous nephrostomy (PCN) is the first choice of treatment for pyonephrosis. Even after PCN insertion some patients end up with complete loss of renal function. We aim to determine the proportion of patients undergoing complete loss of renal function after PCN insertion, the factors facilitating renal function recoverability and the complications of the procedure.

Material and Methods: In this prospective observational study, 100 patients with pyonephrosis were consecutively included over a period of one year. Pre-PCN and post-PCN creatinine clearance (CrCL) were analysed. Associated clinical factors were collected on a data sheet proforma. Data were analysed using Stata 12.1.

Results: Mean age of study participants was 44.4 years (standard deviation: 11.8) where majority (69%) were males. Rate of nephrectomy after pyonephrosis was 15.6%. Among the participants, 77% patients did not have any complications after PCN insertion while 18% had dislodgement and 5% had bleeding. Significant improvement was found in post-PCN CrCL compared to pre-PCN CrCL (p-value: 0.001). Persons having severe hydronephrosis had lower odds of having improved glomerular filtration rate after PCN insertion (adjusted odd's ratio 0.3, p-value: 0.005, 95% confidence interval: 0.1-0.7) compared to those having moderate hydronephrosis.

Conclusion: Early PCN insertion is imperative for salvaging a pyonephrotic kidney. It is cost-effective and allows the patient to undergo definitive endourologic surgery for underlying pathology, thus avoiding a potential nephrectomy

Keywords: Pyonephrosis, obstructive uropathy, nephrostomy, urosepsis, hydronephrosis, PCN

INTRODUCTION

Infected hydronephrosis (HN) is defined as a bacterial infection of a hydronephrotic kidney. Pyonephrosis is defined as infected HN associated with suppurative destruction of the renal parenchyma and total or near-total loss of renal function (1). Obstructive pyonephrosis is an acute emergency that can lead to the rapid development of urosepsis and even septic shock, potentially resulting in mortality (2). Early decompression of the collecting system is the most important step in managing pyonephrosis. Urinary diversion can be achieved through percutaneous nephrostomy (PCN) or retrograde ureteral stenting. Although there is no clear consensus regarding the superiority of either method, PCN insertion has become the procedure of choice for draining pyonephrotic kidneys (3,4). However, urinary diversion does not always lead to renal function recovery even after definite treatment of underlying pathological processes. This may be due to other simultaneously occurring pathological processes like interstitial fibrosis and cell apoptosis (5). In this study, we aimed to assess the efficacy of PCN in the management of patients with pyonephrosis and its associated morbidities. Our primary objective was to determine the proportion of patients undergoing nephrectomy after PCN placement. We have also determined the proportion of patients demonstrating improvement in renal function post-PCN insertion, the factors associated with improvement in creatinine clearance (CrCL), after PCN insertion, and examined the intraoperative and postoperative complications of the procedure.

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MATERIAL and METHODS

This was a hospital-based prospective study conducted in a tertiary care hospital in Kolkata from June 2023 to June 2024.

Inclusion Criteria

Patients with pyonephrosis and systemic inflammatory response syndrome (SIRS) attending the Outpatient and Emergency Department of Seth Sukhlal Karnani Memorial Hospital.

Exclusion Criteria

Patients in the infantile age group and patients with coagulopathy.

Methodology

Patients presenting with pyonephrosis with features of the SIRS underwent PCN insertion under local anesthesia. HN was graded according to the Society of Fetal Urology grading system (6,7).

Drain fluid creatinine level was measured on day 1 of PCN insertion. We also measured the total 24-hour urine volume and serum creatinine. CrCL was calculated from drain fluid creatinine using the following formula: CrCL = (UV/P) (1.73/A), where U = creatinine concentration of 24-hour urine volume (mg/dL), V = total volume of urine per minute, i.e., V/1440 mL/min; P = plasma creatinine concentration (mg/dL), A = concentration factor accounting for differences in body surface area as obtained from the height-weight chart.

Similarly, CrCL was measured again, two months post-PCN insertion, from the drain fluid creatinine levels. Patients with low CrCL (<10 mL/min) underwent a diuretic renogram scan for further evaluation of the glomerular filtration rate (GFR) of the affected kidney. Patients with non-functional kidneys (GFR <10 mL/min) were subjected to nephrectomy. Other patients underwent definitive surgery for the underlying pathology.

Sample Size Calculation

According to the study by NG et al. (8) the rate of nephrectomy after pyonephrosis was 12%. Taking the estimated prevalence (p) to be 12% and absolute precision (d) to be 7%, we calculated the sample size (N) using the formula $N = (1.96)2\ pq/d^2$.

Our estimated sample size was calculated to be 82. Considering a dropout rate of 20%, our initially calculated final sample size was 99. In this study, 100 patients meeting the inclusion criteria who visited the hospital during the aforementioned study period were recruited.

Statistical Analysis

Data were analyzed in Stata 12.1 Descriptive statistics were presented as frequency, percentage, mean, and standard deviation (SD). A paired t-test was used to compare initial CrCL and post-PCN CrCL (after 2 months). Univariable logistic regression was done to show the factors associated independently with improvement in CrCL. The variables with a p-value <0.2 in univariable logistic regression were adjusted in multivariable logistic regression. A p-value of less than 0.05 was considered significant in the final adjusted model.

Ethical clearance: Patients were enrolled after obtaining ethical clearance from the Institutional Ethics Committee of IPGME&R, Kolkota (approval number: IPGMER/IEC/2023/434, date: 03.05.2023).

RESULTS

The mean age of study participants was 44.4 years, with a SD of 11.8, and the majority (69%) were males. The majority of the patients (53%) had comorbidities, with diabetes (29%) being the most prevalent. Other recorded comorbidities included hypertension and hypothyroidism. The most common underlying cause was ureteric calculus (35%), followed by pelviureteric junction (PUJ) calculus (23%), vesicoureteral junction stricture at bladder carcinoma (18%), ureteric stricture (13%), and primary PUJ obstruction (PUJO) (11%). Regarding the anatomical site of obstruction, the most common site was at the PUJ (34%), which included obstruction due to PUJ calculus and primary PUJO. The majority (61%) had a moderate degree of HN (grade 2 or 3), while others demonstrated a severe grade of HN (grade 4). The background characteristics of study participants are depicted in Table 1.

Both urine and pus, obtained after pelvicalyceal system puncture, were sent for culture and sensitivity testing. A discordance was observed between organisms isolated from the urine and pus of the same individual. However, in both urine and pus samples, the most common organism isolated was *E. coli* (49% in urine samples vs. 35% in pus samples). Among urine samples, 40% showed no growth of any organism, whereas among pus samples, the proportion was 21%. The distribution of organisms in bladder urine and PCN urine cultures is shown in Figures 1 and 2.

The rate of nephrectomy after PCN insertion in pyonephrosis was 17%. For the remaining patients, we were either able to perform some definitive surgery (74 out of 100) or they were kept on PCN (9 out of 100) in view of morbidity associated with the definitive surgeries. Following PCN insertion, 77% of patients did not experience any complications, while 18% experienced tube dislodgement and 5% had bleeding. The mean pre-PCN CrCL and mean post-PCN CrCL were 17.7 mL/min (SD +8.4) and 21.3 mL/min (SD +9.8), respectively. Using a paired t-test, this improvement was significant (p-value: 0.001, mean difference =1.9). The outcomes of patients post PCN insertion are tabulated in Table 2. In a multivariable logistic regression analysis, persons with severe HN had lower odds of an improvement in GFR after PCN insertion (adjusted odd's ratio 0.3, p=0.005, 95% confidence interval: 0.1-0.7) compared to those having moderate HN (Table 3). Hosmer-

Table 1. Distribution of study participants according to background characteristics (n=100)

Age (years)	Frequency	Percentage
20-39	36	36.0
40-59	52	52.0
≥60	12	12.0
Gender		
Female	31	31.0
Male	69	69.0
Comorbidities		
Diabetes	29	29.0
Hypertension	4	4.0
Diabetes + hypertension	14	14.0
Hypothyroid	6	6.0
None	47	47.0
Diagnosis		
Malignancy related stricture	18	18.0
Ureteric stricture	13	13.0
Nephrolithiasis	23	23.0
PUJ obstruction	11	11.0
Ureteric calculus	35	35.0
Anatomical site of obstruction		
Pelviureteric junction	34	34.0
Upper ureter	26	26.0
Mid ureter	14	14.0
Lower ureter	7	7.0
Vesicoureteric junction	17	17.0
Ureteroileal anastomosis	2	2.0
Degree of hydronephrosis		
Moderate (grade 2 or 3)	61	61.0
Severe	39	39.0

PUJ: Pelviureteric junction.

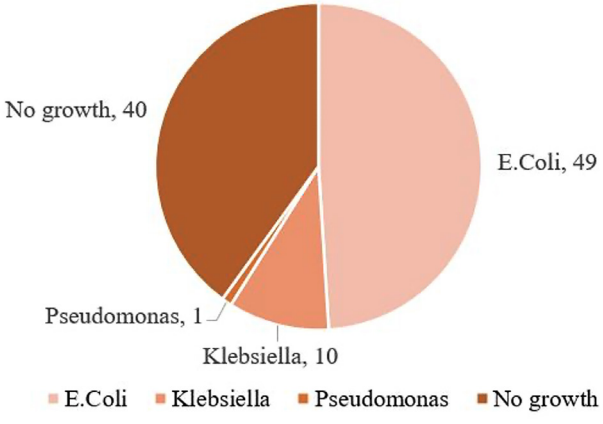

Figure 1. Pie diagrams showing distribution of organsims in bladder urine culture.

Lemeshow goodness-of-fit statistics for the final multivariable logistic regression model were 3.43 with a p-value of 0.49. The adjusted R^2 for the final multivariable regression model was 0.2.

DISCUSSION

In cases of pyonephrosis, PCN has demonstrated several advantages. This procedure is easy to perform under local anesthesia and reduces the bacterial burden by draining pus and necrotic material. This, in turn, decompresses the collecting system, improving renal perfusion and facilitating antibiotic entry into the renal parenchyma to promote better control of sepsis. It also aids in the determination of actual renal function prior to definitive procedures. Direct administration of irrigation fluid and antibiotics is also possible when a PCN catheter is *in situ* (9-11). Although no conclusive evidence of superiority

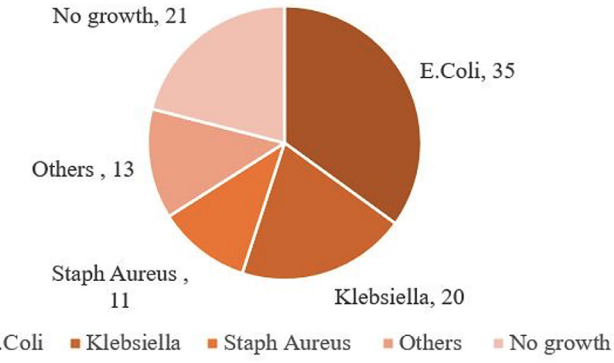

Figure 2. Pie diagrams showing distribution of organsims in PCN urine cultures.

PCN: Percutaneous nephrostomy

Table 2. Distribution of study participants according to outcome after PCN insertion (n=100)

Improvement in creatinine clearance	Number	Percentage
No	34	34.0
Yes	66	66.0
Complications after PCN		
None	74	74.0
Dislodgment	21	21.0
Bleeding	5	5.0
Surgery done		
URSL	33	33.0
TURBT	16	16.0
PCNL	17	17.0
Boari flap	2	2.0
Pyeloplasty	6	6.0
Urinary diversion	9	9.0
Nephrectomy	17	17.0

URSL: Ureteroscopic lithotripsy, TURBT: Transurethral resection of bladder tumour, PCNL: Percutaneous nephrolithotomy.

Table 3. Univariable and multivariable logistic regression showing factors associated with improvement in creatinine clearance among study participants after PCN insertion (n=100)

Independent variables	GFR after PCN insertion		OR (95% CI)	p-value	AOR (95% CI)	p-value	
	Not improved n (%)	Improved n (%)					
Age (in years)							
20-39	12 (33.3)	24 (66.7)	Reference				
40-59	16 (30.8)	36 (69.2)	1.1 (0.5-2.8)	0.8			
≥60	6 (50)	6 (50)	0.5 (0.1-1.8)	0.3			
Gender							
Female	14 (45.2)	17 (54.8)	Reference		2.0 (0.8-5.1)		0.1
Male	20 (29.0)	49 (71.0)	2.0 (0.8-4.8)	0.1			
Comorbidities							
Absent	20 (37.7)	33 (62.3)	Reference				
Present	14 (29.8)	33 (70.2)	1.0 (0.9-1.2)	0.4			
Degree of hydronephrosis							
Moderate	14 (22.95)	47 (77.05)	Reference		**0.3 (0.1-0.7)**		**0.005**
Severe	20 (51.28)	19 (48.72)	**0.3 (0.1-0.7)**	**0.004**			
Diagnosis							
Malignant stricture	6 (33.3)	12 (66.7)	Reference				
Ureteric stricture	6 (46.1)	7 (53.9)	0.6 (0.1-2.5)	0.5			
Nephrolithiasis	8 (34.7)	15 (65.2)	0.9 (0.2-3.4)	0.9			
PUJ obstruction	5 (45.5)	6 (54.5)	0.6 (0.1-2.8)	0.5			
Ureteric calculus	9 (25.7)	26 (74.3)	1.4 (0.4-4.9)	0.6			
Anatomical site of obstruction							
PUJ	13 (38.2)	21 (61.8)	Reference				
Upper ureter	8 (30.8)	18 (69.2)	1.1 (0.1-7.2)	0.8			
Mid ureter	4 (28.6)	10 (71.4)	1.7 (0.1-22.7)	0.7			
Lower ureter	2 (28.6)	5 (71.4)	0.8 (0.1-5.2)	0.8			
Vesicoureteric junction	5 (29.4)	12 (70.6)	0.6 (0.3-11.8)	0.7			
Uretero-intestinal anastomosis	2 (100.0)	0	1.0				

OR: Odd's ratio, AOR: Adjusted odd's ratio, GFR: Glomerular filtration rate, PCN: Percutaneous nephrostomy, PUJ: Pelviureteric junction.

over ureteral stents has been found, PCN has emerged as an initial choice in the management of pyonephrosis. Pearle et al. (12) randomized 42 patients with obstructive uropathy due to ureteric calculus to receive either a PCN or a ureteral stent. There was no difference in outcome parameters [time to resolution of fever or normalization of white blood cell (WBC) count] between the two groups. Stenting was found to be twice as costly as PCN. Ng et al. (8), in a retrospective review of 92 patients, found that the majority of pyonephrotic patients with ureteral obstruction undergoing PCN as interim management were spared open nephrectomy (69% underwent endourologic procedures, 14% open surgeries with 12% nephrectomies, and the remaining 17% had no definitive treatment as the condition resolved or they were unfit). Though no comparisons with ureteral stenting were made, they advised against the routine use of ureteral stents as their smaller sizes can provide less effective drainage, require general anesthesia during the procedure, increase the risk of ureteral perforation during manipulation, and pose a risk of sepsis flare-up due to pressure of irrigation fluid (8). To address the debate regarding the choice between nephrostomy and ureteral stenting, Wang et al. (13) conducted a randomized study comparing the efficacy and safety of ureteral stenting in patients with acute ureteral obstruction and sepsis caused by calculi. They found no difference in time to normalization

of WBC counts and body temperature and comparable complication rates between the two groups. They concluded that if combined with antibiotics, ureteral stenting is safe even in the setting of acute ureteral obstruction with sepsis (13). A cross-sectional study by Kumar et al. (14) among 550 patients with pyelonephritis, 60 of whom had pyonephrosis, found that 44 patients (73.33%) were managed with Double J (DJ) stenting, thus establishing its efficacy and safety in such patients. As of yet, there is no established consensus guiding the choice between PCN and DJ stent in such cases. A clear trend observed among the studies is that earlier studies preferred PCN (8), while more-recent studies show a trend towards the use of DJ stents (13,14). This is probably due to advances and refinements in ureteroscopic instruments and endoscopic techniques. Other factors influencing this choice are cooperation from anesthetists and ready access to operating theatres in high volume tertiary care centres, as was the case of our institute. Nephrostomy is preferred in unstable septic patients (1). Such patients have been excluded from studies supporting DJ stenting. Uncertainties also exist in managing pregnant patients and those with a solitary kidney (13,14).

The review of existing literature has found *E. coli*, to be the most common organism causing retrograde infections in an obstructed kidney (7,8,12,14), a finding further reiterated in our study. We found a disparity between the growth of organisms in bladder urine culture and PCN urine culture. Bladder urine culture was positive in 60% of patients whereas the proportion was 79% for PCN urine culture. In some studies, this disparity between urine and PCN cultures ranges from 27% to 51%. This may be due to antibiotics inhibiting the growth of organisms in the bladder or inhibiting the downward migration of microorganisms to the distal urinary tract due to urinary obstruction. Even if the infection in the lower tract resolves, it may persist in the upper tract due to obstruction. An advantage of PCN is its ability to isolate causative organisms even when bladder urine cultures are sterile, allowing appropriate antibiotics to be instituted (8,15).

Of these patients, 17% underwent nephrectomy. Other procedures performed were laser lithotripsy for ureteric stones, transurethral resection biopsy, urethral stricture surgery, and pyeloplasty. Our rate of nephrectomy was corroborated by other studies [e.g., 10% by Kumar et al. (14), 12% reported by Ng et al. (8)]. However, this rate was much higher in a series of earlier studies, ranging from 35% to 88%, which suggested that nephrostomy followed by nephrectomy was associated with greater operative difficulties and subsequent complications (15-18). This operative difficulty is due to periureteritis and inflammatory perinephric adhesions formed secondary to obstructive uropathy (Figure 3). Recent studies do not support this earlier theory. The improvement in renal function post-PCN may be due to improved renal perfusion, which facilitates antibiotic entry into the parenchyma, and thus causes a reduction in the bacterial burden. Additionally, renal function can return with the control of sepsis. Although the exact pathogenesis of pyonephrosis has not been extensively studied, obstruction and superimposed bacterial infection are considered the two main etiologic factors. Studies have shown that higher degrees of HN directly correlate with the development of pyonephrosis. This is due to increased intrapelvic pressure, which reduces urine production and predisposes the kidney to retrograde bacterial infections (19). With increasing grades of hydronephrosis, parenchymal thickness of the kidney decreases. The parenchymal thickness in a normal kidney is 15-20 mm. Reduced parenchymal thickness adversely affects the recoverability of renal function post-PCN placement. Some studies have shown that a parenchymal thickness <10 mm is associated with non-recoverability of renal function. Our study corroborated this finding, that patients with severe grades of HN had lower odds of recovering renal function post-PCN insertion. Several other factors, such as age, sex, and hemoglobin level, have been found to affect the recoverability of renal function (5,20,21). Males have been found to have a

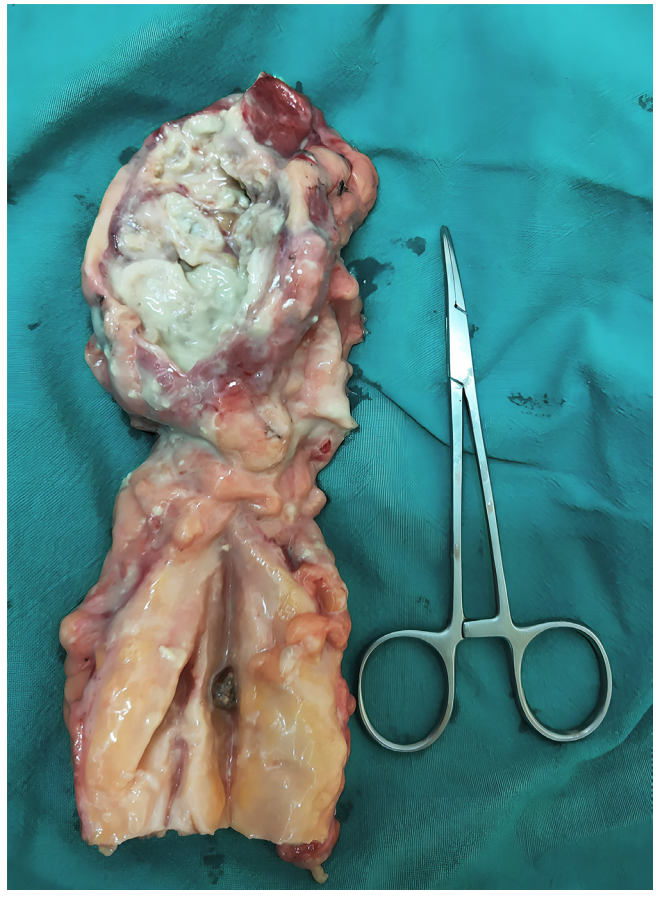

Figure 3. Simple nephrectomy specimen of a pyonephrotic kidney due to a mid-ureteric calculus. Significant intraoperative perinephric adhesions were encountered. Note the thickened walls of ureter secondary to periureteritis caused by obstruction.

more rapid decline in renal function than women due to the protective effect of estrogen (22). These factors were not found to be statistically significant in our study.

However, the Hosmer-Lemeshow goodness-of-fit statistic for the final multivariable logistic regression model was 3.43, with a p-value of 0.49, which indicates that the model fits the data well and predicted probabilities from our model align well with the actual observed outcome. The adjusted R_2 for the final multivariable regression model was 0.2, which indicates that 20% of the variability in the outcome (i.e., improvement in GFR post PCN insertion) is explained by the independent variables included in our model. This is clinically meaningful for decision-making, assessment of prognosis, and patient selection for specific interventions in the context of complex outcomes. Moreover, as human physiology is inherently complex, other factors like genetic predispositions, lifestyle, and individual variability in treatment response may also be responsible for outcome variability, thus highlighting the need for further research in this area.

Study Limitations

However, this study is not without limitations. A study between the two methods of urinary diversion, namely nephrostomy and ureteral stenting, has not been carried out. Whether the type of bacterial pathogens isolated in such patients influences the outcome has not been studied. The state of sepsis was not classified according to APACHE or SOFA scoring. Therefore, whether the severity of sepsis had a role in the non-recoverability of renal function could not be deduced. The timing of symptom onset until decompression can influence the return of renal function. However, in our study, we did not take the starting of symptoms into account as presentations varied. We also excluded the quality of life after PCN, which may influence the choice of urinary diversion.

CONCLUSION

Early PCN insertion is imperative for salvaging a pyonephrotic kidney. It is cost-effective, has minimal anesthesia requirements, is effective in controlling sepsis and promoting subsequent return of renal function. In addition, PCN provides a better yield of bacterial culture, allowing appropriate antibiotic therapy to be instituted. Since the routine insertion of PCN has come into practice, most pyonephrotic cases can now be managed by endourologic procedures, rather than the patient undergoing nephrectomy, as was practiced earlier.

Ethics

Ethics Committee Approval: Patients were enrolled after obtaining ethical clearance from the Institutional Ethics Committee of IPGME&R, Kolkota (approval number: IPGMER/IEC/2023/434, date: 03.05.2023).

Informed Consent: Prospective study.

Acknowledgments

Our biggest gratitude goes out to the study participants whose immense cooperation has made this study possible. We are also thankful to all the faculties, resident doctors and nursing officers working the department of urology for their support in carrying out this elaborate study.

Footnotes

Author Contributions

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

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

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ORIGINAL ARTICLE
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One-stage tunneled de-epithelialized deltopectoral flap for huge head and neck cancer defects in the era of free flaps

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ABSTRACT

Objective: The deltopectoral (DP) flap was and still is a workhorse flap in the reconstruction of head and neck defects following tumor resection, even in the current era of free microvascular flaps.

Material and Methods: We retrospectively recruited, from a prospectively maintained database, all patients with a history of defect reconstruction using one-stage tunneled de-epithelialized fasciocutaneous DP flap following resection of head and neck cancer between June 2020 and June 2023. Patient and disease characteristics, surgery parameters, flap specifics, oncological outcomes, and follow-up data were analyzed and reported.

Results: Eleven patients were recruited; 6 of them were females (54.54%). Head and neck squamous cell carcinoma is the most common pathology (54.5%), followed by papillary carcinoma of the thyroid gland (27.3%). Six patients were operated upon for recurrences, and tumor fungation and/or ulceration was reported in 81.8%. The median age at the time of flap reconstruction was 71 years (range: 46.5-77). Wound complications were reported in 36.4% of patients, with the overall rate of flap necrosis being 27.3%, including 3 patients who suffered from major necrosis at the distal 1/3 of the flap. No delay in receiving adjuvant therapies, according to treatment protocols, was reported for any of the surviving patients.

Conclusion: The one-stage tunneled de-epithelialized fasciocutaneous DP flap is an effective choice with acceptable outcomes for defect reconstruction following resection of locally advanced head and neck cancer, whether on a curative or palliative basis, in relatively old patients with different comorbidities who require rapid treatment sequencing.

Keywords: Surgical flaps, pedicled flap, deltopectoral flap, head and neck defect

INTRODUCTION

The two most common causes of head and neck defects requiring reconstruction are trauma and tumors, with trauma being more reported in the younger population, while head and neck tumors in a relatively older one (1-6).

Therefore, reconstruction for such defects aims to restore aesthetics, enhance residual functions, cover vital structures, and allow good mobility of the preserved structures around the resected area (7,8).

Currently, microvascular free flaps are the standard of care (9,10) for reconstruction of head and neck defects, with Kakarala et al. (11) reporting increased utilization of free flaps associated with an increase in efficiency and flap survivability.

However, there are possible limitations in using the microvascular free flaps regarding the defect site, the patient, the surgeon, and the health care system.

Possible limitations of microvascular free flaps have rekindled interest in pedicled flaps generally, especially the deltopectoral (DP) flap, which was a greatly popular reconstructive tool in the 1960s.

Our study aims to present experience in performing the one-stage tunneled de-epithelialized technique of the DP flap and to evaluate its versatility, success rate, associated morbidity, and oncologic outcomes in a specific group of patients.

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MATERIAL and METHODS

Patient Cohort and Study Design

All procedures performed in the study involving human participants were following the ethical standards of the institutional research committee and were concordant with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All the patients signed a written consent for the surgical maneuvers for resection and reconstruction. This is a retrospective study. Consent for participation in the study itself is not applicable. Approval was obtained from the Institutional Review Board at the Faculty of Medicine Mansoura University (MFM-IRB) (date: 21.07.2024, number: R.24.05.2636).

The prospectively maintained databases of Oncology Center Mansoura University (OCMU) and Mansoura Health Insurance Hospital, Egypt, were searched for cases of locally advanced head and neck cancer that underwent post-resection reconstruction of large defects using one-stage tunneled de-epithelialized fasciocutaneous DP flap between June 2020 and June 2023. All patients signed a written informed consent before any planned procedure.

Data Collection

Patient characteristics such as age, sex, comorbidities, body mass index (BMI), smoking history, type of malignancy and site, and previous therapies were retrieved. Current tumor status and treatment parameters—including the aim and type of surgery, flap specifics, postoperative complications and their management, and adjuvant therapies with oncological outcomes, were evaluated and reported. Patients were followed up until 24 May 2025.

Statistical Analysis

Patient data were analyzed, and statistical values were obtained using SPSS version 26 (SPSS Inc., Chicago, IL). Mean values with standard deviation when symmetrical, or median and range when asymmetrical, were used for continuous variables, and categorical variables were presented as proportions.

Flap Design

In our study of 11 patients, we used a one-stage tunneled de-epithelialized DP flap with no delay technique. After completing the surgical resection and hemostasis check of the recipient site, the flap was classically designed through drawing the conventional two horizontal incisions, starting 2 cm lateral to the parasternal border to incorporate the 2^{nd}-4^{th} internal thoracic artery perforators. The distal end of the flap was designed to extend beyond the DP groove into the anterior shoulder area; however, no delay technique was needed (Figure 1A). The flap was harvested in a lateral-to-medial direction in a subfascial plane, just over the deltoid muscle and deep to its fascia, extending over the deltoid muscle, DP groove, and the pectoralis major muscle (Figure 1B, C). The subcutaneous (SC) tunnel connecting the donor and recipient site was prepared, and the harvested flap was delivered through the tunnel to the recipient site to precisely mark the skin island and determine the exact length of the flap to be de-epithelialized (Figure 1D). The flap was then returned to the donor site to meticulously de-epithelialize the marked skin length while preserving the rich dermal-subdermal plexus (Figure 1E). Again, the flap was transferred through the SC tunnel to suture the edge of the skin island to the edge of the recipient site, and the edge of the de-epithelialized part to the edge of the skin bridge, thus finalizing the flap transfer in one stage (Figure 1F). In the majority of our cases, the donor site was

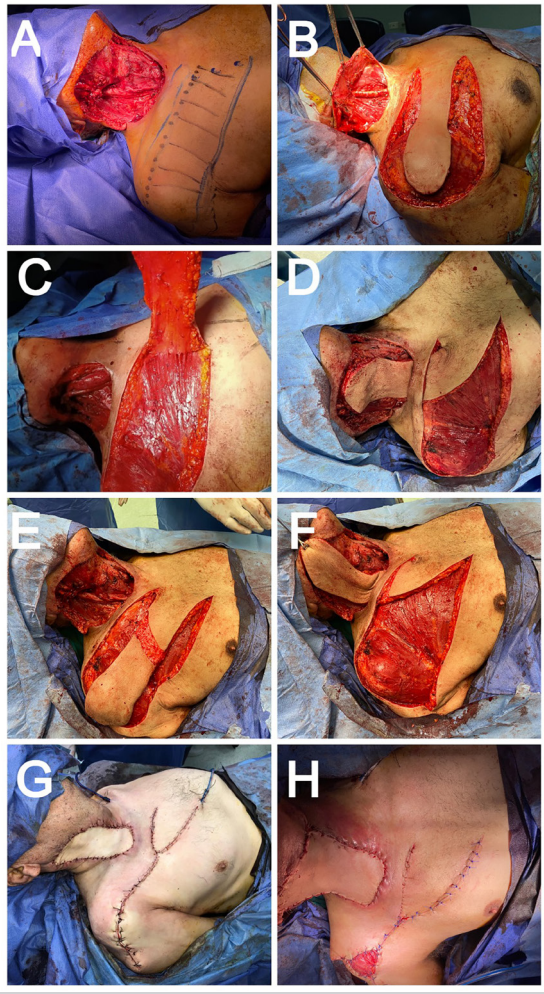

Figure 1. A. Post-resection defect and flap markings. **B, C.** Flap harvest in a lateral to medial direction in the subfascial plane. **D.** Subcutaneous tunnel creation and precisely marking the skin island and part of the flap to be de-epithelialized. **E.** De-epithelialization of the length to be buried under the skin bridge. **F.** Suturing the edge of the skin island to the edge of the recipient site, and the edge of the de-epithelialized length to the edge of the skin bridge. **G.** Final view after full flap insertion and primary wound closure. **H.** Flap insertion with near-primary wound closure leaving a small raw area over the anterior shoulder.

closed primarily by undermining the skin flaps around with no need for skin grafting (Figure 1G), while in others a small raw area was left over the anterior shoulder area (Figure 1H).

Peri-operative Care Regimen

Per our institutional protocol, we administer a single dose of prophylactic low-molecular-weight heparin (LMWH) (enoxaparin sodium 4000-8000 U), at night, and a single dose of preoperative antibiotic prophylaxis 30 minutes before skin incision. The post-operative care involves regular monitoring of vital signs and flap viability, wound care, early mobilization and oral feeding, limiting excessive head and neck movement, deep breathing exercises, and medications such as simple analgesics. Intravenous (IV) antibiotics (sulbactam 500 mg/ampicillin 1000 mg/twice daily) are provided while inpatient, followed by an outpatient oral equivalent for another week; LMWH (enoxaparin sodium 4000-8000 u/once daily) is administered while inpatient and continued for at least two weeks while outpatient. Some patients received therapeutic doses of LMWH based on cardiologists' recommendations. Additionally, oral anti-inflammatory enzyme therapy (chymotrypsin 5 mg/trypsin 5 mg/2 tablets/3 times daily) is prescribed for at least two weeks. Patients with postoperative surgical site infection received IV antibiotics according to culture and sensitivity results.

RESULTS

Our study reports on a total of 11 patients. Five were males (45.45%) and six were females (54.54%). Most were diagnosed with locally advanced head and neck cancer and were treated through surgical resection and reconstruction of the resulting defects using a one-stage tunneled de-epithelialized fasciocutaneous DP flap.

Patient and Disease Characteristics (Table 1)

The median age at the time of flap reconstruction was 71 years (range: 46.5-77), and the median BMI was 27.3 (range: 20.5-36.8). The majority of patients, 7 (63.6%), were non-smokers. Cardiovascular disease was reported in 7 patients (63.6%), followed by hypertension in 4 patients (36.4%) and diabetes mellitus (DM) in only 2 patients (18.2%), with 5 patients (45.45%) having at least two comorbidities.

Head and neck squamous cell carcinoma of different sites was the most common pathology, reported in 6 patients (54.5%), followed by papillary carcinoma of the thyroid gland (PTC) in 3 patients (27.3%).

Six patients (54.5%) were operated upon for recurrent disease, and tumor fungation/ulceration was reported in 9 cases (81.8% of the group) (Figure 2A-C-E).

Of the 5 cases with primary tumors, one case had stage II PTC, one case had stage III skin verrucous SCC, and three cases had stage IV disease: Two cases with stage IVA laryngeal SCC and tongue SCC, and one case with stage IVB mucoepidermoid carcinoma of the parotid gland.

Five of the 6 cases with recurrent disease had malignant pathology: Two cases had stage N1b PTC, two had stage N2b SCC of the lip and tongue, and one had stage N3 nasopharyngeal SCC.

Surgery Parameters and Flap Specifics (Table 2)

Surgery was performed on a curative basis in 9 patients (81.8%) and on a palliative basis in 2 patients (18.2%), based on clinical tumor staging and following the multidisciplinary team (MDT) recommendations, taking into consideration the intraoperative findings,.

Following surgical resections, R0 margins were reported in 6 patients (54.5%), R1 in 3 patients (27.3%), and R2 in 2 patients (18.2%).

The median total operative time was 300 minutes (range: 210-480), and surgical resection resulted in soft tissue defects in the neck region in 7 patients (63.6%), the parotid/neck region in 1 patient (9.1%), and the lower face/neck in another 2 patients (18.2%) (Figure 2B-D-F).

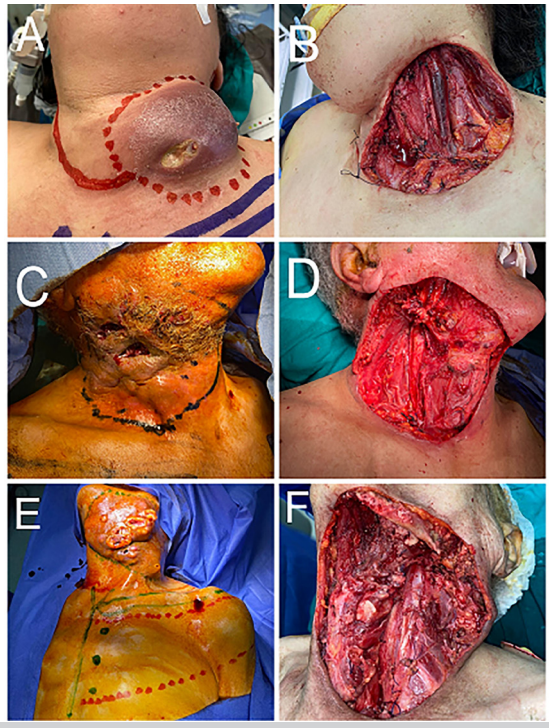

Figure 2. A. Pre-resection and **B.** Post-resection (bilateral BND) (case no. 1). **C.** Pre-resection and **D.** Post-resection of fungating nodal disease in (case no. 5). **E.** Pre-resection and **F.** Post-resection of fungating nodal disease in (case no. 6).

BND: Block neck dissection, PTC: Papillary thyroid cancer, SCC: Squamous cell carcinoma

Table 1. Patient and disease characteristics

Patient	Age at surgery, year	Sex	Comorbidities					Smoking	BMI	Primary Ds; site, pathological type, grade, and TNM	Previous treatment	Current condition (to be treated)/tumor status, TNM, and stage
			DM	HTN	CVD	Hepatic	Others					
1	46.5	F	-	-	-	-	Hypo-thyrodism	-	36.8	Thyroid, PTC (conventional type) (pT3acN0M0, stage I)	TT 1 year before + L-thyroxine suppressive dose	Nodal recurrence, fungating De-differentiated (N1bM0)
2	63	M	+	+	+	-	-	-	32.7	Parotid, mucoepidermoid carcinoma, G3 (T4bN2bM0, stage IVB)	-	Primary, fungating
3	72	F	-	-	-	-	-	-	25.7	Submndibular, PMA	Surgery for 6 times	Local recurrence, multiple/diffuse
4	72.5	F	-	+	+ Valvular HD	-	-	-	20.5	LIP, SCC, G1 (T1N0M0, stage I)	WLE with free margins on lip + lv I, II, III BND	Nodal recurrence, fungating, G2 (N2bM0)
5	71	M	-	-	+ IHD, AF stenting	-	COPD	+	27.3	Larnyx, SCC, G3 (T4aN2cM0, stage IVA)	-	Nodal 1ry, fungating
6	77	F	-	+	+ IHD stenting	-	-	-	25.1	Tongue, SCC, G1 (T3N2bM0, stage IVA)	Chemotherapy (due to critical cardiac condition precluding surgery at a time)	Nodal 1ry, fungating (progress on chemotherapy)
7	60	M	-	-	-	+	-	NA	30.8	Thyroid, PTC (conventional type) (pT1bN1bM, stage II)	TT + central + type 1 modified lateral BND + RAI	Nodal recurrence (N1bM0)
8	53	F	-	-	-	-	-	-	22.2	Tongue , SCC, G2 (T3N0M0, stage III)	Compartmental resection with lv I, II, III BND with SCAIF + CCRT	Nodal recurrence, fungating, G2 (N2bM0)
9	76	M	-	-	+	-	-	NA	27.9	Thyroid, PTC (T3aN1bM0, stage II)	-	Nodal 1ry, infected, about to fungate
10	65	M	-	+	+	-	-	+	26	Nasopharyngeal, SCC (T3N0M0, stage III)	CCRT	Nodal recurrence, fungating (N3M0)
11	75	F	+	-	+	-	-	-	29	Neck skin, Verrucous carcinoma (T3N0M0, stage III)	-	Primary, ulcerating

F: Female, M: Male, DM: Diabetes mellitus, HTN: Hypertensive disease, CVD: Cardiovascular disease, IHD: Ischemic heart disease, AF: Atrial fibrillation, COPD: Chronic obstructive pulmonary disease, (+): Positive, (-): Negative, PTC: Papillary thyroid cancer, SCC: Squamous cell carcinoma, PMA: Pleomorphic adenoma, TT: Total thyroidectomy, BND: Block neck dissection, SCAIF: Supraclavicular artery island flap, CCRT: Concurrent chemo-radiotherapy, 1ry: Primary, NA: Not available.

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Table 2. Surgery parameters and flap specifics

Patient	Aim of surgery	Type of surgery, safety margins status	Operative time, minute	Defect anatomical site	Defect size, cm	Flap harvest time, minute	Hospital stay, days	Postoperative complications			
								Wound	Flap necrosis	Timing, (POD)	Management
1	Curative	Bilateral BND (free margins; R0)	390	Neck	10*9	45	3	-	-	-	-
2	Curative	Total parotidectomy + WLE of the fungating lesion + sacrification of cranial nerve X, XII and lower trunk of VII (infiltrated deep margin; R1)	330	Parotid and neck	12*11	50	3	Infection, resistant Diplococcus bacteria	Major, distal end, category: Partial failure (2aP)	20*	Debridement, skin graft from anterior lateral thigh
3	Curative	Radical resection (free margins; R0)	360	Lower face, neck	15*10	40	3	-	-	-	-
4	Curative	WLE of fungating lesion + marginal mandibulectomy (infiltration of bone safety margin; R1)	210	Neck	7*5.5	55	4	Infection, resistant Gram-negative Bacilli bacteria	Major, distal end, Category: Partial success (1bP)	16*	Debridement, healed by secondary intention
5	Palliative	WLE of fungating lesion + IJV sacrification (tumor residue; R2)	360	Neck	12*8	45	8	Infection	-	2	Conservative measures
6	Palliative	WLE of fungating lesion, ECA sacrification, (tumor residue; R2)	285	Lower face, Neck	14*7	45	10	-	-	-	-
7	Curative	Selective BND (R0)	270	-	-	50	4	-	-	-	-
8	Curative	WLE, sacrification of sternomastoid + IJV + upper trunk of brachial plexus (infiltrated deep and lateral margins; R1)	270	Neck	9*7	40	5	-	-		-
9	Curative	TT + central + radical BND (free margins; R0)	480	Neck	10*5	55	4	Hematoma then seroma at donor site, small area of skin necrosis at donor site	Major, distal end, category: (1bP)	1,15*	Surgical hemostasis, conservative measures
10	Curative	Radical BND (free margins; R0)	240	Neck	8*6	50	3	-	-	-	-
11	Curative	WLE (free margins; R0)	300	neck	11*7	45	3	-	-	-	-

BND: Block neck dissection, WLE: Wide local excision, INJ: Internal jugular vein, ECA: External carotid artery, POD: Postoperative day
(2aP): Partial failure = second flap (free or pedicled) required to rehabilitate defect, (1bP): Reconstruction successful = partial success with loss of some components of flap, but no secondary reconstruction or prosthesis required, *: Timing of evident flap necrosis.

Ten of the 11 patients (90.9%) received a DP flap to cover large skin defects, and in 1 case (9.1%), it was used to provide an additional protective layer over the common carotid artery (CCA). This was necessary due to thinned overlying skin from the previous type 1 modified block neck dissection (BND) and the current resection for nodal recurrence encasing the artery.

The defect size ranged from 7x5.5 cm to 15x10 cm. The median flap harvest time was 45 minutes (range: 40-55). The donor site was primarily closed in 10 patients (90.9%), with a small raw area left at the anterior shoulder region in 1 patient (9.1%).

Wound complications were reported in 36.4% of patients, including wound infection in 3 patients (27.3%) and hematoma followed by seroma collection in 1 patient (9.1%), with a small area of skin necrosis at the donor site in the same patient. Another patient had a cerebral stroke one month postoperatively, followed by an upper limb deep venous thrombosis. The median hospital stay was 4 days (range: 3-10).

The overall rate of flap survival in our study was 72.7% (Figure 3A-H), with flap necrosis reported in 27.3% of patients, as 3 patients suffered from major necrosis at the distal 1/3 of the flap (Figure 4A-H).

Oncological Outcomes and Follow-up Data (Table 3)

The 90-day mortality rate was 36.4%, with no more deaths reported until the end of the follow-up period. The median overall survival was 14.6 months (range: 0-41).

The 4 cases of mortality included the 1st case, who presented to the emergency department with very poor general condition due to rapidly aggressive recurrence, was admitted to the intensive care unit and succumbed just 1 day after. The 2nd, 3rd, and 4th cases had a combination of different risk factors: Old age, chronic comorbidities, and fungating locally advanced tumors, with a resistant wound infection in the 2nd case and gross tumor residues in the 3rd and 4th cases. The cause of death in the second case was sudden cardiac arrest, 2 days after managing flap necrosis; in the third and fourth cases, it was difficult postoperative recovery with cardiopulmonary deterioration.

Following the MDT recommendations, two patients with PTC received treatment: Case no. 7 (with nodal recurrence) and case no. 9 (with locally advanced primary disease) were given adjuvant RAI plus levothyroxine suppressive dose, with case no. 7 also receiving external beam radiotherapy. Patient case no. 4 (with nodal recurrence of lip SCC) received adjuvant weekly paclitaxel 100 mg for 9 weeks. Unfortunately, case no. 8 (with nodal recurrence of tongue SCC) did not receive her planned therapy due to postoperative cerebral stroke, resulting in lost follow-up. The last patient, case no. 3, (with frequently recurrent submandibular pleomorphic adenoma), received adjuvant tamoxifen 20 mg/daily.

No delay in receiving the adjuvant therapies was reported for any of the surviving patients.

The recurrence rate was 54.5% with the most common pattern being nodal recurrence (36.4%), followed by distant and local recurrence in 18.2% and 9.1%, respectively. The median disease-free survival (DFS) was 8 months (range: 1-36).

DISCUSSION

Microvascular free flaps are considered the standard of care for reconstruction of head and neck defects (9,10). However, there are possible limitations for its use regarding the defect site, patient, surgeon, and health care system. For example, the vessel-depleted necks, resulting from previous neck dissection, severe atherosclerotic disease, heavily irradiated tissues, and the donor/recipient sites' aesthetic requirements, are to be considered when choosing these flaps for reconstruction (10,12-15). Age may impact the viability of the donor sites, with poor surgical outcomes (16); however, many studies showed that age is not considered a risk factor for flap failure even in patients up to 90 years old (17,18). Some authors reported that general

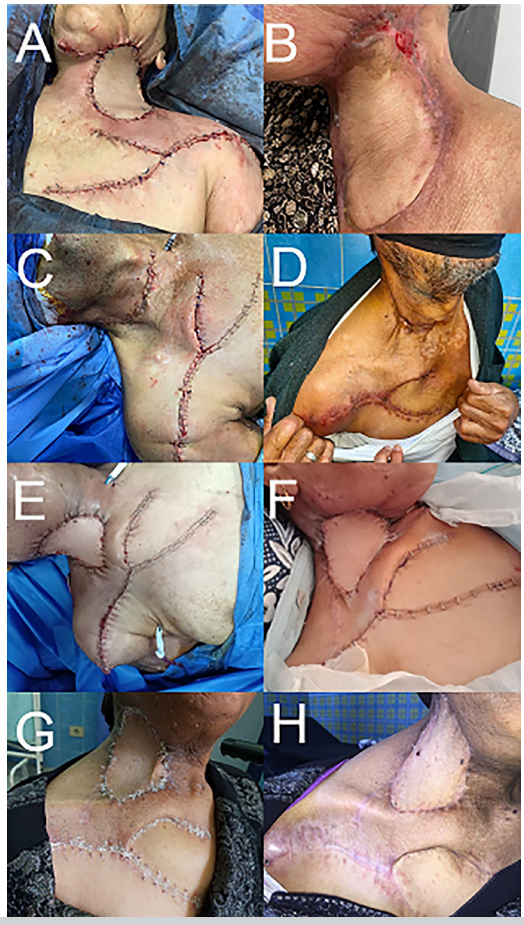

Figure 3. A. Intraoperative and **B.** Eight weeks postoperative of (case no. 3). **C.** Intraoperative and **D.** Three weeks postoperative of (case no. 7). **E.** Intraoperative **F.** Immediately postoperative **G.** Three weeks postoperative and H. Seven weeks postoperative of (case no. 8).

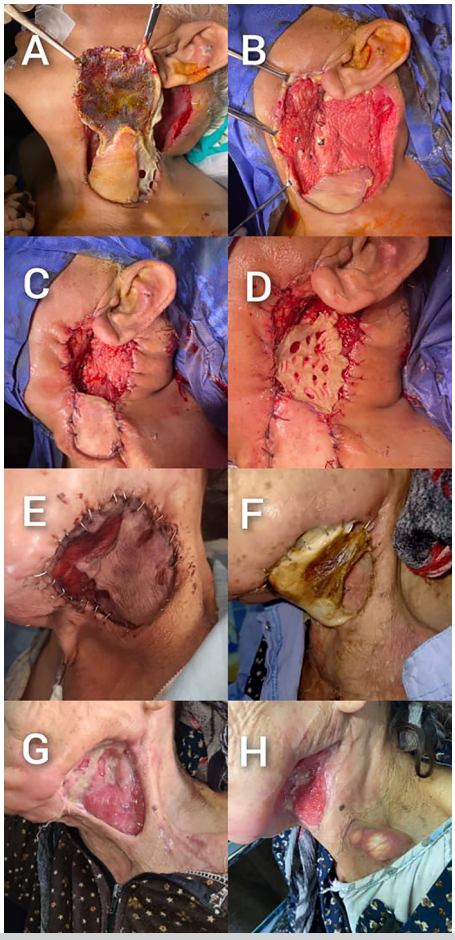

Figure 4. A. Evident major necrosis of the distal end of the flap. **B.** Complete removal of the necrotic tissue. **C.** Approximation of the wound edges as possible to narrow the defect. **D.** Reconstruction by skin graft from anterior lateral thigh (case no. 2). **E.** Congested distal end of the flap with wound dehiscence. **F.** Evident major necrosis of the distal end of the flap. **G, H.** Healing of the defect by secondary intention (case no. 4).

health and comorbidities such as diabetes may interfere with the flaps' survivability (19,20), while others argue that normal glycaemia must be maintained for improved outcomes (21). Another issue is that patients pretreated with chemotherapy and/or radiotherapy, or presenting with recurrent diseases, may not be the best candidates for free flaps (22,23). Despite that, high-volume institutions had extended their indications for the use of free flaps to include many of these conditions (24).

Also, the microvascular free flaps require expertise in microvascular techniques (25) with longer operating time, and a higher rate of revision surgery (9). In contrast, the pedicled flaps are more accessible to both academic and community surgeons (26). Free flaps have logistic, financial, and training burdens on any health system (20,27,28).

Taking into consideration such possible limitations of the microvascular free flaps, interest in the pedicled flaps has been rekindled in general, with special attention given to the workhorse in the head and neck reconstruction, the DP flap.

There are many advantages of using DP flap in the reconstruction of the head and neck defects: It is technically simple with fast harvesting, thus it shortens both operative and anesthesia time. Has a reliable blood supply (29); it provides a large surface area for harvesting thin pliable tissue with minimal bulk (10,30). The procedure has an excellent color and texture matching for the recipient site with minimal functional deficit in the donor site (31,32). It can rotate and easily reach a defect up to the zygomatic arch, increasing its versatility. of course, it can be raised in one stage through either de-epithelialization and tunneling (33), a single incision in the donor area (34,35), or excision of the skin between the recipient and donor site (31).

Table 3. Oncological outcomes and follow-up

Patient	Adjuvant therapy	Recurrence	Pattern of recurrence	Status at last visit	Overall survival, months	Disease free survival, months
1	-	+	Nodal	Died	2	1
2	-	-	-	Died	1	-
3	Tamoxifen 20 mg/daily	+	Local	Alive	43	14
4	Weekly paclitaxel 100 mg/9 weeks	+	Nodal + distant	Alive	8	2
5	-	-	-	Died	0	-
6	-	-	-	Died	0	-
7	RAI + L-thyroxine suppressive dose + EBRT	+	Distant	Alive	46	36
8	-	+	Nodal	Alive	3	2
9	RAI + L-thyroxine suppressive dose	+	Nodal	Alive	31	31
10	-	-	-	Alive	23	-
11	-	-	-	Alive	17	-

(+): Oositive, (-): Negative, RAI: Radio-active iodine, EBRT: External beam radiotherapy, CCRT; Concurrent chemo-radiotherapy.

However, such a flap doesn't come without disadvantages. There may be a need for skin grafting for the donor area (32); however, it could be primarily closed through undermining of the surrounding skin (10), especially in patients with lax skin (31), as was the case in our study of relatively old patients. However, the donor site in only 1 patient was not completely closed in a primary fashion, leaving a very small raw area, without the need for skin grafting.

Another disadvantage is breast asymmetry and nipple distortion affecting cosmetic outcomes in female patients (31); however, given the clinical staging of the tumors and the patients' old age, it did not greatly impact patients' decisions regarding flap selection or their quality of life in our study.

Flap necrosis or failure is considered the most feared complication in the realm of reconstructive surgery, as it leads to prolonged hospitalization, readmission, increased morbidity and mortality, and functional deficits (36); the common causes of DP flap necrosis include pedicle constriction or twisting, flap traction, and folding (37).

A higher incidence of complications, such as flap loss, dehiscence, or fistula reappearance was seen in cases where the DP flap was used for the repair of mucosal-only defects while using techniques such as the reverse tubulation procedure, creating a slit for stoma formation or esophageal anastomosis, or in the reconstruction of the total pharynx, the tongue, its base, and the mouth floor. These complications are mostly due to the high incidence of infection from the contaminated aerodigestive secretions, malignant ulceration, or nearby infected teeth in such a dark, moist and warm environment, thus favoring bacterial growth (29,37-41).

Gilas et al. (29) reported no statistically significant difference in the rate of complications between patients who had received radiotherapy versus those who had not (215 vs. 463 flaps, respectively), albeit with a higher rate of major flap necrosis related to the radiotherapy group (15.1% vs. 21% $p<0.005$). Kirkby et al. (40) reported a 49% flap failure rate in previously irradiated recipient sites. On the contrary, other authors have reported no or minimal flap failure due to recipient site irradiation (36,42).

We used the one stage tunneled de-epithelialized fasciocutaneous DP flap in our group of 11 older and fragile patients for the reconstruction of large soft tissue defects following resection of locally advanced head and neck cancer, with compromised overlying skin. This approach also provided additional coverage for a possibly jeopardized CCA with thin overlying skin from both previous type 1 modified BND and the current resection for nodal recurrence encasing the artery.

We followed the same classic steps described by both Bakamjian (43) and Lash et al. (33), except for the original delay technique used to reduce the risk of necrosis in the distal part of the flap. The delay technique was not used by Gilas et al. (29), with Bakamjian (43) as a co-author. They reported in their article, based on 678 DP flaps over 20 years of experience that there was no statistically significant difference between delayed and non-delayed DP flaps regarding the complication rate. Therefore they abandoned the routine use of the original delay technique. Other studies from Kingdom and Singer (36) did not report that any of their 24 patients experienced flap necrosis when their flaps were extended laterally to the DP groove without using a delaying procedure. In another study of 86 DP flaps by Kirkby et al. (40), the risk of complications was higher, although not statistically significant. Also, Pecorari et al. (44) reported a no-delay technique in their 31 patients with the same frequency of complications, even in comorbid patients, except for those with DM who had a different frequency. Moreover, two comparative trials by Chen et al. (45) and Mir et al. (46) compared conventional DP flaps with laterally extended DP flaps without the delay technique (23 vs. 10, and 15 vs. 17 patients, respectively) that reported comparable rates of overall complications and flap necrosis between groups. Therefore, we did not use a delay technique in our series, which resulted in only 3 cases of necrosis in the distal end of the flap.

Chan and Chan (31) reported a total of 54 patients with a median age of 60 years (range: 37-99). We reported an older group of patients with a median age of 71 years and a narrower range of 46.5-77. They used the DP flaps to cover the skin defects in 63% of their cohort and opted for reconstruction in the form of a one-stage procedure through excision of the skin bridge between the defect and donor site; or through tubulization of the DP flaps over the skin bridge, which was later divided in a staged procedure.

The reported overall complication rates of the DP flap have reached 51% (29). Taking into consideration the different techniques and modifications of the DP flap over the years, and the variable scenarios in which it is being used, Chan and Chan (31) reported a 3.7% rate of partial tip necrosis in 54 patients. Krizek and Robson (38) reported a rate of major necrosis of 10.5% in 86 patients. Andrews et al. (47) reported 16% distal flap loss in 25 patients. Gilas et al. (29) reported in their series of 604 patients 16.9% and 14.2% overall rates of major and minor necrosis, respectively. Mendelson et al. (37) reported a 23% rate of major flap loss in 63 patients. Kingdom and Singer (36) and Mortensen and Genden (35) reported total flap survival with no necrosis in their series of 24 and 16 patients.

Wound complications were reported in 36.4% of our patients, with the overall rate of flap necrosis 27.3%, given the low number of patients, which was 11. Their outcomes were categorized as: 1 case as (2aP) and another two as (1bP), based on a proposed categorization system for results/outcomes for reconstruction with a pedicled flap by Ho et al. (48), which aims to reflect the

complexity of reconstructive surgery and accurately define its outcomes beyond QOL or functional measures.

We thought that the causes for flap necrosis in our three patients were possible pedicle constriction by a tight skin bridge or excess flap traction in irritable patients postoperatively, coupled with the superimposed postoperative infection in two patients that may impair the flap vascularity and promote necrosis in the already randomly extended distal end.

As emphasized by Shaw et al. (28), surgeons should appreciate the broader context of treatment plans devised by the MDT approach when a flap is being selected for defect reconstruction following tumor surgery in the head and neck region, as the most common indication is locally advanced SCC, representing 54.5% of our patients, which often leads to early patient demise. Therefore, any delay to the start of adjuvant therapy due to flap complications may represent only a limited surgical success and could contribute to a broader treatment failure.

There was no reported delay in administering adjuvant therapies according to treatment protocols in our patients. The 4 cases of 90-day mortality were due to multiple factors: Old age, multiple chronic comorbidities, aggressive locally advanced, mostly fungating, diseases, or early aggressive recurrence. None were related to the flap complications. Also, one patient did not receive her therapy due to cerebral stroke and loss of follow-up.

So, we presume that the adoption of the one-stage tunneled de-epithelialized fasciocutaneous DP flap technique in such a clinical scenario proved to be a success in the broader context of treatment plans in our patients, despite some yet acceptable surgical failures.

CONCLUSION

The one-stage tunneled de-epithelialized fasciocutaneous DP flap is an effective choice with acceptable outcomes for defect reconstruction following resection of locally advanced head and neck cancer, whether on a curative or palliative basis, in relatively old patients with different comorbidities requiring a rapid sequence of their treatment plans.

Ethics

Ethics Committee Approval: Approval was obtained from the Institutional Review Board at the Faculty of Medicine Mansoura University (MFM-IRB) (date: 21.07.2024, number: R.24.05.2636).

Informed Consent: All patients signed a written informed consent before any planned maneuver.

Footnotes

Author Contributions

Surgical and Medical Practices - S.A., M.Z., I.N., A.M.A., K.A., A.F., A.A.; Concept - S.A.; Design - S.A., A.A.; Data Collection or Processing - S.A., M.Z., I.N., A.M.A., K.A., A.F., A.A.; Literature Search - S.A., A.M.A.; Writing - S.A., M.Z., A.F., A.A.

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

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ORIGINAL ARTICLE
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Robot-assisted total vs. unicompartmental knee arthroplasty: A systematic review and meta-analysis

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ABSTRACT

Objective: Robot-assisted (RA) surgeries are a major advancement in the medical field, allowing surgeons to operate remotely with minimal direct involvement. Over the past decade, robotic systems have been increasingly used in many areas, including orthopedic procedures. This systematic review and meta-analysis aimed to evaluate the effectiveness of RA-total knee arthroplasty (TKA) and unicompartmental knee arthroplasty (RA-UKA).

Material and Methods: A systematic review and meta-analysis of 12 randomized controlled trials was conducted to compare total and unicompartmental RA-TKA with each other and with the conventional method. A total of 1.538 participants were included in the studies, which were published between January 2014 and November 2024. The main outcomes of interest were range of motion (ROM) and pain measured by the visual analogue scale (VAS). The Cochrane RoB2 tool was used to assess the risk of bias. Subgroup analyses were carried out for RA-TKA and RA-UKA outcomes.

Prospero Registration: CRD42024627463.

Results: RA knee arthroplasty and conventional knee arthroplasty showed no significant differences in either outcome ROM or VAS score for pain with results of [MD =2.30, 95% CI: -1.56 to 6.16] and (MD =0.05, 95% CI: -0.14 to 0.23), respectively. Similarly, the comparison between RA-TKA and RA-UKA in the subgroup analysis also showed no significant difference, with combined results of (MD =2.30, 95% CI: -1.56 to 6.16) and (MD =0.05, 95% CI: -0.14 to 0.23), respectively.

Conclusion: RA knee arthroplasties (RA-TKA and RA-UKA) show similar outcomes to each other and to conventional methods in terms of ROM and pain reduction (VAS), with both robotic techniques showing comparable alternatives to traditional methods. These techniques also offer advantages such as greater precision and less direct involvement from the surgeon, which may help reduce human error. RA-TKA and RA-UKA produce similar results, and either can be used depending on the patient's knee condition and availability of experienced surgeons in robotics. Future studies with standardized protocols, larger sample sizes, and longer follow-up periods are needed to better understand and confirm the long-term benefits and differences between RA-TKA and RA-UKA techniques.

Keywords: Robot-assisted surgery, total knee arthroplasty, unicompartmental knee arthroplasty, range of motion, pain, meta-analysis, RCT

INTRODUCTION

Osteoarthritis (OA) is a progressive, degenerative joint disease and a leading cause of disability worldwide. It is marked by the gradual breakdown of articular cartilage, changes in the subchondral bone, and inflammation of the synovial lining. OA causes pain, stiffness, and limited movement, which can severely affect quality of life especially in people over the age of 50. About 70% of those over 55 years old are affected, and 60% of them are women (1,2). The knee joint is one of the most commonly affected areas, with knee OA making up a large number of cases (1). In the early stages, non-surgical treatments such as physical therapy, medication, and joint injections are often helpful. However, in advanced OA, surgery is usually needed to restore joint function and reduce pain (2,3).

In orthopedics, especially in knee arthroplasty, robot-assisted (RA) techniques have gained significant attention. For end-stage OA in the knee, the main surgical treatment options are total knee arthroplasty (TKA) and unicompartmental knee arthroplasty (UKA) (4,5). TKA focuses only on the damaged part of the knee, preserving the healthy areas, while TKA involves replacing the entire knee joint.

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Traditional manual methods, though effective, rely heavily on the surgeon's skill and experience. In contrast, RA surgery has become a major advancement in modern medicine, improving the surgical treatment of OA by offering greater precision and allowing surgeons to operate with minimal direct involvement through remote control (4).

Previous systematic reviews and meta-analyses have compared RA-TKA with conventional techniques, showing better results for the robotic approach (6-12). However, RA-TKA and RA-UKA have not been compared with each other in any meta-analysis to determine which gives better outcomes.

This systematic review and meta-analysis aim to fill this gap by comparing the outcomes of RA-TKA and UKA with each other, as well as with conventional methods. By focusing on range of motion (ROM) and the visual analog scale (VAS) for pain, this study seeks to provide strong evidence on the functional and clinical effectiveness of robotic systems in knee arthroplasty.

MATERIALS and METHODS

Search Strategy and Databases

A comprehensive search was conducted in PubMed, Google Scholar, and the Cochrane Library for studies on RA-TKA. Randomized controlled trials (RCTs) published between January 2014 and November 2024 were identified. Search terms included " RA-TKA", "TKA","UKA", "ROM" and "pain". Only articles published in English were included.

Inclusion and Exclusion Criteria

RCTs were included if they evaluated RA-TKA in patients over and 18 years old diagnosed with OA requiring arthroplasty. The outcomes of interest were ROM and VAS score for pain. Studies were excluded if they did not report these outcomes, if the authors did not respond, or if the full text was not available.

Study Selection

Title and abstract screening was performed by two independent reviewers. Full texts of eligible or unclear articles were then reviewed independently by the same reviewers based on the inclusion criteria. Any disagreements were resolved through discussion or, if needed, with the help of a third reviewer. The selection process was documented using a PRISMA flow diagram, as shown in Figure 1.

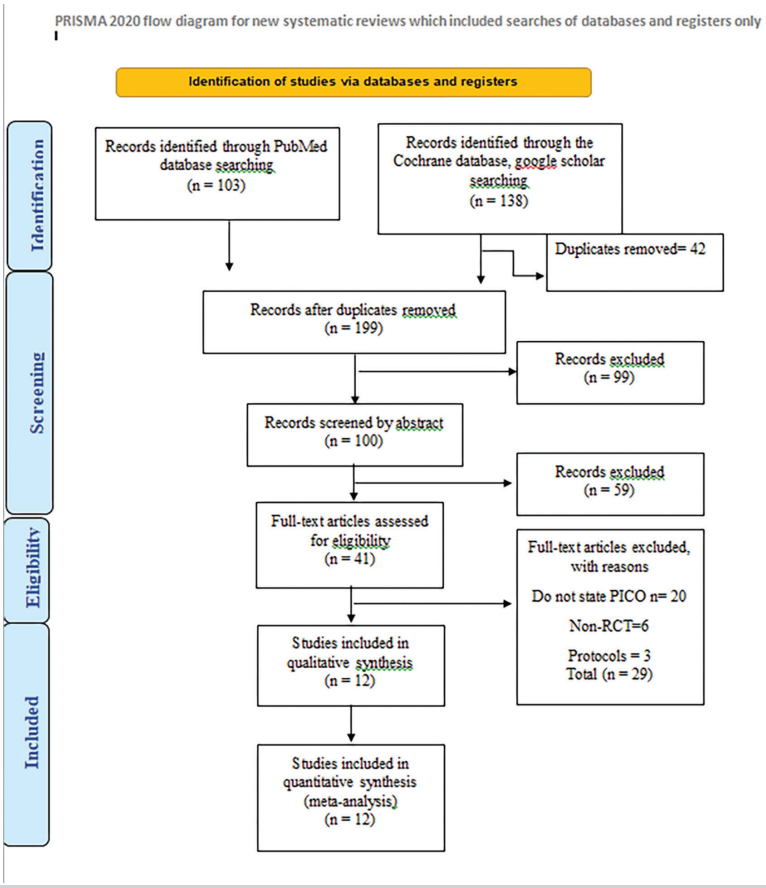

Figure 1. PRISMA flow diagram for study selection.
RCT: Randomized controlled trials

Data Extraction

A specially designed form was used for data extraction. The extracted information included study characteristics (study design, sample size, intervention details, comparison group, follow-up period, and implant used), outcomes of interest (ROM and VAS score for pain), and indicators of study quality. Excel tables were used to manage and organize the data, and review manager 5.4 was used for analysis. Any disagreements were resolved with the help of a third reviewer.

Quality Assessment

Each included study underwent an independent risk of bias assessment by two reviewers using the cochrane risk of bias tool. This tool evaluates key areas such as allocation concealment, random sequence generation, blinding of outcome assessment, blinding of participants and personnel, incomplete outcome data, selective reporting, and other biases (Figure 2). The final risk of bias results were used to determine the strength of the evidence in this study (Figure 3).

Synthesis of Results

A random-effects model was used for all analyses, as differences among study populations were expected. Since all outcomes were continuous data, results were analyzed using mean differences only. No other effect measures were used. Results were reported with a 95% confidence interval (CI). Both primary and secondary outcomes were analyzed. Heterogeneity was assessed using the I^2 statistic, and subgroup analysis was performed to compare RA-TKA and RA-UKA within the RA-TKA group for the outcomes in this meta-analysis.

RESULTS

Study Characteristics

Twelve RCTs met the inclusion criteria after full-text review. These studies evaluated either ROM or VAS score for pain in RA-TKA, including both TKA and UKA. Out of the 12 studies, eight compared RA-TKA with conventional TKA (13-20), three compared RA-UKA with conventional UKA (21-23), and one study compared two RA-TKA alignment techniques, specifically the individualized alignment group and the default alignment group (24). Eleven of the studies reported ROM as an outcome (13-23) while six studies reported VAS scores for pain (Table 1) (13,20,22-24). In the study by Adamska et al. (13) two robotic systems NAVIO and CORI were used, and separate data were provided for each system for both ROM and VAS outcomes as shown in Table 2.

A total of 1.657 participants were included across all 12 studies, with sample sizes ranging from 60 to 351. These studies were conducted across a broad geographic population. Full details are presented in Table 1.

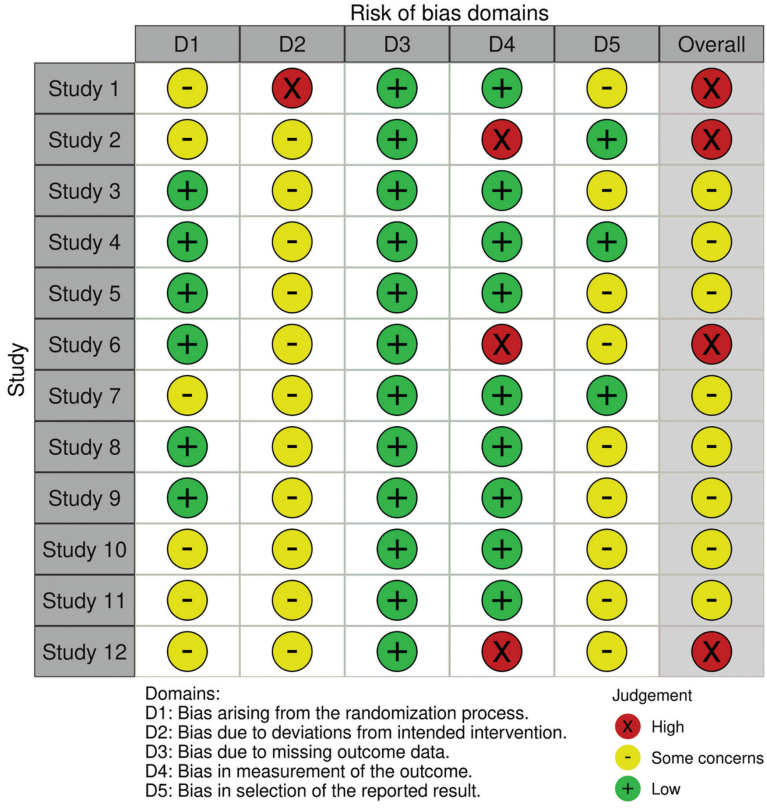

Figure 2. Risk of bias traffic plot.

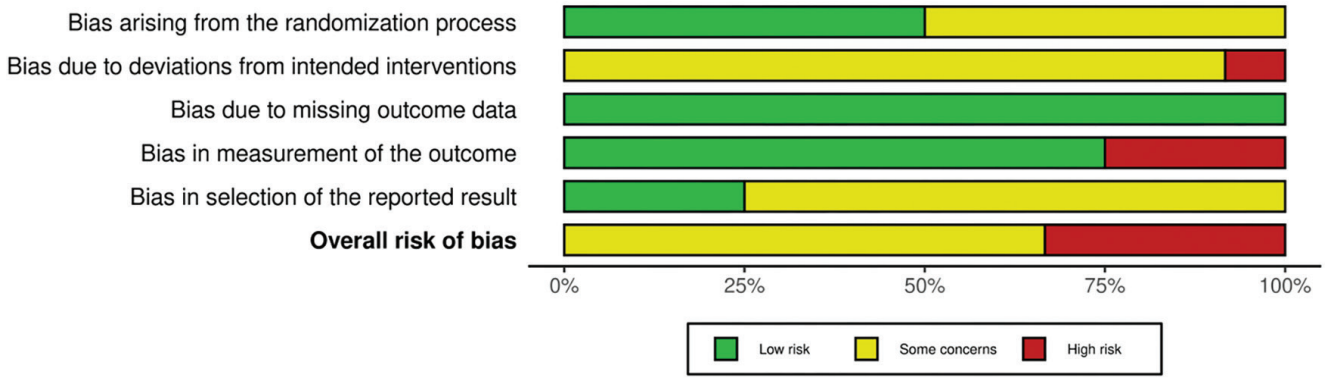

Figure 3. Risk of bias summary plot.

Outcomes

RA and conventional knee arthroplasty showed no significant difference in both outcomes ROM and VAS score for pain. Neither technique showed clear superiority over the other. The combined effect for ROM was (MD =2.30, 95% CI: -1.56 to 6.16), showing a slight tilt in favor of the conventional technique, as seen in Figure 4. For the VAS pain outcome, the combined effect was (MD =0.05, 95% CI: -0.14 to 0.23), as shown in Figure 5.

Subgroup Analysis

In the subgroup analysis of ROM, the RA-TKA subgroup showed a pooled effect of (MD: 2.61, 95% CI: -1.95 to 7.16) with high heterogeneity (I^2=96%), indicating large variation among the studies and no statistical significance (p=0.26), as the CI crosses zero. Similarly, the RA-UKA subgroup had a pooled effect of (MD: 1.38, 95% CI: -3.17 to 5.94) with moderate heterogeneity (I^2=65%) and also no statistically significant effect (p=0.55). Numerically, RA-TKA showed a greater potential improvement in ROM than RA-UKA. However, when comparing the two subgroups (RA-TKA vs. RA-UKA), the test for subgroup differences showed no statistically significant difference (p=0.71, I^2=0%), suggesting that both techniques have a similar effect on ROM. The overall pooled mean difference across both subgroups was (MD: 2.30, 95% CI: -1.56 to 6.16), further supporting the conclusion that RA-TKA and RA-UKA produce similar ROM outcomes, as shown in Figure 6.

Similarly, for the second outcome, VAS score for pain, the pooled mean difference for the RA-TKA subgroup was (MD: 0.06, 95% CI: -0.18 to 0.30) with moderate heterogeneity (I^2=37%) and no statistical significance (p=0.61). For the RA-UKA subgroup, the pooled mean difference was (MD: 0.26, 95% CI: -0.74 to 1.26) with low heterogeneity (I^2=0%) and no statistical significance (p=0.55). The test for subgroup differences showed no significant difference between RA-TKA and RA-UKA (p=0.71), suggesting that both techniques had similar outcomes in terms of pain reduction. The overall pooled mean difference for VAS across both subgroups was 0.05 (95% CI: -0.14 to 0.23), indicating a similar effect in pain relief, as shown in Figure 7.

Risk of Bias

In the risk of bias assessment, four studies were found to have a high risk of bias, while eight studies showed a moderate risk of bias. The main reasons for these ratings were issues in the randomization process, deviations from the intended interventions, and selective reporting of results. No studies were rated as having a low risk of bias. The detailed risk of bias assessment for each study is shown in Figures 2 and 3.

DISCUSSION

This systematic review and meta-analysis aimed to evaluate the comparative effectiveness of RA-TKA and UKA, both in comparison with each other and with conventional surgical techniques. The analysis focused on two key clinical outcomes: ROM and pain, measured by the VAS. Our findings show that robotic techniques, whether used for total or unicompartmental procedures, produce similar results to conventional methods, with no statistically significant advantage in either ROM or VAS scores.

Subgroup analyses further confirmed that RA-TKA and RA-UKA had similar outcomes, with both showing comparable pooled effects for ROM and pain. Although RA-TKA showed slightly better results numerically for improving ROM compared to RA-UKA, this difference was not statistically significant. These findings suggest that the choice between RA-TKA and RA-UKA should depend on patient-specific factors, such as the severity and location of joint damage, the surgical indication, and any existing medical conditions.

Our results suggest that robotic techniques in knee arthroplasty lead to similar clinical outcomes as conventional methods. Although robotic systems may provide better precision and more consistent surgical planning, their clinical benefits in terms

Table 1. Characteristics of included studies

Study	Publication year	Study design	Blinding	Country	No. of participants	Intervention group	Comparison group	Follow-up period	Implant	Robotic arm
Cho et al. (14)	2019	RCT	Not blinded	South Korea	351	Robotic TKA	Conventional TKA	11 years	NexGen	ROBODOC® system
Wang et al. (24)	2024	RCT	Double blind	China	113	Individualized alignment group TKA	Default alignment group TKA	3 months	KUNWU-TKA	KUNWU-TKA system
Batailler et al. (21)	2023	RCT	Not blinded	United States	66	Robotic UKA	Conventional UKA	6.5±0.7 months	Journey II Uni	BlueBelt Navio image-free robotic surgical system
Gilmour et al. (23)	2018	RCT	Single blinded	UK	139	Robotic UKA	Conventional UKA	2 years	Restoris MCK	Mako robotic-arm interactive orthopedic system
Blyth et al. (22)	2021	RCT	Double blind	UK	139	Robotic UKA	Conventional UKA	3 months-1 years	Restoris MCK	Mako robotic arm-assisted system
Yuan et al. (19)	2024	RCT	Single blinded	China	60	Robotic TKA	Conventional TKA	1 year	Cemented posterior stabilized (PS)	YUANHUA-TKA robot
Tian et al. (18)	2023	RCT	Not mentioned	China	144	Robotic TKA	Conventional TKA	3 months	Zimmer Biomet	Hangzhou Jianjia Robot
Yuan et al. (20)	2021	RCT	Single blinded	China	60	Robotic TKA	Conventional TKA	3 months	YUANHUA-TKA	YUANHUA-TKA system
Adamska et al. (13)	2023	RCT	Triple blinded	Poland	215	Robotic TKA	Conventional TKA	1 year	Journey II prosthesis	NAVIO and CORI robotic systems
Thiengwittayaporn et al. (17)	2021	RCT	Single blinded	Thailand	152	Robotic TKA	Conventional TKA	Not mentioned	Legion® PS	NAVIO® system
Lychagin et al. (16)	2022	RCT	Double blind	United States	68	Robotic TKA	Conventional TKA	1 year	TSolution-one	TSolution-one robot
Li et al. (15)	2022	RCT	Single blinded	China	150	Robotic TKA	Conventional TKA	3 months	Legion system	HURWA-ROBOT technology

RCT: Randomized controlled trials, TKA: Total knee arthroplasty, UKA: Unicompartmental knee arthroplasty.

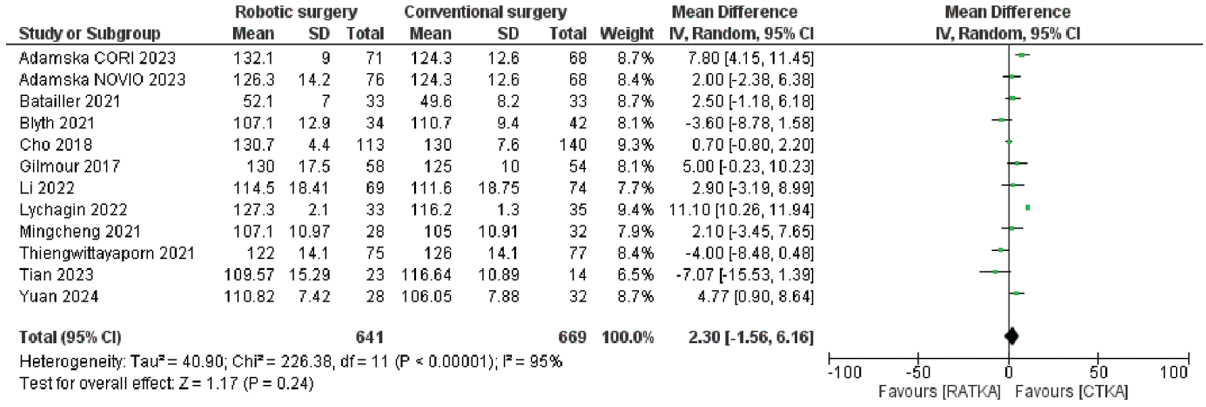

Figure 4. Forest plot for comparison of robotic and conventional technique for ROM.

CI: Confidence interval, SD: Standard deviation, IV: Intravenous, ROM: Range of motion

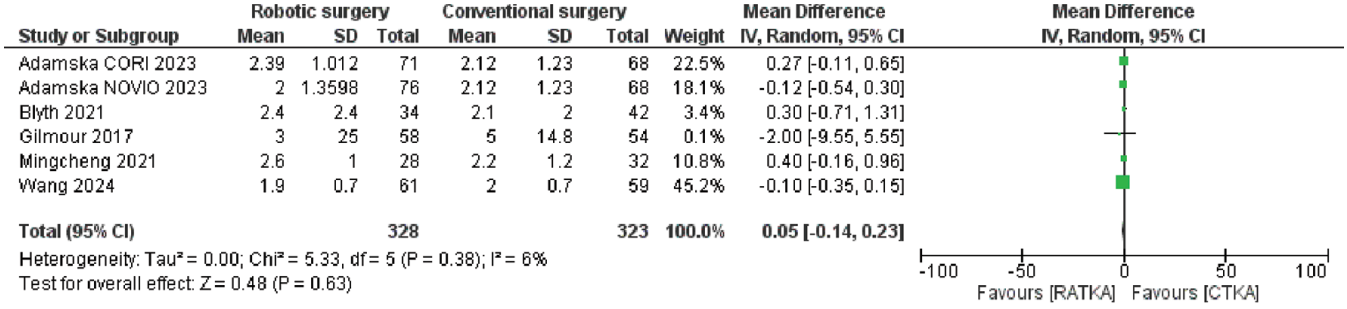

Figure 5. Forest plot for comparison of robotic and conventional technique for VAS for pain.

CI: Confidence interval, SD: Standard deviation, IV: Intravenous, VAS: Visual analogue scale

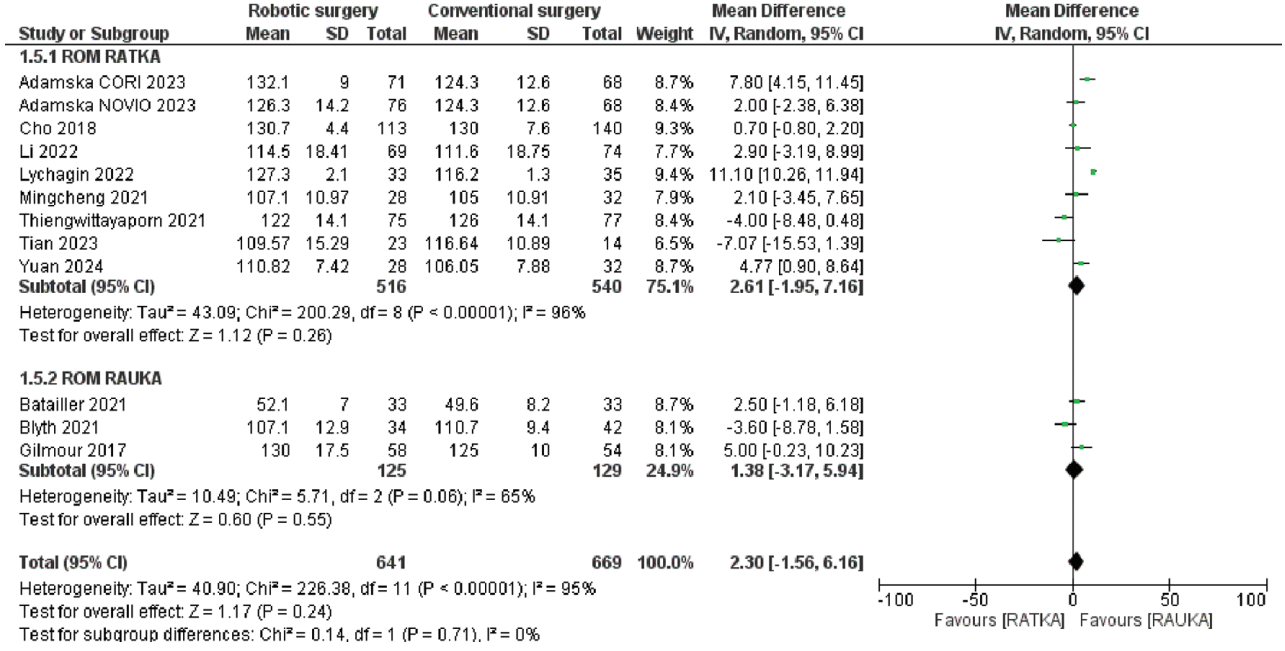

Figure 6. Forest plot of sub-group analysis for ROM.

CI: Confidence interval, SD: Standard deviation, IV: Intravenous, ROM: Range of motion

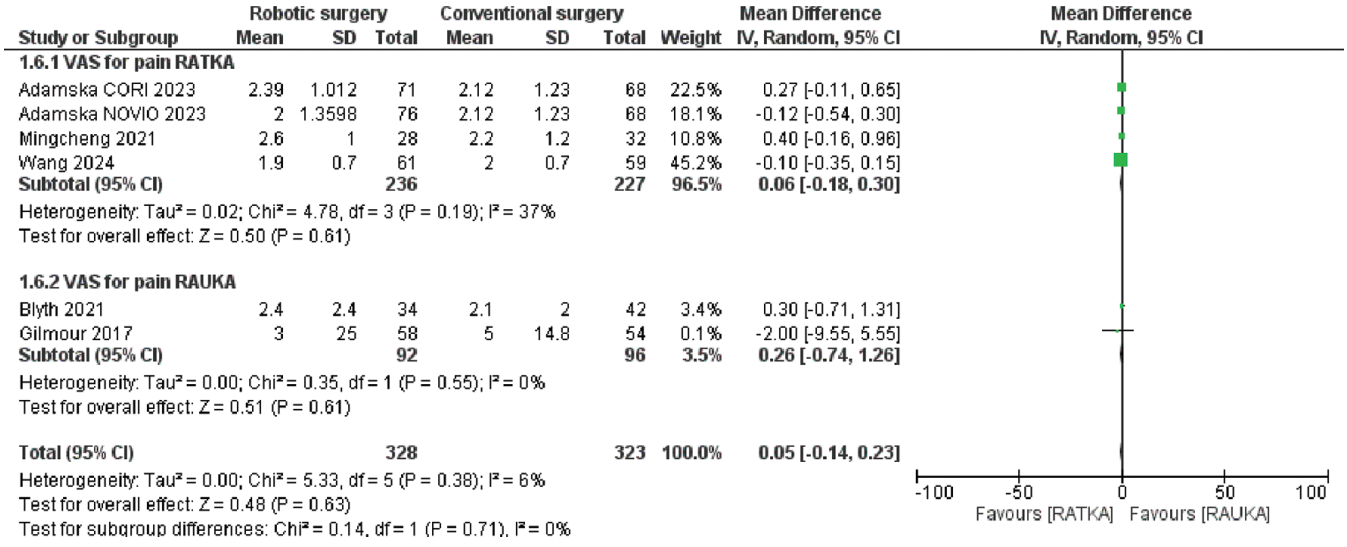

Figure 7. Forest plot of sub-group analysis for VAS for pain.

CI: Confidence interval, SD: Standard deviation, IV: Intravenous, VAS: Visual analogue scale

Table 2. Results for outcomes

Study	Outcome	Robotic surgery		Conventional surgery		Mean difference	CI at 95%
		Events/SD	Total	Events/SD	Total		
Cho et al. (14)	Range of motion	130.7 (4.4)	113	130.0 (7.6)	140	0.7	[-0.80, 2.20]
Batailler et al. (21)	Range of motion	52.1±7 [40;67]	33	49.6±8.2 [33.8;69.5]	33	2.5	[-1.18, 6.18]
Gilmour et al. (23)	Range of motion	130.0 (17.5)	58	125.0 (10.0)	54	5	[-0.23, 10.23]
	PVAS	3.0 (25.0)	58	5.0 (14.8)	54	-2	[-9.55, 5.55]
Blyth et al. (22)	Range of motion	107.1 (12.9) UKA	34	110.7 (9.4) TKA	42	-3.6	[-8.78, 1.58]
	PVAS	2.4 (2.4)	34	2.1 (2.0)	42	0.3	[-0.71, 1.31]
Yuan et al. (19)	Range of motion	110.82 (7.42)	28	106.05 (7.88)	32	4.77	[0.90, 8.64]
Tian et al. (18)	Range of motion	109.57±15.29	23	116.64±10.89	14	-7.07	[-15.53, 1.39]
Yuan et al. (20)	Range of motion	107.10±10.97	28	105.00±10.91	32	2.1	[-3.45, 7.65]
	PVAS	2.6±1.0	28	2.2±1.2	32	0.4	[-0.16, 0.96]
Adamska et al. (13)	Range of motion	126.3±14.2	76	124.3±12.6	68	2	[-2.38, 6.38]
	PVAS	2±1.3598	76	2.12±1.23	68	-0.12	[-0.54, 0.30]
Adamska CORI 2023	Range of motion	132.1±9.0	71	124.3±12.6	68	7.8	[4.15, 11.45]
	PVAS	2.39±1.012	71	2.12±1.23	68	0.27	[-0.11, 0.65]
Thiengwittayaporn et al. (17)	Range of motion	122.0 (14.1)	75	126.0 (14.1)	77	-4	[-8.48, 0.48]
Lychagin et al. (16)	Range of motion	(127.3±2.1°)	33	(116.2±1.3°)	35	11.1	[10.26, 11.94]
Li et al. (15)	Range of motion	114.5 (18.41)	69	111.6 (18.75)	74	2.9	[-3.19, 8.99]
Wang et al. (24)	PVAS	1.9±0.7	61	2.0±0.7	59	-0.1	[-0.35, 0.15]

CI: Confidence interval, SD: Standard deviation, PVAS: Visual analogue scale for pain, TKA: Total knee arthroplasty.

of ROM and pain are not clearly superior. It is also important to note that the idea that robotic surgery reduces the need for surgical skill should be viewed with caution. In practice, robotic-assisted arthroplasty requires dedicated training and experience. Many early-career orthopedic surgeons may not yet be skilled in using robotic systems. Therefore, both conventional and robotic techniques require a high level of surgical expertise, though the skills needed may differ.

This study is also the first to directly compare RA-TKA and RA-UKA. While both robotic techniques showed similar outcomes, the high heterogeneity found in the ROM subgroup analysis highlights the differences among the included studies in terms of design, patient characteristics, and surgical methods.

Implications

The findings of this study have important implications for both clinical practice and future research. RA-TKA and RA-UKA offers a viable alternative to conventional techniques, especially in hospitals where robotic systems are already part of the surgical process. The similar outcomes between RA-TKA and RA-UKA suggest that either technique can be chosen based on the patient's specific condition and the surgeon's familiarity with the method, without expecting a clear clinical advantage.

For healthcare systems, adopting robotic technology in orthopedic surgery requires careful consideration of cost-effectiveness, the learning curve for surgeons, and institutional training programs. As robotic systems continue to improve, future efforts should focus not only on technological development but also on strong training pathways to help surgeons use these systems safely and effectively. Standardizing surgical protocols and including patient-reported outcomes will also be important for understanding the real-world benefits of robotic surgery.

Study Limitations

This study has several limitations that should be acknowledged. First, there was significant variability among the included studies, which contributed to the high heterogeneity observed in the ROM analysis. Second, the number of studies directly comparing RA-TKA and RA-UKA was limited, which made it difficult to draw strong conclusions about which technique is more effective. Third, many of the included studies had a moderate to high risk of bias, highlighting the need for better-designed trials with standardized methods and proper blinding. Lastly, the outcomes analyzed in this study ROM and VAS for pain do not fully reflect other important clinical and functional aspects of robotic knee arthroplasty, such as alignment accuracy, implant longevity, or patient-reported satisfaction.

CONCLUSION

RA-TKA shows clinical outcomes similar to those of conventional methods in terms of ROM motion and pain reduction. Subgroup analysis further supports that RA-TKA and RA-UKA provide comparable results, making both techniques suitable options for the surgical treatment of knee OA. While robotic methods may offer greater precision, they also come with a steep learning curve and require specialized training an important consideration, especially for early-career orthopedic surgeons who may not yet have hands-on experience with robotic systems. Therefore, the choice between RA-TKA and RA-UKA should be based on individual patient needs, the surgeon's expertise, and the resources available at the healthcare institution.

Future research should aim to overcome the current limitations by conducting high-quality RCTs with larger sample sizes and standardized protocols. It will also be important to explore the long-term outcomes of robotic knee arthroplasty to better understand its potential benefits and support its wider adoption in clinical practice.

Ethics

Ethics Committee Approval: There is no need for ethical approval as this study does not involve primary data collection from human participants and is a systematic review and meta-analysis of published data.

Informed Consent: Not necessary.

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Footnotes

Author Contributions

Concept - S.B.R., N.U.; Design - S.B.R., N.U.; Data Collection or Processing - N.U., M.T., Y.A., S.T., H.N.T.; Analysis or Interpretation - S.B.R., N.U., S.T., N.A., H.N.T.; Literature Search - S.B.R., N.U., Y.A.; Writing - S.B.R., M.T.

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ORIGINAL ARTICLE
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Genetic profiling and pathway analysis in bladder carcinoma: Implications for therapeutic targeting

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ABSTRACT

Objective: Bladder carcinoma represents a significant challenge in oncology due to its heterogeneous molecular nature. This study aimed to identify key genetic factors and molecular pathways involved in bladder carcinoma pathogenesis to facilitate the development of targeted therapies.

Material and Methods: The top 30 genes associated with bladder carcinoma were retrieved from the disease gene network database. Comprehensive bioinformatic analysis was performed using various enrichment tools, including gene ontology biological process, cellular component, molecular function analyses, and pathway mapping through WikiPathways and metabolite associations through human metabolome database. Drug interactions were evaluated using DrugMatrix data.

Results: Gene ontology analysis revealed significant enrichment of cancer-related biological processes, cellular components, and molecular functions. Pathway analysis identified strong associations with head and neck squamous cell carcinoma, cancer pathways, pleural mesothelioma, endometrial cancer, and bladder cancer pathways. Key genes including *CDKN2A*, *PTEN*, *EGFR*, *PIK3CA*, *HRAS*, *FGFR3*, and *TP53* were implicated across multiple pathways. Metabolite analysis showed significant associations with phosphatidylinositol derivatives, highlighting the importance of the PI3K pathway. Drug interaction analysis revealed potential modulatory effects of several compounds including sertraline, valproic acid, and hydroxyurea on gene expression patterns in bladder carcinoma.

Conclusion: This study provides comprehensive insights into the molecular underpinnings of bladder carcinoma, highlighting interconnected pathways and potential therapeutic targets. The significant overlap with other cancer types suggests common oncogenic mechanisms that could be exploited for therapeutic intervention. Further validation of these findings in clinical samples may facilitate the development of personalized treatment approaches for bladder carcinoma patients.

Keywords: Bladder carcinoma, gene expression, pathway analysis, therapeutic targets, molecular oncology

INTRODUCTION

Bladder carcinoma represents one of the most common malignancies of the urinary tract, with significant morbidity and mortality worldwide (1). According to global cancer statistics, bladder cancer ranks as the tenth most commonly diagnosed cancer, with an estimated 573,000 new cases and 213,000 deaths annually (2). The disease disproportionately affects males, with a male-to-female ratio of approximately 3:1, and incidence rates vary significantly across different geographical regions (3).

The etiology of bladder carcinoma involves complex interactions between genetic and environmental factors. Established risk factors include tobacco smoking, occupational exposure to aromatic amines, arsenic in drinking water, and chronic urinary tract infections (4). Additionally, genetic predisposition plays a crucial role in determining individual susceptibility to the disease (5). Understanding the interplay between these factors is essential for developing effective preventive and therapeutic strategies.

From a pathological perspective, bladder carcinomas are classified into two major categories: Non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) (6). NMIBC accounts for approximately 75% of cases at initial diagnosis and is generally associated with better prognosis, although recurrence rates remain high (7). In contrast, MIBC represents a more aggressive form with poorer outcomes and higher risk of metastasis, necessitating more aggressive treatment approaches (8).

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Despite advances in diagnostic techniques and treatment modalities, the management of bladder carcinoma remains challenging, with limited improvement in survival rates over the past decades (9). Conventional treatment options include surgery, intravesical therapy, chemotherapy, and radiation therapy, each with its own limitations and side effects (10). Recent developments in targeted therapies and immunotherapies have shown promise, but their efficacy varies significantly among patients, highlighting the need for better understanding of the underlying molecular mechanisms (11).

Molecular characterization has revealed distinct genomic alterations associated with bladder carcinoma, including mutations in tumor suppressor genes such as tumor protein p53 (*TP53*) and *RB1*, as well as oncogenes like *FGFR3* and *RAS* family members (12). These genetic alterations contribute to dysregulation of critical cellular processes, including cell cycle control, apoptosis, and DNA damage response, ultimately leading to tumor development and progression (13).

Recent advances in high-throughput genomic technologies have enabled comprehensive profiling of bladder carcinomas, revealing complex molecular landscapes and potential therapeutic targets (14). Integrated analyses of genomic, transcriptomic, and proteomic data have identified distinct molecular subtypes with different clinical behaviors and treatment responses (15). Furthermore, epigenetic alterations, including DNA methylation and histone modifications, have emerged as important regulators of gene expression in bladder cancer, adding another layer of complexity to the disease (16).

Understanding the intricate network of signaling pathways involved in bladder carcinogenesis is crucial for identifying potential therapeutic targets (17). Key pathways implicated in bladder cancer development include phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR, MAPK, WNT/β-catenin, and JAK/STAT signaling, which regulate various cellular functions such as proliferation, survival, and invasion (18). Targeting these pathways represents a promising approach for developing novel therapeutic strategies with improved efficacy and reduced toxicity (19).

In this study, we aimed to comprehensively analyze the genetic and molecular landscape of bladder carcinoma by examining the top 30 genes associated with the disease from the disease gene network (DisGeNET) database (20). Through detailed pathway analysis, gene ontology (GO) enrichment, and exploration of metabolite and drug interactions, we sought to identify key molecular mechanisms and potential therapeutic targets for bladder carcinoma.

Objectives

1. To identify and characterize the key genetic factors associated with bladder carcinoma through comprehensive bioinformatic analysis of DisGeNET data.

2. To elucidate the significant biological processes, cellular components, and molecular functions associated with bladder carcinoma-related genes using GO enrichment analysis.

3. To map the molecular pathways implicated in bladder carcinoma pathogenesis and identify potential points of therapeutic intervention.

4. To explore associations between bladder carcinoma genes and metabolites, as well as drug interactions, to facilitate the development of targeted therapeutic approaches.

MATERIAL and METHODS

Data Acquisition

The top 30 genes associated with bladder carcinoma were retrieved from the DisGeNET database (https://www.disgenet.org/). DisGeNET is a comprehensive platform that integrates information on gene-disease associations from various expert-curated databases and text-mining-derived associations. The selection of genes was based on the association score provided by DisGeNET, which considers various factors including the number and type of sources supporting the gene-disease association and the number of publications.

GO Enrichment Analysis

GO enrichment analysis was performed to identify the biological processes, cellular components, and molecular functions associated with the selected genes. The analysis was conducted using the GO_Biological_Process_2023, GO_Cellular_Component_2023, and GO_Molecular_Function_2023 databases. The enrichment analysis identified statistically significant associations between the gene set and specific GO terms.

The statistical significance of enrichment was calculated using a hypergeometric test, which compares the observed overlap between the gene set and each GO term to the expected overlap by chance. The resulting p-values were adjusted for multiple testing using the Benjamini-Hochberg method to control the false discovery rate (FDR). Terms with adjusted p-values less than 0.05 were considered statistically significant. The results were visualized as bar graphs depicting the -log10 (adjusted p-value) for each significant term.

Pathway Analysis

To identify the signaling pathways and biological networks associated with bladder carcinoma, the gene set was analyzed using the WikiPathways_2024 database. WikiPathways is a community-curated resource of biological pathways that provides comprehensive coverage of various biological processes and disease mechanisms.

The pathway enrichment analysis was performed using a similar approach to the GO enrichment analysis, with statistical

significance determined by a hypergeometric test and p-values adjusted using the Benjamini-Hochberg method. For each significantly enriched pathway, the analysis provided information on the overlap (number of genes from the input set that are part of the pathway), p-value, adjusted p-value, odds ratio, combined score, and the specific genes involved.

Subcellular Localization Analysis

To understand the subcellular distribution of the bladder carcinoma-associated genes, enrichment analysis was performed using the Jensen_COMPARTMENTS database. This database provides information on protein localization based on experimental evidence, annotations, and predictions. The analysis identified cellular compartments where the proteins encoded by the selected genes are significantly enriched, offering insights into their functional roles within the cell.

Tissue Expression Analysis

Tissue-specific expression patterns of the bladder carcinoma-associated genes were examined using the Jensen_TISSUES database. This analysis helped identify tissues where the selected genes are predominantly expressed, providing context for their role in bladder carcinoma pathogenesis and potential implications for tissue-specific therapeutic targeting.

Transcription Factor Analysis

The regulatory mechanisms governing the expression of bladder carcinoma-associated genes were investigated using the ChIP-X Enrichment Analysis (ChEA_2022) database. This analysis identified transcription factors that significantly regulate the expression of the selected genes, offering insights into the upstream regulatory networks involved in bladder carcinoma.

Metabolite Association Analysis

To explore the metabolic aspects of bladder carcinoma, the gene set was analyzed for associations with specific metabolites using the human metabolome database (HMDB) database. The HMDB provides detailed information on small molecule metabolites found in the human body. This analysis identified metabolites that are significantly associated with the selected genes, suggesting potential metabolic alterations in bladder carcinoma.

Drug Interaction Analysis

The potential interactions between the bladder carcinoma-associated genes and various drugs were examined using the DrugMatrix database. This analysis identified drugs that significantly modulate the expression of the selected genes, offering insights into potential therapeutic agents for bladder carcinoma. The results included information on the drug name, concentration, vehicle, organism, tissue, treatment duration, direction of gene expression change (up or down), and the specific genes affected.

Data Visualization and Interpretation

The results of the various analyses were visualized using bar graphs and tables to facilitate interpretation. The bar graphs depicted the -log10 (adjusted p-value) for each significant term, facilitating the comparison of the statistical significance of different terms. The tables provided detailed information on each significant finding, including the specific genes involved.

The interpretation of the results focused on identifying key biological processes, pathways, and potential therapeutic targets relevant to bladder carcinoma. Particular attention was given to patterns and commonalities across different analyses, as well as to findings with strong statistical significance and biological relevance. The results were contextualized within the current understanding of bladder carcinoma biology and compared with findings from previous studies to identify novel insights and confirm established knowledge.

Statistical Analysis

Combining R version 4.0.1 with many Bioconductor programs guarantees thorough data evaluation by means of statistical analysis. Using the limma program, which performed empirical Bayes moderation to enhance variance estimates across genes, genes with a modified p-value of 0.05 and an absolute log2 fold change ≥1 were regarded as significant, and differentially expressed genes were discovered. Hierarchical clustering heatmaps and volcano plots created using ggplot2 and pheatmap, respectively helped visualize patterns of gene expression. Functional enrichment studies for GO and KEGG pathways were conducted using the clusterProfiler software with the Benjamini-Hochberg correction to control the FDR at 5%. Furthermore, a protein-protein interaction network built utilizing STRING database data was shown in Cytoscape, and a statistically significant evaluation based on enrichment p-values was presented. Using TARGETSCAN and MIRBASE, microRNA-target interactions were evaluated. Metabolomic pathway enrichment was done with Enrichr and MetaboAnalyst 6.0, where enrichment statistics, including p-values and adjusted p-values, were computed and visualized using bubble plots based on -log10 transformation of the p-values.

RESULTS

GO Analysis

GO biological process analysis (Figure 1)

GO analysis for biological processes revealed significant enrichment of pathways crucial for cancer development and progression. The top enriched terms included processes related

to cell proliferation, signal transduction, apoptosis regulation, and response to external stimuli. These findings suggest that the selected bladder carcinoma-associated genes are primarily involved in cellular processes that regulate growth, survival, and response to environmental factors, which are critical aspects of cancer biology.

4.1.2 GO cellular component analysis (Figure 2)

Analysis of cellular components showed significant enrichment of terms related to membrane structures, cytoplasmic components, and nuclear regions. The enrichment of membrane components suggests that many bladder carcinoma-associated proteins are involved in cell-cell interactions, signal transduction, and membrane-bound receptor functions. The presence of both cytoplasmic and nuclear components indicates the involvement of these genes in diverse cellular processes spanning multiple compartments.

4.1.3 GO molecular function analysis (Figure 3)

The molecular function analysis revealed significant enrichment of terms related to protein binding, kinase activity, transcription factor activity, and receptor function. These findings highlight the diverse functional roles of bladder carcinoma-associated genes, particularly in signalling pathways, gene regulation, and cellular response mechanisms.

4.2 Pathway Analysis (Table 1)

The WikiPathways analysis identified multiple significantly enriched pathways associated with bladder carcinoma genes (Table 1). The most significantly enriched pathway was "head and neck squamous cell carcinoma" (adjusted p-value $=3.09\times10^{-27}$), with 15 out of 30 genes mapping to this pathway. Other significantly enriched pathways included "cancer pathways" (20/30 genes, adjusted p-value $=3.51\times10^{-23}$), "pleural mesothelioma" (18/30 genes, adjusted p-value $=7.36\times10^{-18}$), "endometrial cancer" (11/30 genes, adjusted p-value $=5.60\times10^{-13}$), and notably "bladder cancer" (9/30 genes, adjusted p-value $=1.37\times10^{-10}$).

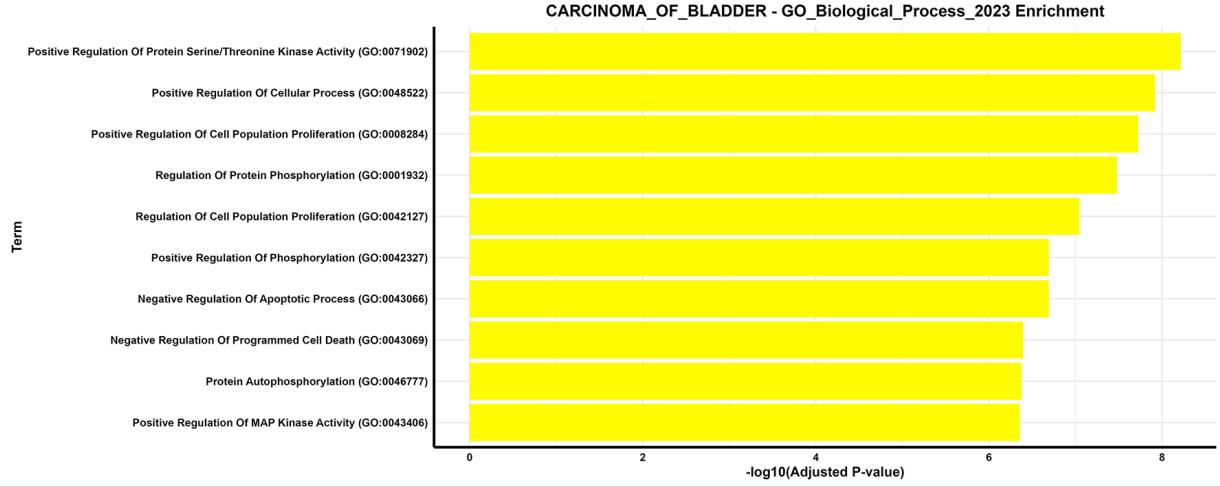

Figure 1. This bar graph for GO_Biological_Process_2023 depicts the relationship between -log10 (adjusted p-value) and terms as listed.

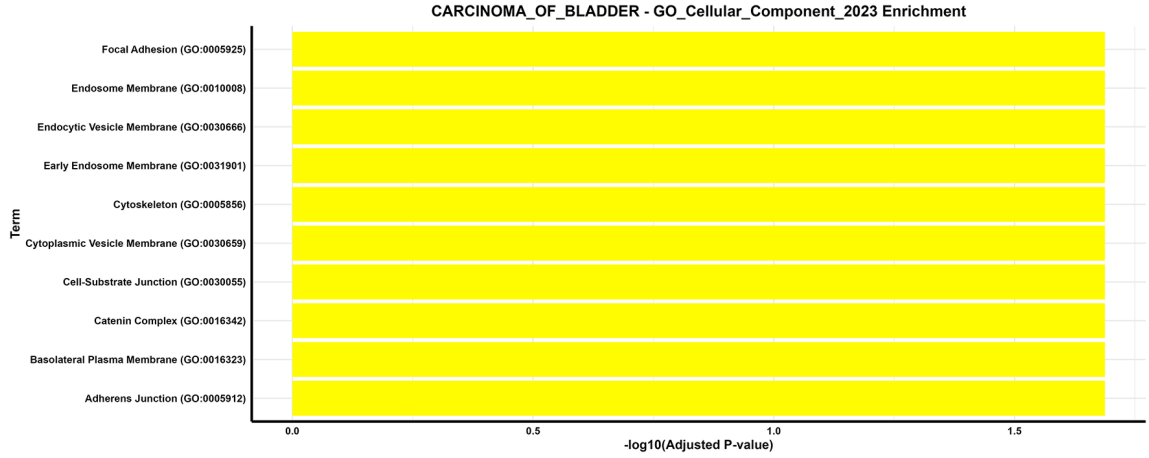

Figure 2. The bar graph for GO_Cellular_Component_2023 demonstrates -log10 (adjusted p-value) versus terms arranged sequentially.

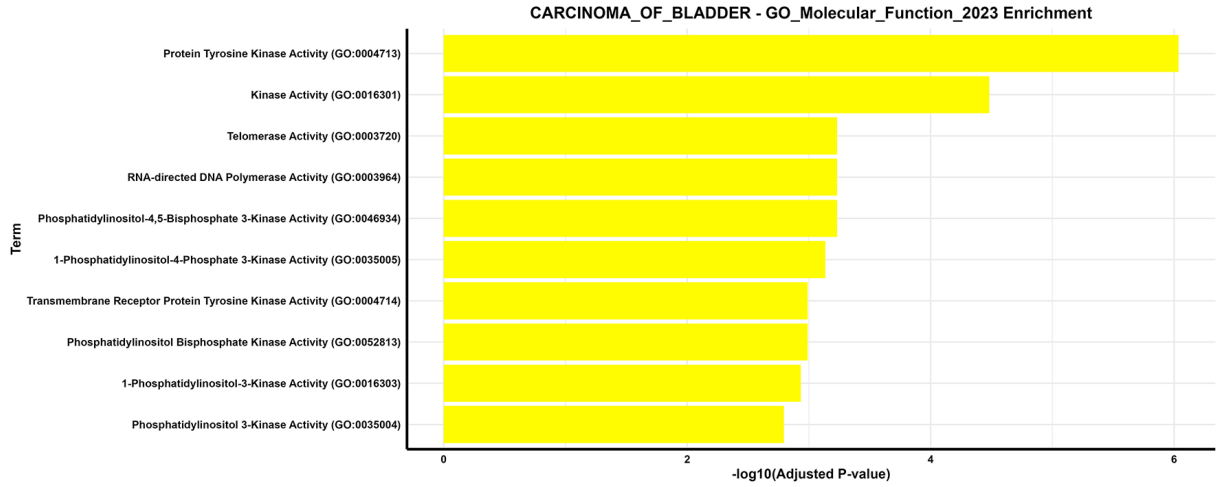

Figure 3. GO_Molecular_Function_2023 is illustrated with a bar graph that maps -log10 (adjusted p-value) against terms.

Table 1. Presented here is a table for WikiPathways_2024_

Term	Overlap	p-value	Adjusted p-value	Old p-value	Old adjusted p-value	Odds ratio	Combined score	Genes
Head and neck squamous cell carcinoma WP4674	15/73	0.0000000000000000000008668776	0.0000000000000000003094753	0	0	343.31034	22,973.582	*CDKN2A;PTEN;EGFR;PIK3CG;MTOR;VEGFA;TERT;CCND1;PIK3CA;ERBB2;AKT1;CTNNB1;HRAS;FGFR3;TP53*
Cancer pathways WP5434	20/507	0.0000000000000000001967454978 99	0.0000000000000000000351190 71375	0	0	80.01232	4,551.732	*GSTM1;CDKN2A;WNT5A;PTEN;EGFR;MTOR;VEGFA;AR;TERT;CCND1;PIK3CA;CDH1;ERBB2;AKT1;BIRC5;CTNNB1;HRAS;FGFR3;TP53;WNT3*
Pleural mesothelioma WP5087	18/437	0.0000000000000000006182996077 0625	0.0000000000000000000735776 5331704	0	0	69.99165	3,579.209	*CD274;CDKN2A;WNT5A;PTEN;EGFR;PIK3CG;MTOR;VEGFA;TERT;CCND1;PIK3CA;CDH1;AKT1;CTNNB1;HRAS;FGFR3;TP53;WNT3*
Endometrial cancer WP4155	11/63	0.0000000000000000000062763670913309 70	0.0000000000000000000560165762901289	0	0	221.75911	10,315.678	*CCND1;PIK3CA;CDH1;ERBB2;PTEN;AKT1;CTNNB1;HRAS;FGFR3;TP53;EGFR*
DNA damage response only ATM dependent WP710	12/109	0.0000000000000000000293032287856619 02	0.0000000000000000000209225053 5296260	0	0	136.58419	6,143.091	*CCND1;PIK3CA;CDKN2A;ERBB2;WNT5A;PTEN;AKT1;CTNNB1;HRAS;TP53;PIK3CG;WNT3*
Breast cancer pathway WP4262	12/154	0.0000000000000000000215568135258803 9960	0.0000000000000000000126304047 8987992	0	0	93.08920	3,786.722	*CCND1;PIK3CA;ERBB2;WNT5A;PTEN;AKT1;CTNNB1;HRAS;TP53;EGFR;WNT3;MTOR*
Bladder cancer WP2828	9/40	0.0000000000000000000269530385252110 0024	0.0000000000000000001374604964785760 01	0	0	275.65438	11,151.604	*CCND1;CDH1;CDKN2A;ERBB2;HRAS;FGFR3;TP53;EGFR;VEGFA*

Table 1. Continued

Term	Overlap	p-value	Adjusted p-value	Old p-value	Old adjusted p-value	Odds ratio	Combined score	Genes
Gastrin signaling WP4659	11/115	0.000000000000000006931725707981400161	0.000000000000000030932825971867002 2	0	0	110.59008	4,369.461	*CCND1;PIK3CA;CDH1;CDKN2A; AKT1;BIRC5;CTNNB1;HRAS;EGFR; MTOR;VEGFA*
Glioblastoma signaling WP2261	10/82	0.000000000000000021363986678023000982	0.000000000000000084743813822 8244992	0	0	138.18056	5,304.036	*CCND1;PIK3CA;CDKN2A;ERBB2; PTEN;AKT1;HRAS;TP53;EGFR; PIK3CG*
EGFR tyrosine kinase inhibitor resistance WP4806	10/84	0.000000000000000027523047678472601241	0.000000000000000098257280212 1471009	0	0	134.43243	5,126.111	*CCND1;PIK3CA;ERBB2;PTEN; AKT1;HRAS;FGFR3;EGFR;MTOR; VEGFA*

Key genes that appeared across multiple pathways included *CDKN2A, PTEN, EGFR, PIK3CG, MTOR, VEGFA, TERT, CCND1, PIK3CA, ERBB2, AKT1, CTNNB1, HRAS, FGFR3*, and *TP53*. The high representation of these genes across different cancer pathways suggests common oncogenic mechanisms shared between bladder carcinoma and other cancer types.

The significant enrichment of DNA damage response pathways, particularly the "DNA damage response only ATM dependent" pathway (12/30 genes, adjusted p-value $=2.09\times10^{-12}$), highlights the importance of genomic instability in bladder carcinoma pathogenesis. Additionally, the presence of signalling pathways such as "gastrin signaling" and "EGFR tyrosine kinase inhibitor resistance" underscores the complexity of signalling networks involved in bladder carcinoma.

Subcellular Localization Analysis

The Jensen_COMPARTMENTS analysis indicated significant enrichment of bladder carcinoma-associated proteins in various cellular compartments. The results showed predominant localization in the cytoplasm, plasma membrane, and nucleus, consistent with the diverse functional roles of these proteins in cell signalling, gene regulation, and cellular architecture.

Tissue Expression Analysis (Figure 4)

Analysis of tissue expression patterns using Jensen_TISSUES revealed significant expression of bladder carcinoma-associated genes across multiple tissue types. In addition to the bladder tissue showed significant enrichment, other epithelial tissues also exhibited notable expression levels. This pattern suggests potential systemic effects of these genes beyond the primary site of carcinogenesis and may explain the comorbidities and secondary manifestations often observed in bladder carcinoma patients.

Transcription Factor Analysis (Figure 5)

The ChEA_2022 analysis identified several transcription factors that significantly regulate the expression of bladder carcinoma-

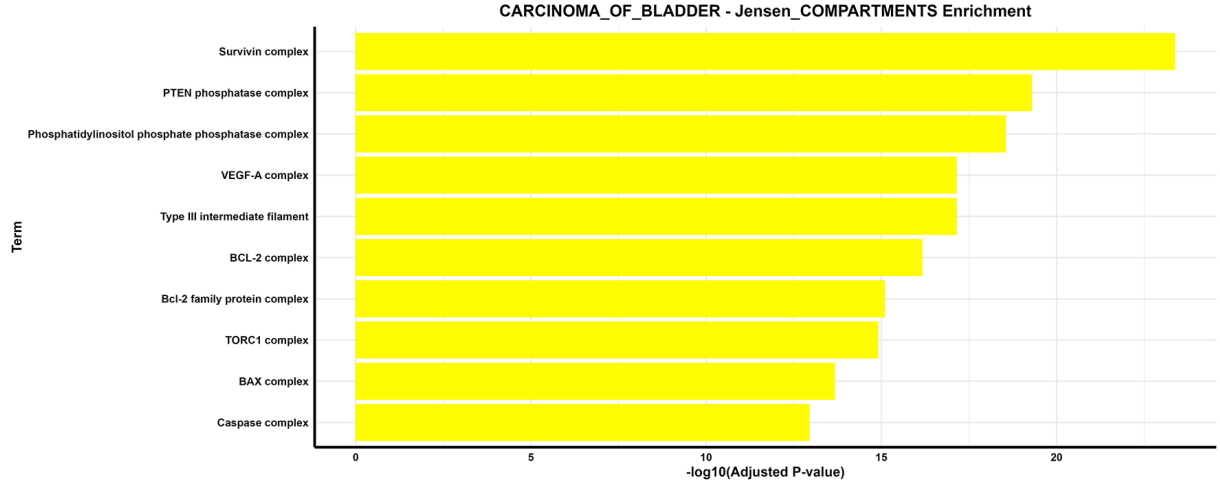

Figure 4A. The depicted bar graph for Jensen_COMPARTMENTS shows -log10 (adjusted p-value) plotted versus the ordered list of terms.

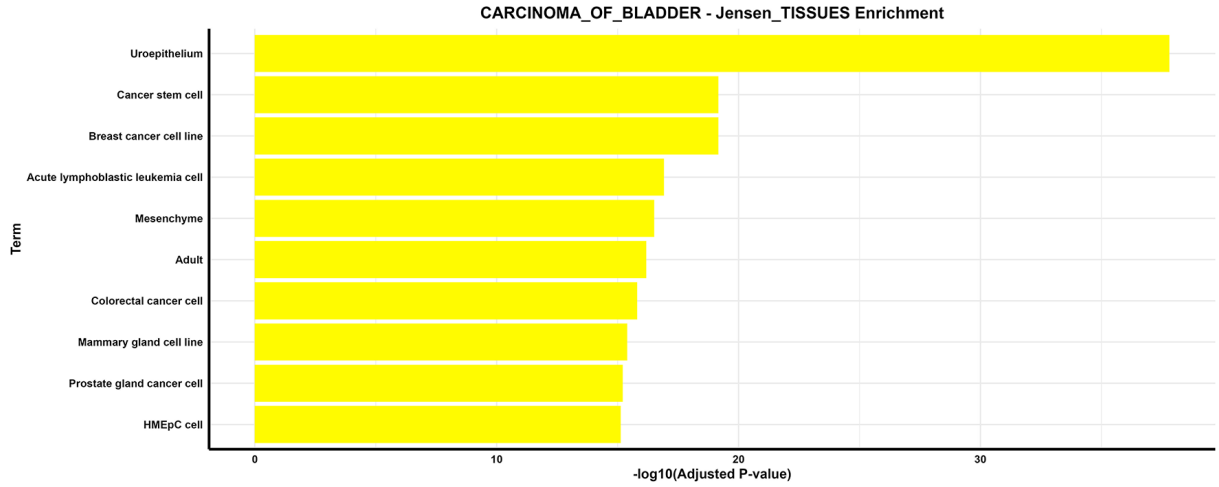

Figure 4B. The depicted bar graph for Jensen_TISSUES shows -log10 (adjusted p-value) plotted versus the ordered list of terms.

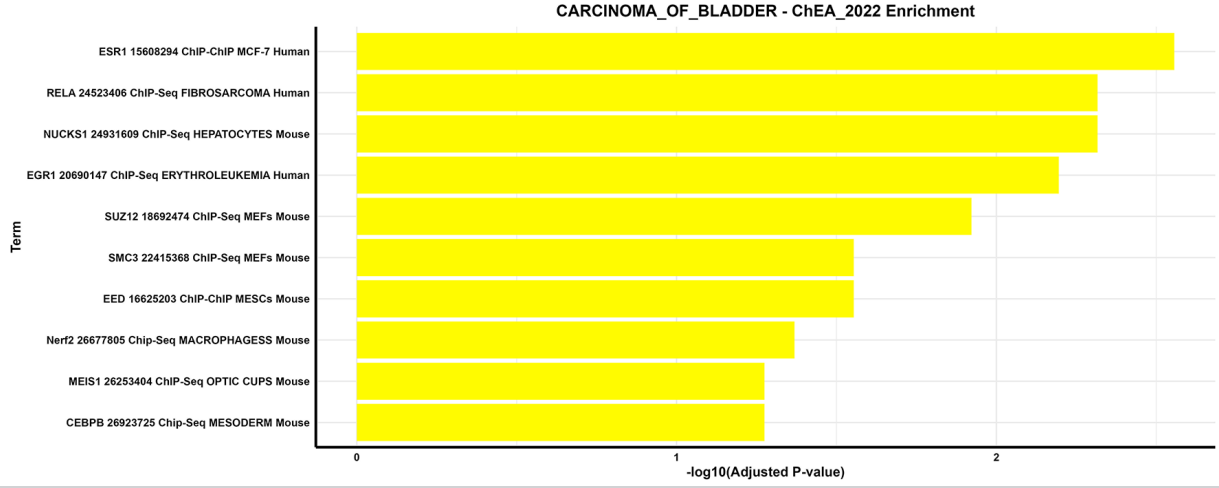

Figure 5. The depicted bar graph for ChEA_2022 shows -log10 (adjusted p-value) plotted versus the ordered list of terms.

associated genes. These transcription factors represent potential upstream regulators in bladder carcinoma pathogenesis and may serve as novel therapeutic targets for modulating the expression of key oncogenes and tumor suppressor genes.

Metabolite Association Analysis (Table 2)

The HMDB_Metabolites analysis revealed significant associations between bladder carcinoma genes and various metabolites, particularly phosphatidylinositol derivatives (Table 2). The most significantly associated metabolite was C11H19O13P (HMDB06953), with an adjusted p-value of 0.00023 and an odds ratio of 92.34, with three genes (*PIK3CA, PTEN, PIK3CG*) showing significant association. Other significantly associated metabolites included various phosphatidylinositol species such as PI(16:0/16:1(9Z)) and PI(16:0/18:1(9Z)).

The consistent association with phosphatidylinositol derivatives highlights the importance of the PI3K pathway in bladder carcinoma. This pathway is known to regulate cell growth, proliferation, survival, and motility, and its dysregulation is a common feature in many cancer types, including bladder carcinoma.

Drug Interaction Analysis (Table 3)

The DrugMatrix analysis identified several drugs that significantly modulate the expression of bladder carcinoma-associated genes (Table 3). Sertraline (23 µM) showed significant downregulation of five genes (*GSTM1, CDH1, AKT1, TTN, VEGFA*) with an adjusted p-value of 0.07 and an odds ratio of 13.34. Other drugs with significant gene expression modulation included valproic acid, stavudine, hydroxyurea, amoxicillin, pentobarbital, phenylhydrazine, chlortetracycline, and colistin.

The diverse range of drugs identified in this analysis, including antidepressants (sertraline), anticonvulsants (valproic acid), and antibiotics (amoxicillin, chlortetracycline), suggests potential off-target effects that could be exploited for bladder carcinoma treatment. Particularly interesting is the downregulation of genes like *AKT1*, *VEGFA*, and *EGFR*, which are key players in cancer signalling pathways and established therapeutic targets.

Table 2. Shown is a table for HMDB_Metabolites

Term	Overlap	p-value	Adjusted p-value	Old p-value	Old adjusted p-value	Odds ratio	Combined score	Genes
C11H19O13P (HMDB06953)	3/27	0.000008693467	0.0002323831	0	0	92.34259	1,076.0626	*PIK3CA;PTEN;PIK3CG*
1,2-dihexadecanoyl-sn-glycero-3-phospho-(1'-myo-inositol) (HMDB09778)	3/77	0.000206692166	0.0002323831	0	0	29.87387	253.4583	*PIK3CA;PTEN;PIK3CG*
PI(16:0/16:1(9Z)) (HMDB09779)	3/77	0.000206692166	0.0002323831	0	0	29.87387	253.4583	*PIK3CA;PTEN;PIK3CG*
C41H75O13P (HMDB09780)	3/77	0.000206692166	0.0002323831	0	0	29.87387	253.4583	*PIK3CA;PTEN;PIK3CG*
PI(16:0/18:0) (HMDB09781)	3/77	0.000206692166	0.0002323831	0	0	29.87387	253.4583	*PIK3CA;PTEN;PIK3CG*
PI(16:0/18:1(11Z)) (HMDB09782)	3/77	0.000206692166	0.0002323831	0	0	29.87387	253.4583	*PIK3CA;PTEN;PIK3CG*
PI(16:0/18:1(9Z)) (HMDB09783)	3/77	0.000206692166	0.0002323831	0	0	29.87387	253.4583	*PIK3CA;PTEN;PIK3CG*
PI(16:0/18:2(9Z,12Z)) (HMDB09784)	3/77	0.000206692166	0.0002323831	0	0	29.87387	253.4583	*PIK3CA;PTEN;PIK3CG*
PI(16:0/20:0) (HMDB09785)	3/77	0.000206692166	0.0002323831	0	0	29.87387	253.4583	*PIK3CA;PTEN;PIK3CG*
PI(16:0/20:2(11Z,14Z)) (HMDB09786)	3/77	0.000206692166	0.0002323831	0	0	29.87387	253.4583	*PIK3CA;PTEN;PIK3CG*

Table 3. The table presents DrugMatrix

Term	Overlap	p-value	Adjusted p-value	Old p-value	Old adjusted p-value	Odds ratio	Combined score	Genes
Sertraline-23 uM in DMSO-Rat-Primary rat hepatocytes-0.67d-dn	5/300	0.00007693805	0.07015019	0	0	13.33898	126.35365	*GSTM1;CDH1;AKT1; TTN;VEGFA*
Valproic Acid-1500 mg/kg in Water-Rat-Liver-3d-dn	5/307	0.00008577889	0.07015019	0	0	13.02517	121.96423	*GSTM1;CDH1;AKT1; EGFR;TTN*
Stavudine-58 mg/kg in Water-Rat-Liver-0.25d-dn	4/215	0.00028579270	0.07015019	0	0	14.40685	117.56344	*GSTM1;NUMA1; CDH1;TTN*
Hydroxyurea-400 mg/kg in Saline-Rat-Liver-1d-dn	4/221	0.00031731410	0.07015019	0	0	14.00425	112.81293	*GSTM1;CDH1;EGFR;V EGFA*
Amoxicillin-1100 mg/kg in Water-Rat-Liver-3d-dn	4/267	0.00064750804	0.07015019	0	0	11.52793	84.64245	*GSTM1;CDH1;EGFR; VEGFA*
Pentobarbital-20 mg/kg in Water-Rat-Liver-1d-dn	4/267	0.00064750804	0.07015019	0	0	11.52793	84.64245	*CDH1;EGFR;TTN; VEGFA*
Hydroxyurea-400 mg/kg in Saline-Rat-Liver-3d-dn	4/269	0.00066585467	0.07015019	0	0	11.43977	83.67549	*GSTM1;CDH1;EGFR; VEGFA*
Phenylhydrazine-78 mg/kg in Water-Rat-Liver-0.25d-dn	4/272	0.00069406357	0.07015019	0	0	11.30999	82.25695	*CDH1;EGFR;TTN; VEGFA*
Chlortetracycline-1500 mg/kg in CMC-Rat-Liver-5d-dn	4/273	0.00070365233	0.07015019	0	0	11.26737	81.79240	*GSTM1;CDH1;TTN; VEGFA*
Colistin-121 mg/kg in Water-Rat-Liver-5d-up	4/273	0.00070365233	0.07015019	0	0	11.26737	81.79240	*GSTM1;CDH1;EGFR; TTN*

DISCUSSION

This comprehensive analysis of bladder carcinoma-associated genes has provided valuable insights into the molecular underpinnings of this malignancy, revealing complex networks of genes, pathways, and potential therapeutic targets. The findings highlight the multifaceted nature of bladder carcinoma pathogenesis and offer several directions for future research and therapeutic development. The GO analysis revealed significant enrichment of biological processes related to cell proliferation, signal transduction, and response to external stimuli, consistent with the hallmarks of cancer (21). The involvement of these processes underscores the dysregulation of fundamental cellular functions in bladder carcinoma, contributing to uncontrolled growth, evasion of apoptosis, and altered response to environmental cues. Similarly, the enrichment of cellular components across various compartments, including membranes, cytoplasm, and nucleus, reflects the widespread impact of bladder carcinoma-associated genes on cellular architecture and function. These findings align with previous studies that have demonstrated the complex cellular alterations accompanying bladder carcinoma development and progression (22). One of the most striking observations from our pathway analysis is the significant overlap between bladder carcinoma and other cancer types, particularly head and neck squamous cell carcinoma, pleural mesothelioma, and endometrial cancer. This overlap suggests common oncogenic mechanisms that transcend tissue-specific boundaries, potentially offering opportunities for therapeutic approaches with broader applicability across multiple cancer types (23). Key genes implicated across numerous pathways include TP53, CDKN2A, PTEN, EGFR, PIK3CA, and HRas proto-oncogene, GTPase which represent central nodes in the oncogenic network and promising targets for therapeutic intervention. The involvement of these genes aligns with previous studies highlighting their crucial roles in bladder carcinoma pathogenesis (24). The significant enrichment of DNA damage response pathways, particularly the ataxia-telangiectasia mutated-dependent pathway, emphasizes the importance of genomic instability in bladder carcinoma development. This finding is consistent with the high mutation burden observed in bladder carcinoma, especially in patients with a history of tobacco exposure or occupational exposure to carcinogens (25). Targeting DNA damage response mechanisms represents a promising therapeutic strategy, as evidenced by the emerging role of poly(ADP-ribose) polymerase (PARP) inhibitors in various cancers with defects in DNA repair pathways (26). The metabolite association analysis revealed a strong link between bladder carcinoma genes and phosphatidylinositol derivatives, highlighting the central role of the PI3K pathway in this malignancy. The PI3K/AKT/mammalian target of rapamycin pathway is a key regulator of cell growth, proliferation, and survival, and its dysregulation is a common feature in many cancer types, including bladder carcinoma (27). The consistent association with phosphatidylinositol metabolites provides a metabolic perspective on this pathway and suggests potential opportunities for metabolic targeting in bladder carcinoma treatment. The drug interaction analysis identified several compounds that modulate the expression of bladder carcinoma-associated genes, offering insights into potential therapeutic repurposing opportunities. Particularly intriguing is the significant downregulation of cancer-related genes by drugs such as sertraline, valproic acid, and hydroxyurea, which are not conventionally used for cancer treatment. Sertraline, a selective serotonin reuptake inhibitor commonly used for depression and anxiety disorders, has shown anticancer properties in various preclinical studies, including inhibition of cell proliferation, induction of apoptosis, and modulation of signaling pathways (28). Similarly, valproic acid, an anticonvulsant and mood stabilizer, has demonstrated histone deacetylase inhibitor activity, which can alter gene expression patterns and exert anticancer effects (29). These findings suggest potential opportunities for drug repurposing in bladder carcinoma treatment, which could accelerate therapeutic development by leveraging existing drugs with established safety profiles. The transcription factor analysis identified key regulators of bladder carcinoma-associated genes, providing insights into the upstream control mechanisms governing gene expression in this malignancy. Targeting these transcription factors could offer a novel approach to modulating the expression of multiple oncogenes or tumor suppressor genes simultaneously, potentially enhancing therapeutic efficacy (30). This approach is particularly relevant in the context of bladder carcinoma, where complex genetic alterations often necessitate targeting multiple pathways for effective treatment. Our findings also have implications for personalized medicine approaches in bladder carcinoma management. The diverse molecular alterations observed in this study suggest that bladder carcinoma is not a homogeneous disease but rather a collection of molecularly distinct entities that may require tailored therapeutic strategies. This concept aligns with the emerging paradigm of molecular subtyping in bladder carcinoma, which has identified distinct subtypes with different clinical behaviors and treatment responses (31). Integrating the findings from our study with clinical and pathological features could facilitate the development of more precise prognostic and predictive models for bladder carcinoma patients. Despite these valuable insights, our study has several limitations that should be acknowledged. The analysis was based on data from the DisGeNET database, which, while comprehensive, may

not capture all relevant genes associated with bladder carcinoma. Additionally, the enrichment analyses provide statistical associations but do not necessarily establish causal relationships between genes, pathways, and bladder carcinoma. Furthermore, the drug interaction analysis was conducted using preclinical data, and the clinical relevance of these findings requires validation in appropriate models and eventually in clinical trials. Future studies should focus on validating these findings in larger cohorts of bladder carcinoma patients and exploring the functional significance of the identified genes and pathways in experimental models. Additionally, integrating multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, could provide a more comprehensive understanding of bladder carcinoma biology and facilitate the development of more effective therapeutic strategies (32).

Study Limitations

While the analysis that focused on the top 30 genes from the DisGeNET database provides valuable insights, it may not fully capture the molecular heterogeneity of bladder carcinoma. Additionally, drug interaction findings, particularly, those involving compounds like sertraline and valproic acid, are based on data from non-bladder tissues or animal models, necessitating validation in bladder-specific systems. The study also does not explore how the identified genes relate to established molecular subtypes of bladder cancer (e.g., luminal and basal), which limits the context for subtype-specific interpretation and therapeutic relevance.

CONCLUSION

This comprehensive bioinformatic analysis of bladder carcinoma-associated genes has revealed intricate networks of biological processes, signaling pathways, and potential therapeutic targets. The significant overlap with other cancer types suggests common oncogenic mechanisms that could be exploited for therapeutic intervention. Key genes including *CDKN2A*, *PTEN*, *EGFR*, *PIK3CA*, *HRAS*, *FGFR3*, and *TP53* emerged as central nodes in the bladder carcinoma gene network, representing promising targets for therapeutic development.

The metabolite association analysis highlighted the importance of the PI3K pathway in bladder carcinoma, offering a metabolic perspective on this key signaling network. The drug interaction analysis identified several compounds with potential off-target effects on bladder carcinoma-associated genes, suggesting opportunities for drug repurposing in bladder carcinoma treatment.

These findings contribute to a deeper understanding of bladder carcinoma biology and provide a foundation for future research aimed at developing more effective therapeutic strategies. Personalized medicine approaches that consider the molecular heterogeneity of bladder carcinoma may offer improved outcomes for patients with this challenging malignancy.

Ethics

Ethics Committee Approval: This is a bioinformatics manuscript involving secondary analysis. Henceforth, no ethical approval is required. However, we have followed the guidelines of the Declaration of Helsinki. Further, all the data sources were mentioned in the methodology.

Informed Consent: This study is based solely on publicly available data and does not involve human participants, animal subjects, or identifiable personal information.

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Footnotes

Author Contributions

Concept - U.S.A.; Design - U.S.A.; Data Collection or Processing - S.V.; Analysis or Interpretation - A.J.A., S.V.; Literature Search - A.J.A., S.V., U.S.A.; Writing - U.S.A.

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CASE REPORT
Turk J Surg 2025;41(4):448-451

Nipple adenoma; a literature review and our experience with a rare feature

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ABSTRACT

With this review, we aimed to contribute to the literature by reviewing the studies on nipple adenoma and presenting a novel study regarding its occurrence in a male case, for which we have not found any publications worldwide. We have reviewed studies on nipple adenoma, which we rarely encounter in the literature. We also present a 41-year-old male patient, whom we operated on with a diagnosis of nipple adenoma. His postoperative histopathological examination revealed invasive breast carcinoma, a unique case in the literature, together with this review study. Nipple adenoma, which is extremely rare in male patients, is rare in the literature and clinical practice. In light of the data, this case is the second instance of a male patient with nipple adenoma presented in the literature after many years. The fact that it is the only male patient associated with invasive carcinoma makes the case unique. Nipple adenomas require careful examination because they are rare and can be confused with malignancy. Moreover, although its association with malignancy is exceptionally rare, it should still be included in the differential diagnosis for male breast lesions. Safe surgery and postoperative follow-up are recommended.

Keywords: Nipple adenoma, male nipple adenoma, benign breast tumors, male breast cancer

INTRODUCTION

Nipple adenoma is a benign epithelial breast tumor originating from the ducts and isn't a precancerous lesion. It is almost always unilateral. This extremely rare tumor, which constitutes less than 1% of breast specimens, is mostly seen in women in the fourth and fifth decades and is exceptional in men and children. The time between the onset of symptoms and diagnosis varies, but is usually several years. Unilateral breast itching, pain, serous discharge, and crusting are the most common symptoms and can be clinically confused with Paget's disease (1,2). In addition, they suggest a malignant mass because they are observed as irregularly bordered and hypoechoic lesions on ultrasonography and as nodular density with unclear boundaries on mammography. It may be confused with atypical ductal hyperplasia, ductal carcinoma *in situ*, invasive ductal carcinoma, or adenosquamous carcinoma and although rare, it may also be associated with these. Following a preliminary clinical diagnosis based on the specific location and morphology of the tumor, the definitive diagnosis is made by histopathological examination (2-5). Immunohistochemical examinations for some markers such as p63, superior mesenteric artery, calponin, and estrogen receptor may also be required to distinguish it from an invasive or ductal carcinoma (6). Since it is known that the probability of recurrence is extremely low and the prognosis is excellent, excision in the treatment is sufficient to provide negative surgical margins. Unnecessary extensive surgeries are not recommended (4,7). However, since there is insufficient data on whether it is associated with carcinoma, postoperative follow-up is recommended (2).

We reviewed studies on nipple adenoma, a rare entity in the literature. We presented the case of a 41-year-old male patient who was operated on with a diagnosis of nipple adenoma, and whose postoperative histopathological examination revealed invasive breast carcinoma. This case is unique in the literature and is included in our review study.

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CASE REPORT

A 41-year-old male patient presented with hyperemia, protruding roughness of the nipple, and serous discharge in the left nipple for 9 months (Figure 1a). In ultrasonography, the volume of the left nipple has increased and is 6x9 mm; the nipple skin-subcutaneous tissues are eroded, and the nipple has a hypoechoic appearance with a diameter of 2.2 mm in the center. It suggests a dilated duct with dense content. There are no findings in the areola or retroareolar plane on mammography other than a distinct area in the left nipple (Figure 1b, c). Histopathological examination of the punch biopsy revealed nipple adenoma; immunohistochemical examination reported keratin 5/6 and P63 positive, Ki-67 10% (Figure 2). The patient underwent left nipple resection. Frozen section examination was performed to ensure resection with negative surgical margins to prevent recurrence. In the frozen examination, one side was ulcerated, with suspicious findings observed on the incision surface. Thereupon, considering the relatively low breast volume in the male patient, a mastectomy was performed to achieve extended excision, followed by a sentinel lymph node biopsy. The sentinel lymph node was negative for malignancy and the histopathological examination of the mastectomy specimen revealed an invasive breast carcinoma, 0.6x0.5x0.4 cm in size, with unifocal nipple localization, no special type (ductal) (pT1b, pN0, pMx), and the distance to the nearest surgical margin was reported as 4.5 cm. Histological grade 1, Mitotic score 1, ER 70% positive, PR 0% negative, human epidermal growth factor receptor-2 (Cerb B-2) 0 negative, Ki-67 20% positive. There is no indication for RT in the node-negative patient. Postoperative treatment and follow-up with Tamoxifen continue in cases of 6 mm tumor and Grade 1, and no complications or recurrence have been observed for more than 1 year.

DISCUSSION

Nipple adenoma is a rare benign condition that can be confused with Paget's disease of the breast (8). However, it can be confused with malignant lesions and although rare, some publications mention its association with carcinoma (9). In addition, as with other breast lesions, almost all adenomas are seen in women. This makes clinical suspicion difficult in male patients. In the nipple adenoma, which was first described in 1973, in the study published in 1986, consisting of 51 cases, which is still the largest case series known on this subject, in the study published in 2010, 19 cases encountered over 14 years were described, in the study published in 2014, 13 cases were presented, and in studies where 11 cases in 2021 and 12 cases in 2022 were presented, the patients are almost exclusively female (4,6,7,10-12). Finally, in 2023, Weigelt et al.'s (13) 50-case study, which revealed their 20-year experience and is the largest nipple adenoma series published to date, also included female patients only. Although it is stated in this and many similar publications

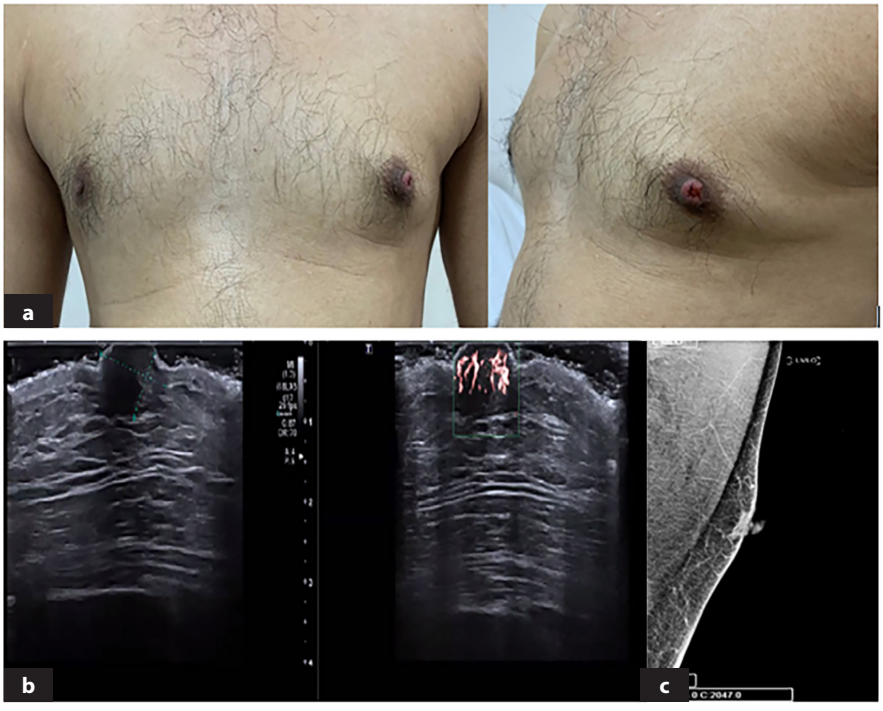

Figure 1. Clinical and radiological images of nipple adenoma. **a)** Hyperemia and serous discharge in the left nipple. **b)** On ultrasonography, the volume of the left nipple has increased and is 6x9 mm, the skin-subcutaneous tissues are eroded, with the central nipple showing a hypoechoic appearance with a diameter of 2.2 mm, suggesting a dilated duct with dense content in the foreground. **c)** In mammography, there are no findings other than prominence in the left areola.

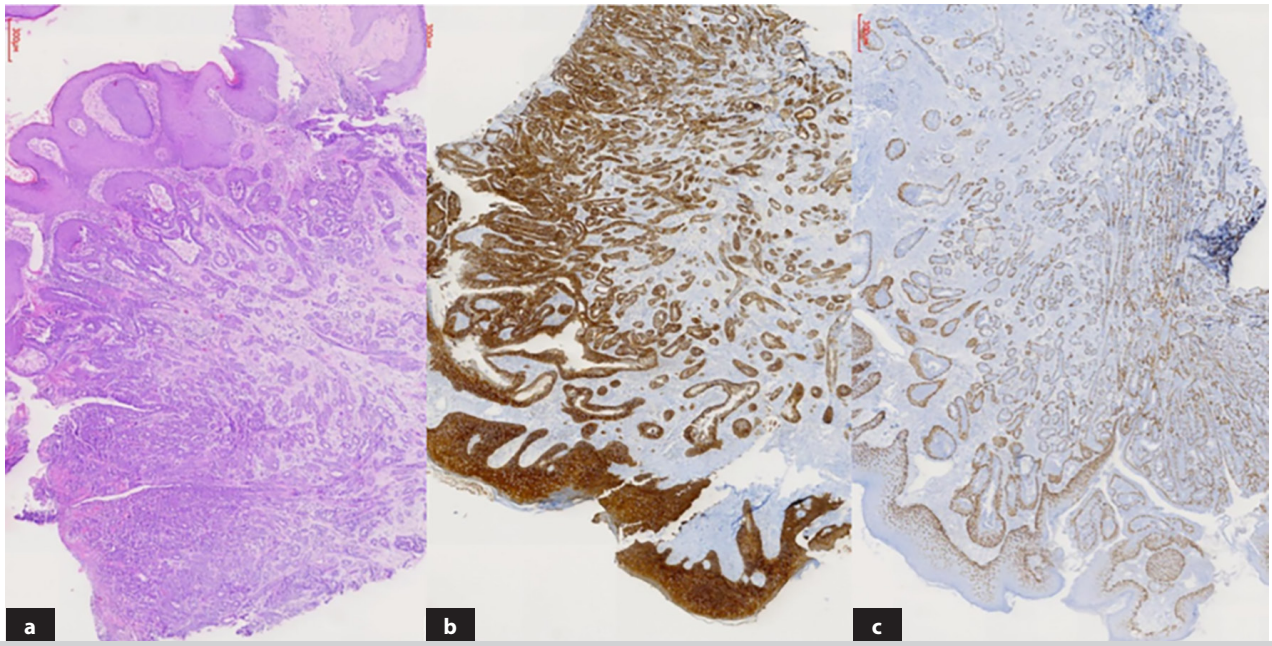

Figure 2. Histopathological examination of punch biopsy of nipple adenoma. **a)** Lesion consisting of proliferation of benign glands and ducts scattered within the stroma under the squamous epithelium on the surface, x4 magnification. **b)** Duct epithelia and squamous epithelium stained positively with keratins 5 and 6. **c)** Myoepithelial cells covering the ducts externally were stained positively with p63. The preservation of the outer myoepithelium shows that the lesion is benign and not invasive.

that the incidence rate in men is less than 5%, no study has been found that examines male nipple adenomas in detail. However, the only known case of male nipple adenoma was reported by Boutayeb et al. (14) in 2012 and was subsequently introduced into the literature by these authors (6). On the other hand, although nipple adenoma is similar to invasive carcinoma, its association is so rare that it can be called coincidental. A study of 5 cases was published in 1995, and upon detailed examination, all of them were female patients (9). Considering the data, the case we experienced involves the second male patient with nipple adenoma presented after many years. Additionally, it is the first male patient in the literature associated with invasive carcinoma, which makes the case unique.

However, in the study that mentioned the adenoma-carcinoma association, it was stated that three of the cases presented with a subareolar mass and two with a palpable mass in the lower inner quadrant, accompanied by nipple findings (9). On the other hand, in the study that emphasized that adenoma is a benign lesion that can be expressed as "florid papillomatosis of the nipple duct" and in the male case in whom a nipple adenoma was detected, with no progression in the postoperative follow-up, it is noteworthy that the clinical features of the case include findings limited to the nipple and that there is no palpable mass or other radiological findings (14). The findings in our case did not include a mass, as is often seen in cases with carcinoma, both clinically and radiologically. However, unlike the male case report in the literature without accompanying carcinoma, our case also presented with serous nipple discharge, in addition to other nipple findings. As a result, it was determined that our case had associated carcinoma.

CONCLUSION

Nipple adenomas require careful examination because they are rare and can be confused with malignancy. Moreover, since it may be associated with malignancy, especially in cases with palpable findings and duct-related symptoms, although it can be considered exceptional, it should be included in the differential diagnosis of male patients, as in all other breast lesions. A safe surgery and postoperative follow-up are recommended.

Ethics

Informed Consent: Written-signed informed consent was obtained from the patient.

Footnotes

Author Contributions

Surgical and Medical Practices - B.G., B.P.; Concept - B.G.; Design - B.G.; Data Collection or Processing - C.G., H.B.; Analysis or Interpretation -B.P.; Literature Search - B.G.; Writing - B.G.

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

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VIDEO ARTICLE
Turk J Surg 2025;41(4):452-453

How I do it: Submucosal hemorrhoidectomy with advanced bipolar technology-modified Parks' method

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ABSTRACT

Park's method of submucosal hemorrhoidectomy has not gained widespread clinical use despite its minimally invasive nature. However, combining this technique with modern bipolar technology LigaSure™ offers a promising approach to surgical treatment of hemorrhoidal disease.

A patient with stage III hemorrhoidal disease underwent surgery under subarachnoid anesthesia in the Lloyd Davis position. The procedure involved lifting external hemorrhoids with an Allis clamp to expose internal hemorrhoids. Using monopolar coagulation, a linear incision was made in the distal skin covering left lateral external hemorrhoids. The surgeon carefully separated varicose veins from sphincter fibers. The LigaSure™ device was then used to dissect hemorrhoidal tissue in the submucosal layer toward the hemorrhoidal artery origin. The artery was ligated 1 cm above the dentate line using bipolar technology while preserving the mucosa.

Similar techniques were applied to remove right posterior and anterior hemorrhoidal tissue. The result showed three small incisions on the anoderm with complete preservation of the anal canal mucosa.

The modified technique allows excision of hemorrhoidal tissue and ligation of arteries without sutures, preserving the lining of the anal canal. This approach potentially results in shorter hospital stays, less postoperative pain, and promotes rapid recovery.

Keywords: Minimal invasive surgery, proctology, rectum

INTRODUCTION

Submucosal hemorrhoidectomy - Park's method has not found wide application in clinical practice, even though it is less invasive (1). However, combining the technique with modern bipolar technology LigaSure™ provides a new perspective on this procedure when choosing surgical treatment for hemorrhoidal disease (2).

CASE REPORT

Patient with hemorrhoidal disease III stage. After subarachnoid (spinal) anesthesia, the patient was placed in a Lloyd Davis position.

An Allis clamp was used to lift the external hemorrhoids to expose the internal hemorrhoids. Using monopolar coagulation, a linear incision was made in the distal part of the skin covering the left lateral external haemorrhoids.

Using monopolar coagulation, the surgeon carefully separated the varicose veins from the sphincter fibres. The LigaSure™ device was then used to dissect the hemorrhoidal tissue in the submucosal layer towards the origin of the hemorrhoidal artery. Finally, the artery was ligated 1 cm above the dentate line using state-of-the-art bipolar technology while preserving the mucosa.

The surgeon removed the right posterior, and right anterior hemorrhoidal tissue in a similar fashion.

The result is shown as three small incisions on the anoderm with full preservation of the anal canal mucosa.

For a more detailed view of all stages of the operation, please refer to the Video 1.

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CONCLUSION

A modified technique allows excision of hemorrhoidal tissue and ligation of the hemorrhoidal artery without sutures, preserving the anal canal mucosa. This approach may result in a shorter hospital stay, less postoperative pain, and fewer complications associated with surgery. The patient was discharged the day after surgery. According to the visual analogue scale, pain is noted at a level of 2 points. Complete healing of the postoperative wound took 14 days.

Video 1. https://youtu.be/2xvNCYSc1D8

Ethics

Informed Consent: Informed consent was obtained from the patient.

Footnotes

Author Contributions

Concept - S.K.E.; Design - S.K.E.; Data Collection or Processing - S.K.E., A.A.O.; Analysis or Interpretation - S.K.E., A.A.O., A.Y.K.; Literature Search - S.K.E., A.A.O., A.Y.K.; Writing - S.K.E., AA.O., A.Y.K.

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VIDEO ARTICLE
Turk J Surg 2025;41(4):454-457

A simple and sterile method for collecting wound fluid after negative pressure wound therapy

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ABSTRACT

The collection fluid of negative pressure wound therapy (NPWT) is a promising material for diagnostic and research of the wound. However, a standardized method for wound fluid collection has not yet been established. Only a few techniques have been described as drilling the canister or disrupting the suction port system. A simple and sterile method for collecting wound bed fluid directly after NPWT is demonstrated.

Keywords: Wound, wound fluid collection, negative pressure wound theraphy

INTRODUCTION

Studying the wound fluid from various types of chronic wounds after negative pressure wound therapy (NPWT) has become a widely used approach for both diagnostic and therapeutic applications (1,2). Most published studies have been performed after NPWT with instillation. However, a standardized method for wound fluid collection has not yet been established. Only a few techniques have been described in the English literature, which involve drilling the canister, using a specially designed canister, or disrupting the suction port system (1,3,4).

Collecting wound exudate from NPWT systems for laboratory evaluation—whether for clinical research or therapeutic decision-making—remains a significant challenge. To date, there is no consensus on specimen collection, and only a limited number of studies provide methodological details.

As the periwound skin is colonized by microorganisms, any non-sterile manipulation during wound fluid sampling may introduce contaminants and interfere culture results if the intension of wound fluid collection is to assess microbiological burden on the wound bed. The primary aim of collecting wound fluid under sterile conditions is to allow reliable analyses and measurements that accurately reflect the wound bed environment.

This brief report introduces a simple and sterile method for collecting wound bed fluid directly after NPWT. The technique is designed to ensure most accurate measurements for both clinical and research purposes, without compromising the integrity of the closed negative pressure system.

Technique and Commentary

Steps for Collecting Wound Fluid After NPWT (Figures 1-8, Video 1):

- The NPWT device is turned off at least 15 minutes before sample collection.
- The drapes sealing the wound are carefully removed.
- A sterile 60 mL catheter-tip syringe is prepared, and the plunger is removed.
- The foam covering the wound surface is sterilely removed using a clamp or forceps.
- The foam is placed inside the syringe barrel, and the plunger is reinserted.

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Figure 1. Foam removal after sterile gloving.

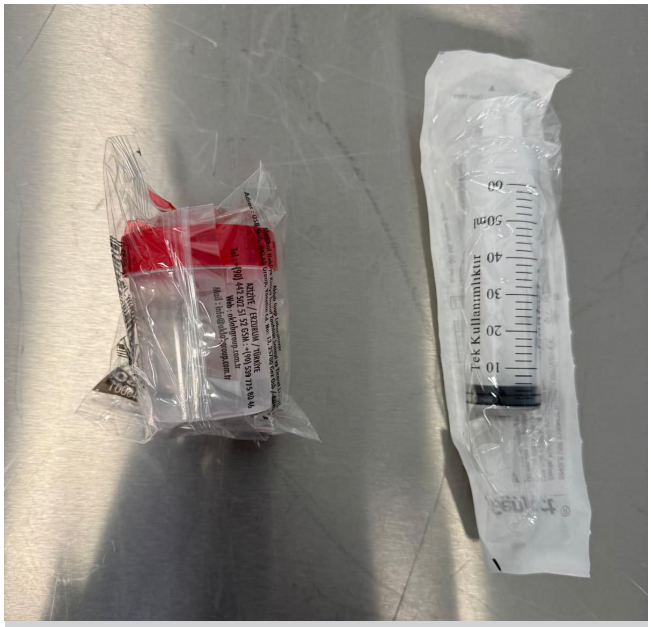

Figure 2. Sterile 60 mL-syringe and urine container to be used in the wound fluid collection process.

Figure 3. Plunger of the syringe removal to place the foam.

Figure 4. Placing the foam inside the barrel.

Figure 5. Re-insertion of the plunger to start fluid collection process

• The plunger is pressed down to compress the foam, expelling wound fluid into a sterile urine container.

For our laboratory, 2 mL of wound fluid is sufficient for routine biochemistry and complete blood countanalyses. This method reliably yields 7-10 mL of sterile wound fluid, depending on wound size and volume.

Two previous reports in the English literature described wound fluid collection methods that may compromise sample purity by drilling the canister or incorporating an additional reservoir into the suction system (3,4). Our straightforward technique enables direct collection of wound bed fluid before it contacts any potentially contaminated surface, avoids disruption of the NPWT system, and provides an adequate volume for analysis after conventional NPWT.

Our aim is to present a sterile technique that serves as a scaffold for wound fluid collection method to avoid any contamination that may alter the laboratory and/or microbiological results. Any feedback and modification suggestions from our colleagues worldwide will guide us to develop a better and a collective widely recognized approach.

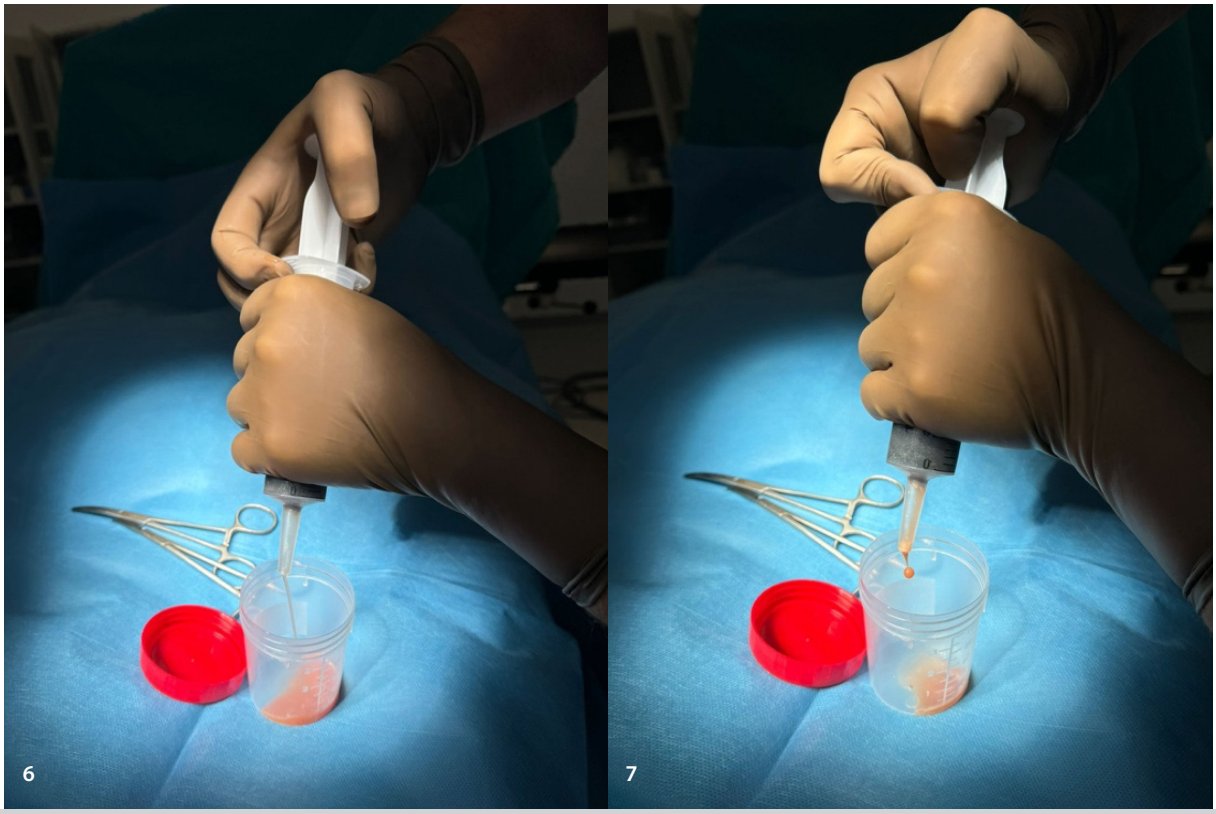

Figure 6 and 7. Collection of the wound fluid by compression, repetitive compressions with enough force may be needed to squeeze the foam.

Figure 8. Collected wound fluid in the container. When the desired amount of fluid is collected the container is the lid is reattached.

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Footnotes

Author Contributions

Concept - H.E.G.; Design - H.E.G.; Data Collection or Processing - H.E.G.; Analysis or Interpretation - H.E.G., M.A.; Literature Search - H.E.G.; Writing - H.E.G., M.A.

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

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Video Link: https://youtube.com/shorts/KcmAU22Ex9o

LETTER TO THE EDITOR
Turk J Surg 2025;41(4):458-459

Critical appraisal of "predictive score for conversion in laparoscopic cholecystectomy – a prospective study" by V et al.

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Keywords: General surgery, laparoscopic surgery, minimal invasive surgery

Dear Editor,

Critical appraisal of "Predictive Score for Conversion in Laparoscopic Cholecystectomy – A Prospective Study" by V et al. (1).

The study by V et al. (1), published in the Turkish Journal of Surgery [2025;41(2):141–146], addresses a significant surgical challenge: Predicting the need to convert a laparoscopic cholecystectomy to open surgery. The authors prospectively evaluated 222 patients undergoing elective laparoscopic cholecystectomy and proposed a two-point preoperative scoring system based on gallbladder wall thickness (>4 mm) and gallbladder contracture seen on ultrasonography. The simplicity of the model and its reliance on widely available imaging make it potentially valuable in day-to-day clinical decision-making.

Despite its merits, several methodological limitations affect the utility and generalizability of the proposed score. While six variables—age, sex, leukocyte count, gallbladder wall thickness, gallbladder size, and CBD were found significant on univariate analysis, only two ultrasonographic variables were included in the final scoring system. This exclusion of clinically significant predictors such as age and male gender, both with p-values of 0.001, is a notable shortcoming. These variables have been well established in previous literature as independent risk factors for conversion. Chin et al. (2) conducted a meta-analysis of 30 studies and confirmed advanced age and male sex among the most consistent predictors for conversion. Similar findings were reported in a Turkish cohort by Sapmaz and Karaca (3).

Another limitation lies in the study's inclusion criteria. By restricting the population to elective cases, the authors may have inadvertently selected for a lower-risk group, thereby limiting the external validity of the model. Emergency cases, which frequently involve inflamed or fibrotic anatomy, represent a significant portion of real-world surgical practice and often carry a higher conversion risk.

Ultrasonography, although practical, is highly dependent on the operator. The study did not assess interobserver variability in measuring gallbladder wall thickness or identifying contracture. Without standardised imaging criteria or training calibration, the reproducibility of these findings across centres remains uncertain.

Furthermore, the scoring system has not undergone internal or external validation. In contrast, recent tools such as Conversion from Laparoscopic to Open Cholecystectomy score (CLOC), integrate both clinical and radiologic variables and have demonstrated external validity in independent cohorts (4).

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To improve the model, the authors might consider incorporating weighted clinical parameters such as age and sex into the scoring system, rather than relying solely on imaging findings. A composite score reflecting both radiological and patient-related variables would likely enhance predictive accuracy. Additionally, including markers of systemic inflammation could further improve discriminatory performance. Ultimately, integrating clinical, biochemical, and imaging parameters into a unified and validated predictive model would represent a more robust tool for preoperative risk stratification.

Future studies should aim to validate this scoring system across multiple centres with surgeons of varied experience levels and include both elective and emergency cholecystectomy cases. Standardization of ultrasonographic measurements and interobserver reliability testing would also be valuable.

In conclusion, the study by V et al. (1) is a commendable effort to simplify preoperative risk stratification in laparoscopic cholecystectomy. However, refinement of the scoring model to include validated clinical predictors and broader patient populations, along with external validation, would enhance its clinical relevance and adoption.

Footnotes

Author Contributions

Analysis or Interpretation - K.N.; Literature Search - K.N., S.M.; Writing - K.N., S.M.

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LETTER TO THE EDITOR
Turk J Surg 2025;41(4):460

Pilonidal sinus disease and intergluteal fold depth

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Keywords: Pilonidal sinus disease, surgical treatment, intergluteal fold

Dear Editor,

I have read with interest the study by Maak et al., which suggests that there is no relationship between the depth of the gluteal fold (IGF) and pilonidal sinus disease (PSD), contrary to previous information (1). The authors made measurements at five points in the sacroperinal region. The data of 105 normal individuals and 95 patients with PSD were measured at five points. I think that there are some shortcomings in the selection of statistical methods and the provision of the necessary data. The authors used the Analysis of Variance (ANOVA) to compare the IGF depth between the two groups (PSD and non-PSD). ANOVA is not suitable for comparing PSD and non-PSD groups because ANOVA is designed for three or more groups. In contrast, this comparison includes only two groups (PSD and non-PSD). For each anatomical measurement (a, b, c, d, e), a pairwise comparison of PSD vs. non-PSD using a t-test at each point would be clearer and statistically appropriate. Inclusion of error bars on Figure 2 will also help readers to better visualize the distribution of IGF in both patients and the population. The mean and standard deviation measurements (if the groups are normally distributed according to the test of normality), containing the p-values for each anatomical measurement for both groups, should be mentioned. Unfortunately, these data are missing, but they are the main point of this article. I would like to thank the authors for their valuable work.

Footnotes

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

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