ISSN: 2564-6850
e-ISSN: 2564-7032

TURKISH JOURNAL OF SURGERY

OFFICIAL JOURNAL OF TURKISH SURGICAL SOCIETY

www.turkjsurg.com

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Volume: 41 Issue: 1 March '25

TURKISH JOURNAL OF SURGERY
OFFICIAL JOURNAL OF TURKISH SURGICAL ASSOCIATION

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Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Online Publication Date: February 2025

ISSN: 2564-6850
e-ISSN: 2564-7032

International scientific journal published quarterly.

TURKISH JOURNAL OF SURGERY
OFFICIAL JOURNAL OF TURKISH SURGICAL ASSOCIATION

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The editorial and publication process of the Turkish Journal of Surgery are shaped in accordance with the guidelines of ICMJE, WAME, CSE, COPE, EASE, and NISO. The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

Turkish Journal of Surgery is indexed in **PubMed Central, Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, Embase** and **Scopus**.

Owner: Turkish Surgical Society

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CONTENTS

ORIGINAL ARTICLES

CASE REPORTS

TURKISH JOURNAL OF SURGERY
OFFICIAL JOURNAL OF TURKISH SURGICAL ASSOCIATION

TURKISH JOURNAL OF SURGERY
OFFICIAL JOURNAL OF TURKISH SURGICAL ASSOCIATION

FROM THE EDITOR-IN-CHIEF'S DESK

The Turkish Journal of Surgery is continuing to innovate to the changing environment of the scientific publishing world. The new year started with the changes on our cover page starting with the turquoise cover to make lasting impression and captivate attention. I believe that visual abstracts or infographics are one of the effective ways to disseminate the research on social media platforms. These eye-catching pictural representations complement to the scientific articles. Hence, we added the "visual abstracts" tag to the website and we will continue to highlight the essence of articles under this tag in future issues. Also, we'll continue to share them in our new Instagram (@TurkJSurgery) and X (formerly Twitter, @TurkJSurgery) addresses along with the latest articles, announcements and contents.

"*Turkish Journal of Surgery Newbies*" tag is dedicated to surgical residents and ones having interest on surgical career. Exclusively, TurkJSurg Newbies platform will be managed by surgical residents in terms of content. So the surgical trainees and also postdoc/medical students can share their study proposals, scientific projects and more in our website. I always prefer to keep my face towards the sunshine, so I sincerely admire our *TurkJSurg Newbies* Committee for their enthusiasm and determination.

Sometimes most difficult thing is the decision to act and the rest is merely tenacity. Our board recognized that all we need is a new plan, a road map and courage to press on to our destination. Since goal setting is the secret of a compelling future, members of the TurkJSurg Editorial board worked very hard to set the new goals. Our ideas grew and grew from a little mustard seed to a big one. Actually, it was a period of change, not austerity. I must confess that I was haunted by some doubts during this journey. Since, TurkJSurg is the official publication of *Turkish Surgical Society*, with the full support of Turkish Surgical Society Executive Committee, we had at hand the opportunity to reorganize our journal. So, many thanks to the executive members who gave the continence to regain my confidence.

And as always, thanks to our readers for their support.

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

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EDITORIAL
Turk J Surg 2025;41(1):1-4

Exploring the disenchantment with tranexamic acid in liver surgery: A hopeful outlook for future developments

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INTRODUCTION

The exploration of tranexamic acid (TXA) in surgical contexts has garnered significant attention over the past few years, particularly regarding its effectiveness in minimizing blood loss during various surgical procedures. The literature reveals a growing body of evidence on the application of TXA, highlighting both its benefits and the complexities surrounding its use (1). Emphasizes the critical role of TXA in reducing perioperative bleeding, which is essential for improving surgical outcomes and minimizing complications such as hematoma and the need for blood transfusions. This systematic review illustrates the shift towards TXA as a primary antifibrinolytic agent following the withdrawal of aprotinin, marking its ascendance in surgical practice.

Further, the comparative analysis conducted by (2) between topical and intravenous administration of TXA in bone surgery adds depth to the understanding of its application. Their findings indicate that both methods effectively reduce blood loss, thereby supporting the notion that TXA can be adapted to various surgical modalities. However, the authors also point out the lack of comprehensive guidelines for optimal dosing, highlighting an area of uncertainty that warrants further investigation (3). Provide a broader narrative on the efficacy and safety of TXA across surgical disciplines, noting its inclusion in the World Health Organization's list of essential medicines. They acknowledge the limited side effects associated with TXA but caution about the potential thromboembolic risks that remain inadequately defined. This narrative review underscores the need for continued research to clarify these risks and optimize dosing strategies, as the clinical evidence for TXA's effectiveness in certain contexts remains inconclusive.

In a more recent umbrella review (4), synthesize findings from multiple studies, reinforcing TXA's protective role against vascular adverse events while also acknowledging the associated risks, particularly at high doses. Their work highlights the variability in effect sizes across different meta-analyses, which introduces a layer of complexity in interpreting the overall efficacy of TXA in surgical settings (5). shift the focus to a specific surgical context -middle ear surgery- where intraoperative bleeding poses significant challenges. Their narrative review reveals a resurgence of interest in TXA, particularly in light of its potential to enhance surgical field visibility. However, they also note the limitations in current literature, including the small number of studies and the heterogeneity in TXA administration methods and bleeding assessment scores. This variability complicates the ability to draw definitive conclusions about TXA's impact on surgical outcomes in this specialty.

Cite this article as: Karaca AS. Exploring the disenchantment with tranexamic acid in liver surgery: A hopeful outlook for future developments. *Turk J Surg.* 2025;41(1):1-4

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Received: 17.02.2025
Accepted: 23.02.2025
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2025.6798

Available at www.turkjsurg.com

Collectively, these articles illustrate the evolving landscape of TXA usage in surgery, revealing both its promise and the challenges that accompany its application. The critical evaluation of these studies highlights the need for further research to address the uncertainties surrounding TXA, particularly in relation to its safety profile and optimal usage protocols across diverse surgical fields.

Literature Review

The article "A Systematic Review of TXA in Plastic Surgery: What's New?" by (1) provides a comprehensive examination of the role of TXA in surgical settings, particularly in the context of plastic surgery. The main thrust of the article revolves around the necessity of minimizing perioperative bleeding to mitigate complications such as hematoma, anemia, and the requirement for allogeneic transfusions. This focus is especially pertinent given the implications of blood loss on patient outcomes, including overall survival rates.

Scarafoni elucidates the pharmacological mechanisms by which TXA operates, highlighting its function as a synthetic derivative of lysine that effectively inhibits fibrinolysis. By blocking the binding sites of plasminogen, TXA prevents the activation of plasmin and the subsequent degradation of fibrin clots, thereby enhancing clot stability. This mechanism is critical in surgical procedures where maintaining hemostasis is essential for patient recovery.

The systematic review synthesizes findings from multiple trials, affirming that TXA is associated with a reduced likelihood of blood transfusions and a decrease in the volume of blood transfused during elective surgeries. Notably, the article emphasizes that the use of TXA does not correlate with an increased risk of thromboembolic events or other significant complications, which supports its safety profile in various surgical contexts. The findings are particularly relevant in light of the withdrawal of aprotinin from the market in 2008, which positioned TXA as a primary agent for managing surgical bleeding.

However, while the article presents a robust case for the efficacy of TXA, it is crucial to consider the broader implications of its use in diverse surgical specialties, including liver surgery. The review does not delve deeply into the specific nuances of TXA application in liver surgery, an area that may require further exploration, especially given the unique hemostatic challenges presented in hepatic procedures. The hopeful outlook for future developments in TXA application could benefit from additional research that addresses its role in this specific surgical context, potentially leading to tailored protocols that optimize patient outcomes.

The article titled "Efficacy of topical vs intravenous TXA in reducing blood loss and promoting wound healing in bone surgery: A systematic review and meta-analysis" by (2) presents a thorough examination of the role of TXA in surgical settings, specifically focusing on its application in bone surgery. The authors provide a systematic review and meta-analysis, emphasizing the efficacy of both topical and intravenous TXA in minimizing blood loss and enhancing wound healing.

One of the critical insights from the article is the comparative analysis of topical versus intravenous administration of TXA. The findings indicate that both methods effectively reduce blood loss when juxtaposed with placebo outcomes. Notably, the study reveals no significant difference in the effectiveness of topical TXA compared to intravenous TXA in the context of blood loss reduction during bone surgeries. This suggests that topical administration could be a viable alternative to intravenous methods, potentially offering advantages such as lower dosage requirements and reduced medical costs.

Moreover, the article highlights a significant gap in the literature regarding comprehensive guidelines for the safe administration of topical TXA, which remains a contentious issue among surgeons. The authors call attention to the need for standardized protocols to optimize the use of TXA in surgical practices, particularly as its application expands beyond traditional uses. This lack of consensus on dosing and administration methods underscores the importance of further research, especially in varying surgical contexts, including liver surgery.

The article titled "TXA for the prevention and treatment of bleeding in surgery, trauma and bleeding disorders: a narrative review" by (3) presents a comprehensive examination of TXA, a fibrinolytic inhibitor, and its application in various surgical contexts, particularly focusing on its efficacy and safety profile. The authors synthesize findings from numerous trials that assess TXA's role in preventing and managing hemorrhage, particularly in patients with underlying bleeding disorders and those on antithrombotic medications.

A critical evaluation of the material reveals that while TXA has been established as a vital tool in reducing bleeding severity, its application is marred by uncertainties regarding its thromboembolic risk. The authors note that although TXA is generally well-tolerated and significantly more potent than its counterpart, ε-Aminocaproic acid, the potential for thrombotic events associated with its use remains an area of concern. This ambiguity is particularly pertinent in the context of liver surgery, where patients may already possess a heightened risk due to underlying liver pathology.

The review highlights the lack of consensus on the optimal dosing of TXA across various surgical indications, which further complicates its clinical application. The authors emphasize that despite extensive research, the evidence supporting TXA's efficacy in certain scenarios is either lacking or ambiguous. This presents a critical juncture for future developments in TXA

research, as addressing these gaps could enhance its safety profile and therapeutic effectiveness.

The article "Does TXA Reduce the Blood Loss in Various Surgeries? An Umbrella Review of State-of-the-Art Meta-Analysis" by (4) presents a comprehensive overview of the efficacy and safety of TXA in surgical contexts. The authors conducted an umbrella review, which synthesizes findings from multiple systematic reviews and meta-analyses, thereby providing a robust examination of the available data on TXA's impact on blood loss across various surgical procedures.

The main insight from the article is the dual nature of TXA as both a protective factor against vascular adverse events and a potential risk factor for complications, particularly in high doses. The authors highlight that while TXA has demonstrated benefits in reducing blood loss in cardiac surgeries, its application is complicated by concerns regarding adverse events, such as seizures, especially in patients with pre-existing conditions like renal impairment or coagulation dysfunction. This nuanced perspective is crucial for clinicians considering TXA for patients undergoing liver surgery, where the balance between minimizing blood loss and mitigating risks is particularly delicate.

Moreover, the article's critical evaluation of the quality of included studies is noteworthy. The authors assert that most studies reviewed were of high quality, with a significant number published post-2016, indicating a growing body of evidence. However, the exclusion of non-English and non-Chinese studies introduces a potential bias, which could limit the generalizability of the findings. Additionally, the variability in effect sizes across different meta-analyses raises concerns about the heterogeneity of results, which could complicate clinical decision-making.

The authors also acknowledge that while TXA may have applications beyond cardiac surgery, these were not addressed in their review due to the absence of relevant meta-analyses. This limitation suggests an area for future research, particularly in the context of liver surgery, where the need for effective hemorrhage control is paramount.

The article "Effects of TXA on Intraoperative Bleeding and Surgical Field Visualization During Middle Ear Surgery: A Narrative Review" by (5) provides a comprehensive examination of the role of TXA as a hemostatic agent in the context of ear surgery, particularly focusing on its effects on intraoperative bleeding and surgical field visibility. The authors emphasize the critical issue of intraoperative bleeding, which can impede surgical outcomes, thereby highlighting the relevance of TXA in this surgical domain.

A significant strength of this narrative review is its thorough approach to synthesizing existing literature on TXA, particularly as interest in its use has surged alongside the rise of endoscopic techniques in ear surgery. The authors reference several systematic reviews that underscore the efficacy of TXA in reducing blood loss and the need for transfusions. However, they also acknowledge the conflicting findings regarding TXA's association with thromboembolic events and mortality, which raises important questions about its safety profile in surgical settings.

Despite its strengths, the review is not without limitations. A major concern highlighted by the authors is the limited number of studies included in the analysis, which restricts the generalizability of the findings. The heterogeneity among the studies regarding TXA administration methods, dosages, and control conditions is particularly problematic. This variability complicates the interpretation of results and precludes a quantitative analysis, which could provide more definitive conclusions about TXA's effectiveness. Furthermore, the authors note that only one of the included trials explicitly reported the absence of side effects, leaving a gap in understanding the potential adverse effects of TXA, particularly in relation to thromboembolic complications.

The authors' narrative approach to reviewing the literature is commendable, as it allows for a qualitative synthesis of the available evidence. However, the scarcity of robust studies and the significant variability in methodologies necessitate caution when drawing conclusions about the efficacy and safety of TXA in middle ear surgery. The authors suggest that further research is needed to clarify these issues and to establish more standardized protocols for TXA use in surgical practice.

CONCLUSION

Collectively, the literature reveals a promising yet complex landscape for TXA in surgery. While its effectiveness in reducing blood loss and the associated risks is well-documented, uncertainties regarding optimal dosing, application in specific surgical contexts, and safety profiles necessitate further research. Future studies should aim to clarify these uncertainties, particularly in specialized areas such as liver surgery, to develop tailored protocols that optimize patient outcomes.

Keywords: Tranexamic acid, bleeding, surgery

Footnotes

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

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ORIGINAL ARTICLE
Turk J Surg 2025;41(1):5-18

Clinical significance of para-aortic lymph node metastasis for prognosis in patients with pancreaticobiliary cancer who underwent radical surgical resections

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ABSTRACT

Objective: To elucidate surgical strategies for patients undergoing radical resection, in cases where solitary distant lymph node metastasis is identified intraoperatively, we investigated the prognostic significance of para-aortic lymph node (PALN) metastases and other regional lymph node (RLN) metastases in pancreatic carcinomas (PC) and biliary duct cancers (BDC).

Material and Methods: This study retrospectively analyzed data from 181 PC patients and 116 BDC patients who underwent radical resections at two institutions between 1994 and 2021.

Results: Among PC patients, metastases were observed in RLN and PALN in 54% and 9% of cases, respectively. Similarly, RLN and PALN metastases were present among BDC patients in 39% and 9% of cases, respectively. Survival analysis revealed that patients with BDC and PALN metastases exhibited significantly reduced disease-free (DFS) and overall survival (OS) compared to those without PALN involvement. Multivariate analysis identified PALN metastasis as an independent predictor of OS in BDC patients ($p<0.05$), while RLN metastasis was independently associated with DFS ($p<0.05$). Additional clinicopathological factors associated with PALN and RLN metastases were also identified. Preoperative serum levels of Duke Pancreas II monoclonal antibody were significantly elevated in patients with PALN metastases. Histological findings of lymphatic or perineural infiltration and hepatic or pancreatic invasion were independently associated with RLN metastases.

Conclusion: Based on these findings, radical resection may be considered for PC patients with isolated PALN metastases only in the absence of additional adverse prognostic factors. Prospective clinical trials are warranted to further refine the criteria for surgical intervention when solitary PALN metastases are detected intraoperatively.

Keywords: Biliary duct carcinoma, pancreatic carcinoma, para-aortic lymph node, node metastasis, histology, prognosis

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer death worldwide, and its lethality is high as only 20% of tumors are deemed radically resectable at the time of diagnosis. About 5% of patients are alive five years after diagnosis, according to the recent review of the meta-analysis by Paiella et al. (1). The para-aortic lymph node (PALN) metastasis was associated with increased poor prognosis when compared with negative PALN regardless of regional nodal status However, definite avoidance of resection of intraoperative metastatic PALN would need further investigation. Thus, the clinical significance of limited PALN metastasis regarding the radicality of distal bile duct cancer and pancreatic cancer remains unclear.

In pancreatic and bile duct cancers, radical surgical resections, such as pancreaticoduodenectomy, distal pancreatectomy, and hepatectomy, are the only curative options, even when RLN metastasis is diagnosed (2-5). However, in cases where node metastasis around the para-aortic area is observed, radical resection should be avoided because of distant metastasis (6). If occult PALN metastasis, which is not detected on preoperative imaging, is diagnosed through intraoperative histological findings using a solitary sampling node, it becomes challenging to

Cite this article as: Nanashima A, Arai J, Hiyoshi M, Imamura N, Hamada T, Tsuchimochi Y, et al. Clinical significance of para-aortic lymph node metastasis for prognosis in patients with pancreaticobiliary cancer who underwent radical surgical resections. *Turk J Surg.* 2025;41(1):5-18

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Received: 07.12.2024
Accepted: 22.01.2025
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2025.6587

Available at www.turkjsurg.com

determine whether to continue the scheduled operation. It is critical to decide whether to recognize PALN metastasis as a systemic or localized disease. The decision-making process regarding the radical resection of pancreaticobiliary cancer with PALN metastasis, is crucial for hepatobiliary-pancreas surgeons. Therefore, an intraoperative histological diagnosis using frozen specimen tissue was performed. However, the clinical significance of this modality in influencing postoperative survival remains unclear. We hypothesize that radical surgery is worthwhile when occult solitary PALN metastasis is first diagnosed using intraoperative PALN node sampling.

To clarify our hypothesis and to determine the institutional strategy for radical surgical resection in cases where a solitary cancer-positive lymph node is observed, we retrospectively examined the postoperative survival of patients with pancreatic and bile duct cancer with or without PALN metastasis who underwent radical resections at two institutes, performed consecutively by the principal author as chief staff, between 1994 and 2021. Additionally, clinicopathological factors associated with PALN were analyzed. The findings of this paper will refer to the mentioned institutional strategy and suggest that they have implications for general practice.

MATERIAL and METHODS

Patients

Either all patients included or only those treated by the authors, were consecutively examined. This study retrospectively collected data on 144 consecutive patients with pancreatic carcinoma (PC) (n=82) and bile duct carcinoma (BDC) (n=62) at the Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences (NUGSBS), who were treated by the first author between April 1994 and March 2015. Other data were obtained from 153 consecutive patients with PBC (PC, n=99 and BDC, n=54), who were treated by the first author, at the Division of Hepatobiliary Pancreatic Surgery, Department of Surgery, University of Miyazaki Faculty of Medicine (UoM) between April 2015 and December 2021. The first author has mainly managed and organized all patients during the study period. The in-hospital data of all patients were retrospectively and consecutively collected from the patient charts at the two institutions. The study design was approved by the Ethics Review Board of NUGSBS and UoM (approval numbers: #24031804, March 19, 2024, and #O-1503, January 24, 2024), and patients' consent was confirmed via an opt-out procedure. This was done through a public announcement at an outpatient clinic and on our institutional website, according to our ethical policy, for a month. No financial support was received for this study, and the authors declare no conflicts of interest. This study adhered to the Declaration of Helsinki's statement on the ethical principles for medical research involving human participants, including research on identifiable human materials and data.

Data were retrieved from both the anesthetic and patient electronic charts and the NUGSBS and UoM databases for the duration of initial hospitalization following radical operations.

Serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9 were measured as tumor markers for PC and BDC before and after the primary treatment every three months. Enhanced computed tomography of the liver was performed every six months after hepatectomy to monitor tumor recurrence. The minimum follow-up period after hepatic resection in patients with BDC who survived was 26 months (range, 12–128 months). The patient outcomes and recurrence or survival information were confirmed during examinations at the outpatient clinic, through periodic reports from other facilities, and via entries in electronic medical records at both institutes. With this information, patient outcomes were determined based on the data collected by the co-author investigators.

If the radiologist of PALN had pointed out the lymph node metastasis, we would not have selected radical operation according to our policy. Preoperative cancer-related contraindications of radical resection are 1) the existence of extra-regional lymph nodes, including PALN swelling over 10 mm with enhancement, diagnosed as distant node metastases by computed tomography, 2) distant organ metastases, 3) cancer invasion to main hepatic arteries and superior mesenteric artery trunk, and 4) the existence of peritoneal dissemination. The preoperative boundary criteria for radical operation is 1) a unilateral abutment (<180 degrees) of soft tissue density from primary cancer to the arterial trunk and 2) extra-regional lymph node (RLN) swelling less than 10 mm. During the operation, the paraaortic regional dissection of surrounding tissues of PALN at the dorsal part of the pancreatic head was performed when the occult solitary PALN metastasis was observed, to detect any other occult PALN metastases. If multiple suspicious nodes of PALN metastasis were macroscopically found, we would not have continued the scheduled radical operations in such cases.

Comparative Measurement of Tumor Markers and Histological Findings Before Surgery

Patient clinicopathological data were retrieved from the archives of our institute. Peripheral blood samples were collected from each patient early in the morning before surgery when the patient was stable. In our hospital, the normal levels of CEA, CA19-9, and Duke Pancreas II monoclonal antibody (DUPAN-II) (7) in patients were <5 ng/mL, <37 U/mL, and <150 U/mL, respectively, and elevated levels were defined as those exceeding these thresholds. Tumor-related factors were compared with the histopathological findings of the resected specimen. For the clinicopathological assessment of PC and BDC, we used the 7th edition of General Rules for the Study of Pancreatic Cancer by the Japan Pancreas Society (8) and the 7th edition of General Rules for

Clinical and Pathological Studies on Cancer of the Biliary Tract by the Japanese Society of Hepato-Biliary-Pancreatic Surgery (9).

Statistical Analysis

For the first survival analyses, univariate and multivariate analyses were performed using the Cox proportional hazards regression model. Disease-free intervals and overall survival were calculated using the Kaplan-Meier method, and differences between groups were tested for significance using the log-rank test (Figures 1, 2). A log-rank regression analysis test was performed to determine independent risk factors, and a 95% confidence interval was indicated for each (Tables 1, 2). A two-tailed p-value of <0.05 was considered significant.

For the comparisons of clinicopathological parameters, and RLV and PALN metastasis, differences in categorical data between the groups and prevalence were assessed using the chi-square test, Fisher's exact test, or Dunnett's multiple comparisontest

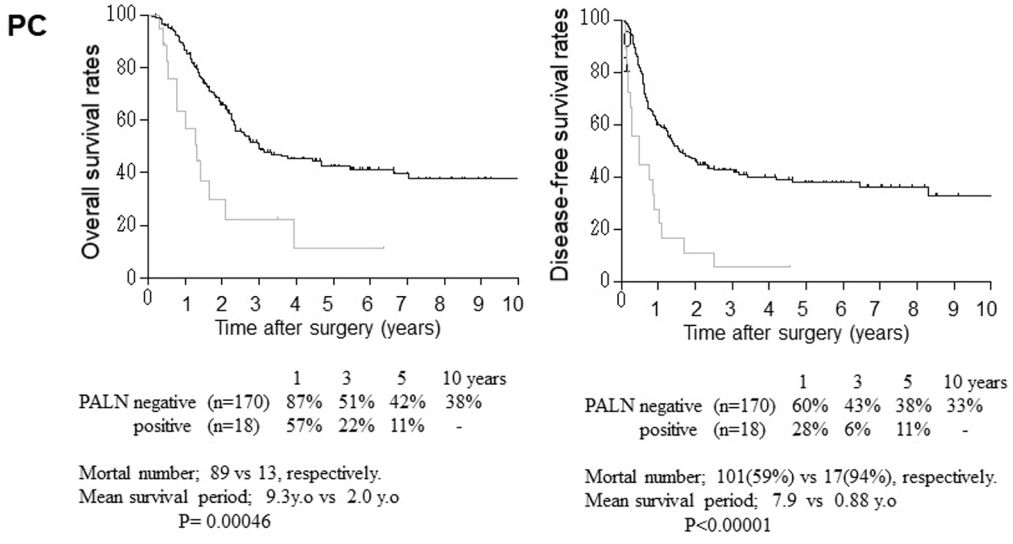

Figure 1. Overall (OS) and disease-free survival (DFS) in patients with pancreatic cancer (PC) with or without para-aortic lymph node (PALN) metastasis. The Kaplan-Meier survival curves and log-rank test. Survival rates in each year, number of cancer deaths, and mean survival periods (months) were compared between patients with PALN metastasis and those without PALN metastasis.

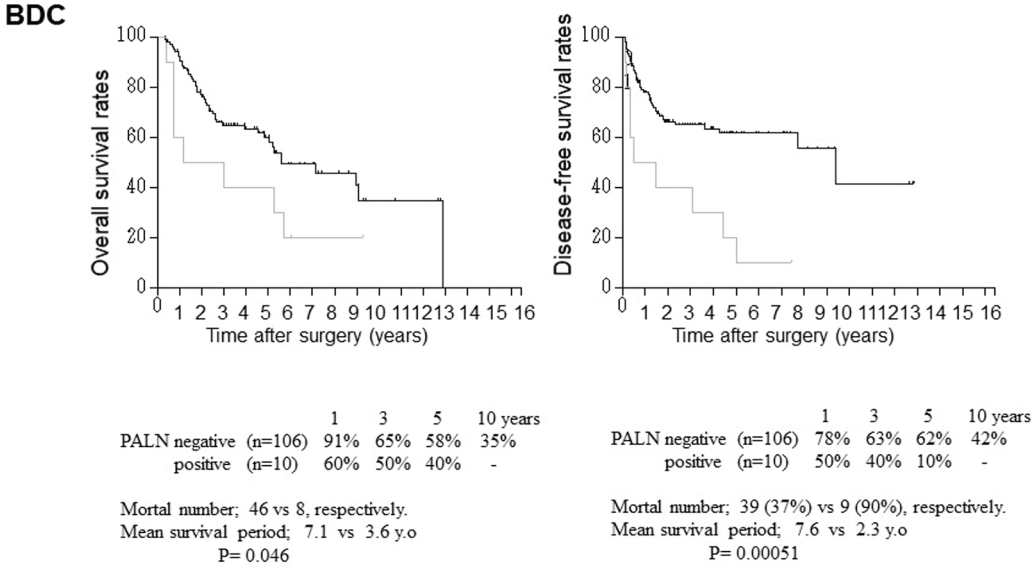

Figure 2. Overall (OS) and disease-free survival (DFS) in patients with bile duct cancer (BDC) with or without para-aortic lymph node (PALN) metastasis. The Kaplan-Meier survival curves and log-rank test. Survival rates in each year, number of cancer deaths, and mean survival periods (months) were compared between patients with and without PALN metastasis.

Table 1. Cox's proportional hazard analysis for patient prognosis in PC undergoing surgical resection (n=181)
a) Overall survival

	Univariate analysis			Multivariable analysis		
	Probability (p-value)	**Risk ratio**	**95% CI Lower-upper**	**Probability (p-value)**	**Risk ratio**	**95% CI Lower-upper**
Age, >70 years (n=112)	0.983	0.995	0.651-1.521			
Sex, female (n=81)	0.428	1.172	0.792-1.735			
CEA, >5 ng/mL (n=32)	0.706	1.099	0.672-1.797			
CA199, >37 U/mL (n=147)	0.004	1.800	1.212-2.674	0.419	1.211	0.761-1.926
DUPAN-II, >150 U/mL (n=21)	0.143	1.504	0.871-2.597			
NAC, yes (n=9)	0.021	0.459	0.237-0.887	0.003	0.269	0.114-0.641
PD, yes[1] (n=117)	0.015	1.711	1.111-2.637	0.076	1.760	0.942-3.288
Morphology, invasive[2] (n=105)	0.004	1.489	1.138-1.949	0.075	0.693	0.462-1.038
Tumor size, >2 cm (n=165)	0.101	1.485	0.925-2.383			
Differentiation,						
Moderately or poorly[3] (n=102)	0.000	2.837	1.768-4.555	0.004	2.442	1.326-4.499
Histologic infiltration, yes						
Lymphatic (n=101)	0.000	3.289	2.094-5.166	0.028	1.967	1.077-3.594
Venous (n=131)	0.000	4.582	2.365-8.876	0.824	0.824	0.320-2.122
Perineural (n=129)	0.000	4.036	2.339-6.964	0.005	2.841	1.376-5.865
Tumor involvement, yes						
Retroperitoneal (n=101)	0.000	2.145	1.400-3.287	0.662	0.878	0.489-1.574
Choledochal (n=60)	0.004	1.653	1.178-2.321	0.259	0.736	0.432-1.253
Duodenal (n=54)	0.000	1.781	1.363-2.326	0.105	1.395	0.932-2.088
Portal vein (n=43)	0.005	1.879	1.208-2.922	0.199	1.461	0.820-2.604
Node metastasis, yes						
Regional (RLN) (n=98)	0.000	3.325	2.162-5.113	0.167	1.481	0.849-2.582
Para-aortic (PALN) (n=17)	0.004	2.447	1.332-4.493	0.234	1.597	0.739-3.449
Cancer positive at surgical margin,						
Proximal bile duct (n= 5)	0.022	3.874	1.212-12.385	0.069	3.268	0.912-11.704
Exposed area (n=14)	0.000	4.966	2.572-9.591	0.041	2.483	1.036-5.948
Histological curability, R1 (n=8)	0.011	2.208	1.197-4.072	0.632	1.195	0.576-2.480
Adjuvant chemotherapy,[4] yes (n=74)	0.686	1.085	0.731-1.609			
Chemotherapy for cancer recurrence, yes (n=60)	0.770	1.063	0.706-1.599			

(Tables 3, 4). Differences in continuous data between groups were evaluated using the Student's t-test or the Mann-Whitney U test Tables 3, 4. Furthermore, parameters with a significance of p-value <0.05 by the univariate analysis were used in the multivariate analysis for associating RLN and PALN metastasis. Statistical analyses were performed using the SPSS software version 23 (Statistical Package for the Social Sciences, Inc., Chicago, IL, USA).

RESULTS

Perioperative Parameters

The basic patient data of 181 PC patients are summarized as follows: A mean age of 68.1±9.4 years at the time of surgery. The mean CEA, CA19-9, and DUPAN-II levels were 10.8±60.5 ng/mL (median 2.6), 509±1.732 U/mL (median 62), and 591±1.605 U/mL (median 92), respectively. The mean tumor size was 3.2±1.7 cm. The mean blood loss was 0.560±1.018 mL (median 1.120 mL). All patients underwent complete macroscopic radical resection without remnant cancer. The final histological curability was classified as R0 in 171 (95%) patients, R1 in 8 (4%), and R2 in 2 (1%). RLN and PALN metastases were observed in 98 (54%) and 17 patients (9%), respectively. Cancer recurred in 117 patients (65%) after surgery. The recurrence was observed in the liver in 61 patients, lymph nodes in 19, lungs in 24, local in 13, peritoneum in 16, bone in 4, and remnant pancreas in 6. All patients except those who experienced recurrence in the

Table 1b) Cancer-free survival

	Univariate analysis			Multivariable analysis		
	Probability (p-value)	Risk ratio	95% CI Lower-upper	Probability (p-value)	Risk ratio	95% CI Lower-upper
Age, >70 years	0.936	1.016	0.690-1.496			
Sex, female	0.279	1.222	0.850-1.757			
CEA, >5 ng/mL	0.440	1.188	0.767-1.842			
CA199, >37 U/mL	0.001	1.911	1.324-2.759	0.258	1.279	0.835-1.960
DUPAN-II, >150 U/mL	0.119	1.501	0.901-2.501			
NAC, yes	0.051	0.232	0.061-1.020			
PD, yes	0.461	1.155	0.788-1.693	0.801	1.078	0.600-1.937
Blood loss, >1500 mL	0.098	1.788	0.897-2.033			
Morphology, invasive	0.000	1.609	1.243-2.082	0.389	0.839	0.562-1.251
Tumor size, >2 cm	0.540	1.139	0.752-1.752			
Differentiation,						
Moderately or poorly	0.000	2.860	1.858-4.403	0.005	2.195	1.271-3.789
Infiltration, yes						
Lymph duct	0.000	3.726	2.417-5.746	0.062	1.727	0.973-3.065
Venous	0.000	4.358	2.425-7.835	0.870	1.068	0.486-2.349
Perineural	0.000	3.654	2.286-5.841	0.013	2.206	1.180-4.121
Tumor involvement, yes						
Retroperitoneal	0.000	2.853	1.885-4.320	0.970	1.011	0.578-1.768
Choledochal	0.033	1.404	1.029-1.917	0.131	0.674	0.404-1.125
Duodenal	0.000	2.018	1.520-2.679	0.051	1.522	0.997-2.322
Portal vein	0.007	1.762	1.168-2.658	0.570	1.173	0.676-2.036
Node metastasis, yes						
Regional (RLN)	0.000	3.705	2.460-5.580	0.110	1.536	0.908-2.600
Para-aortic (PALN)	0.004	2.779	1.632-4.731	0.198	1.578	0.788-3.158
Cancer positive at surgical margin,						
Proximal bile duct	0.041	3.337	1.052-10.588	0.217	2.209	0.627-7.785
Exposed area	0.000	4.838	2.684-8.721	0.101	2.049	0.870-4.823
Curability, R1	0.010	2.146	1.199-3.842	0.749	1.133	0.527-2.440
Adjuvant chemotherapy, yes	0.360	0.840	0.579-1.219	0.099	0.670	0.416-1.078
Chemotherapy for cancer recurrence, yes	0.001	1.862	1.283-2.702	0.077	1.539	0.954-2.485

CI: Confidence interval, CEA: Carcinoembryonic antigen, CA19-9: Cancer antigen-19-9, DUPAN-II: Duke pancreatic mono-clonal antigen type 2, NAC: Neoadjuvant chemotherapy by gemcitabine+S-1, PD: Pancreaticoduodenectomy, R1: Histologically cancer positive at the cutting edge of specimens
[1]: Otherwise, distal pancreatectomy in 60, and total pancreatectomy in 4.
[2]: Otherwise, nodular type in 46, cystic type in 28, and dilated main duct type in 2 patients.
[3]: Otherwise, papillary in 3, well in 37, mucinous in 2, acinar in 4, adenosquamous in 2, anaplastic in 2, unknown in 29 patients
[4]: Six months after surgery as S-1 alone

remnant pancreas underwent chemotherapy. Three of the six patients with recurrence in the remnant pancreas underwent total pancreatectomy. Of the 181 patients, 50 survived without cancer recurrence (28%), 22 with cancer recurrence (12%), 94 died of cancer (52%), and 15 died of other diseases without cancer recurrence (8%); thus, 87 patients (48%) were censored.

The basic patient data of the BDC cohort (116 patients) were described as follows: A mean age of 68.5±11.4 years at the time of surgery. Distal BDCs were observed in 68 patients (59%), and proximal BDCs were observed in 48 patients. The mean CEA and CA19-9 levels were 5.1±18.9 ng/mL (median 2.4) and 2.815±25,639 U/mL (median 37), respectively. The mean tumor size was 1.9±1.7 cm (median 1.6 cm). Pancreaticoduodenectomy was performed in 78 patients (68%), hepatectomy in 45 patients (39%), and hepato pancreaticoduodenectomy in 7 patients. All patients underwent complete macroscopic radical resection

Table 2. Cox's proportional hazard analysis for patient prognosis in BDC undergoing surgical resection (n=116)
a) Overall survival

	Univariate analysis			Multivariable analysis		
	Probability (p-value)	**Risk ratio**	**95% CI Lower-upper**	**Probability (p-value)**	**Risk ratio**	**95% CI Lower-upper**
Age, >70 years (n=75)	0.052	0.564	0.316-1.006			
Sex, female (n=31)	0.984	1.003	0.739-1.362			
Jaundice, yes (n=85)	0.115	1.740	0.874-3.466			
CEA, >5 ng/mL (n=10)	0.040	2.128	1.034-4.379	0.660	1.280	0.427-3.839
CA19-9, >37 U/mL (n=109)	0.005	2.222	1.272-3.883	0.003	3.325	1.103-10.019
Cholangitis of bile duct, yes (n=29)	0.026	2.042	1.087-3.835	0.495	1.398	0.535-3.652
PBMJ, yes (n=4)	0.002	5.256	1.834-15.068	0.672	0.776	0.239-2.517
Blood loss, >1500 mL (n=26)	0.008	2.163	1.220-3.836	0.051	2.817	0.996-7.968
Morphology, invasive[1] (n=97)	0.150	1.974	0.781-4.989			
Tumor size, >2 cm (n=31)	0.229	1.438	0.795-2.603			
Differentiation,[2]						
Moderately or poorly (n=52)	0.056	1.712	0.986-2.975			
Infiltration, yes						
Lymph duct (n=73)	0.008	2.390	1.252-4.561	0.025	4.042	1.191-13.718
Venous (n=77)	0.001	3.640	1.711-7.744	0.025	5.290	1.240-22.71
Perineural (n=78)	0.000	5.376	2.290-12.619	0.004	7.529	1.930-29.374
Depth, beyond subserosa[3]	0.000	2.283	1.452-3.590	0.654	1.195	0.548-2.604
Organ invasion, yes						
Liver (n=21)	0.710	1.096	0.676-1.776			
Gallbladder (n=6)	0.257	1.276	0.837-1.946			
Pancreas (n=47)	0.026	1.696	1.066-2.699	0.169	2.012	0.743 -5.449
Duodenum (n=18)	0.416	1.350	0.655-2.780			
Vascular invasion, yes						
Portal vein (n=9)	0.002	2.215	1.340-3.660	0.864	1.188	0.166-8.506
hepatic artery (n=2)	0.046	2.532	1.017-6.301	0.922	1.152	0.068-19.435
Node metastasis, yes						
Regional (RLN) (n=45)	0.003	2.254	1.310-3.877	0.255	1.625	0.705-3.745
Para-aortic (PALN) (n=10)	0.049	2.215	1.010-4.614	0.049	6.896	1.008-61.629
Cancer positive at surgical margin						
Proximal bile duct (n=23)	0.080	1.643	0.943-2.862			
Exposed area (n=10)	0.000	7.039	3.205-15.458	0.006	18.114	2.339-140.733
Distal bile duct (n=18)	0.348	1.611	0.595-4.361			
Histological curability, R1 (n=18)	0.005	2.156	1.259-3.691	0.140	2.851	0.708-11.473
Adjuvant chemotherapy, yes[4] (n=33)	0.078	1.632	0.947-2.811			
Chemotherapy for cancer recurrence, yes (n=48)	0.000	3.158	1.821-5.477	0.000	5.438	2.400-12.320

without remnant cancer. RLN and PALN metastases were observed in 45 (39%) and 10 patients (9%), respectively. The final histological curability by surgery was classified as R0 in 98 patients (85%), R1 in 18 (15%), and R2 in none. Postoperative complications of Clavien-Dindo classification greater than II were observed in 65 patients (56%). Adjuvant chemotherapy, administered over six months, after surgery, as S-1 alone or as a gemcitabine-cisplatin combination, was administered in 33 patients (28%). Cancer recurrence was observed in 48 patients (41%) after surgery; in the liver in 23 patients, lymph node in 8, lung in 5, local in 12, peritoneum in 12, and bone in 1 patient. Out of the 116 patients, 50 survived without cancer recurrence

Table 2b) Cancer-free survival						
	Univariate analysis			**Multivariable analysis**		
	Probability (p-value)	**Risk ratio**	**95% CI Lower-upper**	**Probability (p-value)**	**Risk ratio**	**95% CI Lower-upper**
Age, >70 years	0.048	0.544	0.298-0.994	0.010	3.662	1.370-3.661
Sex, female	0.563	0.905	0.645-1.270			
Jaundice, yes	0.126	1.765	0.853-3.652			
CEA, >5 ng/mL	0.105	1.854	0.979-3.909			
CA199, >37 U/mL	0.145	1.561	0.858-2.838			
Cholangitis of the proximal bile duct, yes	0.008	2.368	1.248-4.491	0.481	1.427	0.531-3.836
PBMJ, yes						
Blood loss, >1500 mL	0.059					
Morphology, invasive	0.056					
Tumor size, >2 cm	0.100					
Differentiation,	0.118					
Moderately or poorly						
Histologic infiltration, yes	0.019	1.996	1.118-3.565	0.110	2.027	1.143-9.831
lymphatic						
venous	0.009	2.485	1.255-4.922	0.028	3.352	1.560-8.792
perineural	0.071	2.760	1.323-5.759			
Depth, beyond subserosa	0.001	4.165	1.845-9.403	0.350	1.704	0.557-5.216
Organ invasion, yes	0.000	2.646	1.618-4.326	0.879	0.939	0.418-2.109
Liver						
Gallbladder	0.863	0.952	0.545-1.665			
Pancreas	0.169	1.368	0.875-2.138			
Duodenum	0.007	2.022	1.214-3.368	0.097	2.585	0.842-7.934
Vascular invasion, yes	0.210	1.597	0.769-3.317			
Portal vein						
Hepatic artery	0.001	2.916	1.536-5.535	0.836	1.218	1.258-6.765
Node metastasis, yes	0.002	4.998	1.813-13.781	0.321	3.971	0.140-2.383
Regional (PLN)						
Para-aortic (PALN)	0.000	3.166	1.769-5.667	0.013	2.917	1.258-6.765
Cancer positive at surgical margin	0.001	3.373	1.626-6.999	0.447	0.577	0.140-2.383
Proximal bile duct						
Exposed area	0.221	1.477	0.791-2.757			
Distal bile duct	0.000	4.789	2.181-10.516	0.242	2.551	0.530-12.260
Histological curability, R1	0.596	1.300	0.493-3.425			
Adjuvant chemotherapy, yes	0.048	1.921	1.003-3.024	0.049	2.763	1.005-7.597
Chemotherapy for cancer recurrence, yes	0.249	1.632	0.786-2.530			
	0.000	5.735	3.147-10.450	0.000	12.944	4.640-36.104

CI: Confidence interval, CEA: Carcinoembryonic antigen, CA19-9: Cancer antigen-19-9, DUPAN-II: Duke pancreatic mono-clonal antigen type 2, NAC: Neoadjuvant chemotherapy by gemcitabine+S-1, PD: Pancreaticoduodenectomy, R1: Histologically cancer positive at the cutting edge of specimens,
[1)]: Otherwise, papillary, nodular, or flat type without invasiveness in 19 patients
[2)]: Otherwise, papillary in 14, well in 49, unknown in 1 patient
[3)]: Mucosal in 17 patients, subserosal in 60, serosal in 23, and extraserosal in 16
[4)]: S-1 alone (n=30) or gemcitabine-cisplatin combination (n=3) for 6 months

Table 3. Relationship between clinicopathological factors and regional or para-aortic lymph node metastasis in PC

a) Univariate analysis

	RLN metastasis		Probability	PALN metastasis		Probability
	Negative (n=83)	Positive (n=98)	(p-value)	Negative (n=164)	Positive (n=17)	(p-value)
Age (years)	69.3±8.8	67.0±9.9	0.190	68.5±9.4	64.0±9.2	0.103
Gender, Male/female	47/36	44/54	0.846	91/73	9/8	1.0
CEA (ng/mL)	14.6±86.5	7.7±24.1	0.884	6.8±20.5	50.6±189.8	0.886
CA199 (U/mL)	449±2280	557±1130	<0.001	406±982	1473±4710	0.115
DUPAN-II (U/mL)	543±2018	630±1188	0.004	569±1685	778±620	0.0012
Neoadjuvant chemotherapy, no/yes	78/5	93/4	0.810	92/72	13/4	0.056
Operation, DP/ PD/ TP	36/44/3	24/73/1	0.009	56/106/2	4/13/0	0.588
Morphology, Nodular/mixed/invasive/cystic/MPD	14/1/40/26/2	27/1/68/2/0	<0.001	36/1/97/28/2	5/1/10/0/0	0.106
Histological differentiation, Papillary/ well/moderately/poorly/other	1/19/52/5/6	1/23/58/12/4	0.379	2/39/90/23/10	1/5/9/2/0	0.887
Tumor size (cm)	3.16±2.20	3.26±1.23	0.024	3.17±1.78	3.74±1.21	0.067
Tumor infiltration, no/yes						
Lymphatic duct	55/28	19/79	<0.001	73/91	1/16	0.125
Venous	37/46	8/90	<0.001	45/119	1/16	0.126
Perineural	36/47	10/88	<0.001	43/121	2/15	0.0047
Extra-pancreatic involvement, no/yes						
Retro-pancreatic	55/28	21/77	<0.001	75/89	0/17	<0.001
Choledochal	69/14	51/47	<0.001	113/51	6/11	0.038
Duodenal	73/10	54/44	<0.001	116/48	10/7	0.436
Portal vein	70/13	67/31	0.022	126/38	10/7	0.332
PALN metastasis, no/yes	81/2	83/15	0.0037	-	-	-
Histological curability R, 0/ 1	82/1	91/7	0.062	156/8	17/0	<.001
Adjuvant chemotherapy, no/yes	48/35	59/39	0.864	92/72	15/2	0.021
Cancer recurrence, no/yes	49/34	15/83	<0.001	63/101	1/16	0.016
Recurrence-free survival (days)	1385±472	472±553	<0.001	948±1129	333±416	<0.002
Overall survival (days)	1599±1275	815±802	<0.001	1235±1139	595±582	0.0028

b) Multivariate logistic regression analysis

	PLN				PALN			
	Probability p-value	Odds ratio	95% CI lower	95% CI upper	Probability p-value	Odds ratio	95% CI lower	95% CI upper
Op., PD	0.363	0.260	0.014	4.719				
CA199, >37 U/mL	0.957	1.028	0.377	2.801				
Dupan-II, >150 u/mL	0.598	1.000	1.000	1.000	0.023	4.921	1.243	19.475
Morphology, invasive	0.261	1.614	0.701	3.719				
Size, >20 mm	0.406	1.637	0.511	5.244				
Lymphatic invasion	0.089	2.483	0.872	7.070				
Venous invasion	0.884	0.887	0.176	4.458				
Perineural invasion	0.104	3.222	0.786	13.217	0.141	0.2807	0.025	1.689
Extra-pancreatic involvement Retro-pancreatic	0.080	2.681	0.888	8.091	0.997	5.760	0.001	16.355
Choledochal	0.383	1.654	0.535	5.114	0.226	2.380	0.585	9.673
Duodenal	0.189	2.376	0.654	8.627				
PALN metastasis, yes	0.502	1.889	0.295	12.106				

DP: Distal pancreatectomy, TP: Total pancreatectomy, CI: Confidence interval, CEA: Carcinoembryonic antigen, CA19-9: Cancer antigen-19-9, DUPAN-II: Duke pancreatic mono-clonal antigen type 2, NAC: Neoadjuvant chemotherapy by gemcitabine+S-1, PD: Pancreaticoduodenectomy

Table 4. Relationship between clinicopathological factors and regional or para-aortic lymph node metastasis in BDC

a) Univariate analysis

	RLN metastasis		**Probability**	**PALN metastasis**		**Probability**
	Negative (n=71)	**Positive (n=45)**	**(p-value)**	**Negative (n=106)**	**Positive (n=10)**	**(p-value)**
Age (years)	69.8±10.6	66.4±12.3	0.092	69.5±10.2	58.2±17.3	0.027
Gender, male/female	55/16	30/15	0.286	79/27	6/4	0.454
Total bilirubin (mg/dL)	1.49±2.40	1.45±1.39	0.120	1.51±2.14	1.10±0.40	0.593
Alkaline phosphatase (U/mL)	475±438	634±540	0.037	521±477	702±562	0.196
CEA (ng/mL)	6.0±24.3	3.8±3.6	0.089	5.3±19.8	3.0±2.2	0.928
CA199 (U/mL)	4394±33262	502±995	0.0019	3075±26940	324±729	0.310
Jaundice, no/yes	20/51	10/35	0.677	28/78	3/7	0.713
PBMJ, no/yes	69/2	43/2	1.0	103/3	9/1	0.809
Operation, PD/HPD/Hepatectomy Morphology, Papillary/nodular/invasive/IPNB	44/4/23 15/31/24/1	26/7/12 3/6/36/0	0.238 0.300	66/7/33 17/7/81/1	4/4/2 0/0/10/0/0	0.0092 0.362
Cholangitis of the proximal bile duct, no/yes	52/19	31/14	0.484	81/25	6/4	0.078
Histological differentiation, papillary/well/moderately/poorly/other	12/31/19/9	2/19/19/5	0.134	13/43/36/14	1/5/3/1/0	0.535
Tumor size (cm)	1.56±1.55	2.34±1.69	0.036	1.72±1.57	3.54±1.62	0.0006
Depth of invasion, m,fm/ss/se/si	16/35/12/8	1/23/13/8	0.056	15/49/21/13	0/5/2/3	0.252
Tumor infiltration, no/yes Lymphatic duct Venous Perineural	 37/34 31/40 30/41	 5/40 6/39 6/39	 <0.001 0.001 0.002	 41/65 37/69 35/71	 0/10 0/10 1/9	 0.033 0.052 0.238
Extra-pancreatic involvement, no/yes Liver Gallbladder Pancreas Duodenum Portal vein Hepatic artery	 63/8 68/3 52/19 63/8 68/3 70/1	 38/7 43/2 19/26 3510 39/6 44/1	 0.017 0.055 0.0005 0.196 0.163 0.333	 87/19 104/2 67/39 88/18 100/6 104/2	 6/4 6/4 3/7 10/0 7/3 10/0	 0.201 <0.001 0.029 0.358 0.011 0.907
Number of node metastasis	0.82±4.09	1.94±1.56	<0.001	1.17±3.59	1.96±2.22	0.226
PALN metastasis, no/yes	69/2	37/8	0.0139	-	-	-
Cancer positive at cutting edge, no/yes Bile duct Exposed area	 58/13 68/3	 35/10 38/7	 0.578 0.079	 87/19 100/6	 6/4 6/4	 0.202 0.002
Histological curability, R, 0/1	57/14	30/15	0.212	82/24	4/6	0.029
Cancer recurrence, no/yes	49/34	15/83	<0.001	67/39	1/9	0.00034
Recurrence-free survival (days)	14195±1105	787±942	<0.001	1203±1096	836±941	0.171
Overall survival (days)	1605±1083	1059±943	0.0014	1411±1058	1206±1132	0.400

b) Multivariate logistic regression analysis							
	RLN metastasis			PALN metastasis			
	Probability p-value	95% CI lower	95% CI upper	Probability p-value	Odds ratio	95% CI lower	95% CI upper
Age, >70				0.161	0.182	0.017	1.969
ALP, >400 U/mL	0.694	0.221	2.731				
CA199, >37 U/mL	0.177	0.680	8.084				
Size, >20 mm Operation, PD	0.876	0.292	4.241	0.156 0.286	4.380 4.345	0.569 0.292	33.702 64.649
Lymphatic invasion	0.016	1.376	22.468	0.997	2.512	0.001	100.678
Venous invasion	0.361	0.104	2.282				
Perineural invasion	0.032	1.152	22.523				
Organ involvement Liver Gallbladder Pancreas Portal vein	0.026 0.002	2.123 3.455	24.448 42.159	 0.290 0.143 0.204	 3.325 7.843 2.788	 0.359 0.497 0.573	 30.797 123.835 13.560

PBMJ: Pancreaticobiliary maljunction, HPD: Hepato-pancreaticoduodenectomy, DP: Distal pancreatectomy, TP: Total pancreatectomy, CI: Confidence interval, CEA: Carcinoembryonic antigen, CA19-9: Cancer antigen-19-9, DUPAN-II: Duke pancreatic mono-clonal antigen type 2, NAC: Neoadjuvant chemotherapy by gemcitabine+S-1, PD: Pancreaticoduodenectomy

(43%), 13 survived with cancer recurrence (11%), 43 died of cancer (37%), and 10 died of other diseases without cancer recurrence (9%); therefore, 73 patients (63%) were censored.

Relationship Between Clinicopathological Parameters and Disease-free and Overall Survival After Surgery

Figure 1 illustrates that the disease-free survival (DFS) and overall survival (OS) of patients with paraaortic lymph node (PALN) metastasis was significantly lower than for those without PALN involvement; however, three patients survived for more than three years. Figure 2 demonstrates that the DFS and OS of patients with BDC and PALN metastasis were significantly lower than those without PALN, however, five patients survived for greater than 3 years. To clarify the influence of other clinicopathological factors on survival in patients with BDC compared with those with PC, we performed comprehensive survival analyses. With respect to OS in patients with PC (Table 1a), univariate analysis showed that 17 parameters, including RLN and PALN metastases, were significantly associated with OS. Furthermore, multivariate analysis showed that NAC, poorer histological differentiation, and histological evidence of lymphatic and perineural infiltration of cancer were independently related factors for OS, whereas RLN and PALN were not ($p<0.05$). With respect to DFS in patients with PC (Table 1b), univariate analysis showed that 17 parameters, including RLN and PALN metastases, were significantly associated with DFS. Furthermore, multivariate analysis revealed that poorer histological differentiation and histological evidence of perineural infiltration were independently related factors, whereas RLN and PALN were not ($p<0.05$).

With respect to OS in patients with BDC (Table 2a), univariate analysis showed that 17 parameters, including RLN and PALN metastases, were significantly associated with OS. Furthermore, multivariate analysis revealed that the serum CA19-9 levels, histological evidence of lymphatic, venous, and perineural infiltration of cancer, PALN, positive margin at the exposed surgical margin, and chemotherapy for recurrence were independent factors of OS ($p<0.05$). With respect to DFS of patients with BDC (Table 2b), univariate analysis showed that 14 parameters, including RLN and PALN metastases, were significantly associated with DFS. Furthermore, multivariate analysis revealed that histological lymphatic infiltration of cancer, RLN, histologically non-curative resection, and chemotherapy for cancer recurrence were independent associated factors, whereas PALN was not ($p<0.05$).

Relationship Between PALN Metastasis and Other Clinicopathological Factors

Table 3 lists the correlations between RLN and PALN metastases and other clinicopathological factors in patients with PC. Univariate analysis revealed that 16 parameters were significantly associated with the presence of RLN metastasis, and nine parameters were significantly associated with the presence of PALN metastasis ($p<0.05$), (Table 3a). Multivariate regression analysis showed that no factors were associated with RLN. A higher serum DUPAN-II level before surgery was significantly associated with the presence of PALN metastasis ($p<0.05$) (Table 3b). Table 4 details the correlations between RLN and PALN metastases and other clinicopathological factors in patients with BDC. Univariate analysis showed that 13 parameters were

significantly associated with RLN metastasis, and 10 parameters were significantly associated with PALN metastasis ($p<0.05$) (Table 4a). Multivariate regression analysis (Table 4b) revealed that histological lymphatic or perineural infiltration and hepatic or pancreatic involvement were significantly, independently associated with RLN metastasis ($p<0.05$); no other factors were associated with the presence of PALN metastasis.

DISCUSSION

Specific PBC markers such as CEA or CA19-9 levels are commonly used in Japan to diagnose or evaluate malignant tumor aggressiveness (10-13). The existence of paraaortic lymph node swelling or a positivity on a positron emission computed tomography before surgery is a worrisome indication of distant node metastasis, which is considered a non-curative factor for surgery on digestive organs, including surgery for PBC (14,15). However, in the era of systemic solid chemotherapy or immunotherapy, some investigators have shown better survival with scheduled surgery, even with positive PALN cancer (12,16-19). Furthermore, the concept of oligometastasis in organs distant from the PBC has been proposed, but the significance of radical surgery remains controversial (11). Thus far, it has been reported that PALN metastasis is associated with the worst patient survival, and the preoperative or intraoperative diagnosis of PALN metastasis resulted in unresectability (6,20,21). Recently, with respect to bile duct cancer, the 5-year survival rate varies from 5% to 15%, depending on cancer locations such as intrahepatic, perihilar or distal bile duct (22). Recently, Terasaki et al. (23) showed that the frequency of metastasis in PALNs was 4.7%, with 5-year OS rates and efficacy index both at 0%, which were worse than those of RLN metastasis. For distal cholangiocarcinoma, the rates of PALN metastasis were 4.0%, 25.0%, and 0.99. These results are better compared to those for proximal cholangiocarcinoma (23,24). In contrast, Hempel et al. (25) and other investigators reported that PALN metastasis, a predictive factor, can be confirmed during postoperative pathological diagnosis (10,24). The survival of patients with PALN metastasis who underwent radical surgery was poorer than that of those without PALN metastasis; however, the survival of patients with PALN metastasis who underwent surgery was better than that of patients who did not undergo surgery (26,27). This issue regarding the significance of radical surgery in cases of PALN metastasis remains unclear, and this might be influenced by neoadjuvant or adjuvant chemotherapy with novel, effective anti-cancer drugs (19,21). Due to the oligometastatic condition, the significance of metastasectomy has been elucidated in patients with PC undergoing adjuvant chemotherapy (28). The number of intraoperative PALN metastases is a notable issue (12,20,29) that we recently experienced. In case a solitary PALN is unexpectedly found during intraoperative sampling, we were challenged to choose whether an appropriate strategy was borderline resectable, or unresectable. Fortunately, additional oncological difficulties are not observed in PBC surgery. Thus, the present study attempted to clarify our hypothesis and establish an institutional strategy for cases of solitary PALN metastasis in PBC that were conducted before the era of aggressive chemotherapy. The study was conducted at two institutes where, for 27 years, the principal author performed the same quality radical operations with PALN dissection or sampling. Until 2015, when we initially found the PALN metastasis by intra-operative frozen section pathology, we considered the possibility of localized PALN metastasis in the case of solitary or tiny node metastasis. The concept or strategy of conversion chemotherapy for PALN metastasis could not be considered because of the lack of solid evidence worldwide. In recent years, we may attempt conversion chemotherapy when the preoperative or intraoperative PALN metastases are detected, because we can choose some effective chemotherapy regimens at this stage (19,21,25).

First, patient survival with PALN metastasis from PBC was examined. The results demonstrated that patients with PBC and PALN metastasis had poorer survival than those without PALN metastasis. However, the 5-year OS of patients with PALN metastasis remained stable in both PC and BDC groups, and a two-year median survival period was observed. In this study, cases of unexpected solitary PALN metastasis with curative surgery based on preoperative imaging diagnosis were included, whereas cases of multiple PALN metastases were not. Certainly, DFS was poor, however, this can be improved in the future using adjuvant chemotherapy or chemotherapy in recurrent cases (26-28). Furthermore, in the second step, the statistical weights of PALN for patient survival and other regional node metastases (PLN) were examined along with various clinicopathological factors using multivariable analyses. In a recent nationwide Japanese study, gemcitabine, and S-1 combination therapy as neoadjuvant chemotherapy were found to be significantly beneficial for the survival of patients with PC. CA19-9 level, a valuable marker of PC aggressiveness, showed high significance in the univariate analysis in this study; however, this may have been influenced by obstructive jaundice or NAC. Thus, this was not observed in multivariate analysis. During this long period, anti-cancer drugs have gradually been developed. Until the early 2010s, the medical evidence of adjuvant chemotherapy was not well established. At this stage, the adjuvant chemotherapy with S-1 for a duration of 6-12 months has been available in my country. However, the effective regimen and the administration period are not established at this stage. As a result, the rate of adjuvant chemotherapy use was not frequent in the present study. Adjuvant chemotherapy has been available since 2016. Recently, the significance of adjuvant chemotherapy in perihilar BDC patients with occult PALN positivity who underwent radical

hepatic resection was reported (30). Thus, the development of neoadjuvant or adjuvant chemotherapy may change the treatment strategy of PBC with solitary or occult PALN metastasis. Histological features of cancer, such as lower differentiation and vascular infiltration, were consistent markers associated with poor DFS and OS in this series, as well as in a previous study (12,16,20,24,31,32). Recently, preoperative endoscopic ultrasonography-guided fine needle aspiration or biopsy (EUS-FNA or FNB) has been shown to perform better than pancreatic duct aspiration in most patients with PC (33). However, most samples could not be used to evaluate all PC patients' survival predictions. In contrast, in BDC CA19-9 was a significant marker for poor survival and histological vascular infiltration in this study and in a previous study (34). No NAC was administered in this study. CA19-9 remains the most reliable surrogate marker at this stage. If multiple nodes or related findings of advanced local extension of the primary cancer are found, it is generally reasonable to decide on an exploratory laparotomy (10-12,16,24). Usually, the diagnostic accuracy of regional or distant node metastasis using preoperative multimodal image diagnosis with conventional ultrasonography, computed tomography, magnetic resonance, and positron emission tomography, is approximately 4-21% in the field of pancreaticobiliary cancers (PBC) (11-12,35,36).

In both PC and BDC, the impact of PALN and PLN metastasis on survival differed. In PC, these tended to be associated with poor survival; however, multivariate analysis did not identify the association. Additionally, other histological markers might exhibit malignant behavior. In BDC, both PALN and PLN were significantly associated with poor survival. In addition to PC, other histological factors may contribute to aggressiveness. As described above, a previous study demonstrated that the histological factors related to tumor vascular infiltration showed a higher significance in terms of poor survival (12,16,20,24,31,32). Furthermore, as a surgical factor, cancer-positive margins, such as exposed margins or R1 resection, were significantly associated with poor prognosis in this study as well as in previous reports (11,16,24,35,36). In this series, R12 patients (n=10, 5%) were included, and we have routinely performed the intraoperative pathological diagnosis of cancer infiltration at the resected edge. Even now, the final pathological diagnosis has often changed, particularly in BDC, due to the accompanying cholangitis or degree of dysplasia. A lower degree of pathological diagnostic ability was observed in two patients with R2 during the operation. Although both PALN and PLN were prognostic factors, solitary PALN metastasis was not a definitive prognostic factor, determining the decision for radical surgery in our study. Even in PC, the lymphatic flow into the PALN depends on the location of the primary tumor, whether it is in the pancreatic head or tail. PALN metastasis from the pancreatic tail would be considered a distant metastasis via the systemic lymphatic flow, although the pathological evidence is not easily clarified.

Next, the clinicopathological factors associated with PLN and PALN were examined. On univariate analysis of PC, many clinicopathological factors were significantly more associated with PLN than with PALN. None of the factors was related to PLN metastasis, whereas only DUPAN-II was significantly associated with PALN metastasis. DUPAN-II is associated with tumor aggressiveness in PC. In BDC (in this study), histological infiltration of cancer and organ involvement was significantly associated with PLN metastasis, whereas no association with PALN metastasis was observed in a previous report (24). Some PALN metastases may be skip metastases, but they do not follow the course of lymph vessels, unlike other PLN metastases in BDC. In gallbladder cancer, such a direct metastatic route has been identified in a previous report (37). Based on our hypothesis, if such a case exists without other prognostic factors, it is possible to perform radical surgery when a solitary PALN metastasis is observed. To elucidate the clinical significance of regional node metastasis, including PALN, the efficacy index calculated based on the survival rate or period would be required (38).

We aimed to assess how radical surgery affects outcomes in this study, and based on our findings, we can determine a strategy as follows: 1) If solitary PAL was observed during preoperative or intraoperative examination in PC, and NAC was mostly successful, with DUPAN-II levels > than 150 U/mL, and there was no retropancreatic involvement, then radical surgery is considered. In addition, histological differentiation and vascular infiltration were investigated using preoperative biopsy specimens and discussed with the pathologists. If DUPAN-II levels increase to >150 U/mL and retro-pancreatic infiltration is positive, PALN node dissection is attempted. If an increased level of the promising alternative tumor marker for malignant behavior, DUPAN-II, is observed and is accompanied by suspicious PALN metastasis or pre- and intraoperative PALN swelling, NAC or conversion chemotherapy should be considered. This is especially relevant given the current availability of effective anticancer drugs. This indicates better survival, and suggests that R1 resection is prospectively permissible. 2) When a solitary PAL is observed during preoperative or intraoperative examination, in BDC, PAL metastasis alone is considered a significantly poor prognostic factor, and radical surgery must be limited to younger patients (<70 years). If CA19-9 is very high, i.e., >100 U/mL, R0 or non-exposed surgery cannot be achieved. Even if histological findings associated with poor prognostic factors were not observed in the preoperative specimens, radical surgery should be performed in the prospective setting.

Study Limitations

The limitations of the present study are as follows: 1) retrospective two-institutional consecutive cohort for a long period but not

prospective; all these patients included or only those treated by the principal author, which might introduce the selective bias; although the minimal follow-up period was the same at both two institutes, the maximum follow-up was longer at the former institute; 2) the number of patients with PALN metastasis was not high in the recent 6 years due to institutional bias; 3) In this study, we did not operate PBC patients with PALN metastasis by the preoperative radiological imaging diagnosis such as a larger size, enhancement of contrast media by computed tomography, increased number, or positron emission tomography, which was excluded from the evaluation. If we have a database of this group, we must compare patient survival compared to those with occult PALN metastasis who underwent an operation. This comparison may show the clinical significance of the operation in PALN-positive patients who were intraoperatively diagnosed; 4) DUPAN-II levels were not routinely examined, and this must be examined prospectively; 5) surgical indications at the two institutions were due to operator decision bias. These limitations must be verified via interim survival analysis using the proposed operative indication conducted over the next 5 years, as outlined in the prospective institutional criteria for PBC. However, these unexpected and contradictory results must be confirmed in a more significant number of participants at a single institute.

CONCLUSION

We conducted a retrospective and consecutive analysis of the outcomes of 297 patients with PBC, consisting of 181 patients with PC and 116 patients with BDC who underwent curative surgical resections focusing on solitary PALN metastasis. We analyzed the relationship between PLN and PALN metastasis, conventional clinicopathological parameters, and patient long-term survival. Although histological findings of cancer infiltration, differentiation, and organ involvement were significantly associated with poor prognosis, independent prognostic factors before surgery were limited. They varied between PC and BDC in the multivariable analysis. A prospective trial based on the present results is necessary to clarify the institutional operative indication when a solitary PALN metastasis is diagnosed by sampling during surgery, until a definite proposal or recommendation is provided by nationwide guidelines. Novel adjuvant chemotherapy regimens or treatments for recurrence are expected to control PALN metastasis or other oligometastases in distant regions of PBC.

Ethics

Ethics Committee Approval: This study protocol was approved by the two institutions and the study design was approved by the Ethics Review Board of NUGSBS and UoM (approval numbers: #24031804, March 19, 2024, and #O-1503, January 24, 2024).

Informed Consent: Informed consent was obtained.

Acknowledgments

The entire text was edited by the English editing company for science and medicine, Elsevier (reference number ASLESTD1045174) on February 20th, 2024.

Footnotes

Author Contributions

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

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

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

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ORIGINAL ARTICLE
Turk J Surg 2025;41(1):19-23

Clinical outcomes of early and delayed cholecystectomy for acute gallstone-related disease

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ABSTRACT

Objective: Laparoscopic cholecystectomy is the definitive treatment for gallstone-related disease. Early laparoscopic cholecystectomy (ELC) is recommended for management of acute gallstone-related disease, as delayed laparoscopic cholecystectomy (DLC) is associated with recurrent presentations and complications. This series evaluated the outcomes of ELC and DLC in patients presenting acutely to secondary care.

Material and Methods: All cholecystectomies performed for patients presenting with acute gallstone-related disease including biliary colic, acute cholecystitis, gallstone pancreatitis and obstructive jaundice over a 24-month period were included. Clinical outcomes including hospital stay, peri-operative complications, re-presentation of gallstone-related disease, and repeat hospital admissions and imaging were recorded for ELC and DLC cases.

Results: Of 105 cholecystectomies performed, only 6.7% were ELC. The mean time from index presentation to cholecystectomy was 3.4 days and 119.6 days for ELC and DLC, respectively. Over one-third of patients (38.8%) undergoing DLC experienced recurrent gallstone-related disease between index presentation and surgery. Re-admission to hospital for gallstone-related symptoms was seen in 25.5% of patients. The mean additional inpatient stay for readmission for gallstone-related disease in the DLC group was 3.3 days, with 30.6% requiring repeat imaging.

Conclusion: DLC is associated with significant recurrence of gallstone-related complications. Re-admission to hospital incurs additional inpatient stay, and investigation, leading to a negative impact on patients' health and additional financial burden.

Keywords: Cholecystectomy, gallstones, pancreatitis, cholecystitis, biliary colic, choledocholithiasis

INTRODUCTION

Gallstones or cholelithiasis are the leading cause of acute admissions for gastrointestinal disease, affecting up to 20% of patients (1). Cholelithiasis is associated with a spectrum of diseases, including biliary colic, acute cholecystitis, gallstone-related pancreatitis, and obstructive jaundice secondary to choledocholithiasis. Surgical resection with laparoscopic cholecystectomy remains the mainstay for symptomatic gallstone disease. However, the optimal timing for cholecystectomy remains unclear. Traditionally, delayed laparoscopic cholecystectomy (DLC) has been advocated, in particular for acute cholecystitis, due to perceived increased technical difficulty secondary to acute inflammation (2). However, there is increasing evidence supporting the use of early laparoscopic cholecystectomy (ELC) in the management of acute gallstone presentations. A meta-analysis of seven randomised controlled trials, demonstrated that ELC (<7 days of presentation) in acute cholecystitis was not associated with increased intra-operative complications, such as bile duct injury, when compared to DLC (>6 weeks after index presentation) (3). Conversion rates between ELC and DLC were comparable, with ELC shown to shorten hospital stay by 4 days (3). These findings have been supported by further meta-analysis (4,5), all advocating the use of ELC for acute cholecystitis.

Similar findings have been demonstrated for the management of biliary colic. Only a single randomised control trial of 75 patients compared the outcomes of ELC (defined as <24 hours after diagnosis) and DLC (mean time 4.2 months after diagnosis) for biliary colic (6). DLC was associated with increased operating times, hospital stays and repeat hospital admissions for symptomatic gallstones. Expert review of these

Cite this article as: Vithayathil M, Yong C, Dawas K. Clinical outcomes of early and delayed cholecystectomy for acute gallstone-related diseas. *Turk J Surg.* 2025;41(1):19-23

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Received: 12.11.2024
Accepted: 25.01.2025
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2025.6568

Available at www.turkjsurg.com

findings suggested ELC was beneficial for management of biliary colic (7). A single trial of 50 patients for the use of ELC (defined as performed <3 days from admission) in mild acute gallstone pancreatitis again demonstrated no increase in complication rate and patients who underwent ELC experienced a shorter hospital stay (8,9), though these findings are limited to mild cases of pancreatitis. Currently, the European Association for the Study of Liver Diseases recommends cholecystectomy during the same admission, or a delay of no longer than 2 weeks from presentation with acute gallstone related pancreatitis (10,11). Similarly, in patients with choledocholithiasis, ELC 72 hours after endoscopic retrograde cholangiopancreatography (ERCP) sphincterotomy is associated with fewer recurrent biliary events with no difference in conversion rates or postoperative complications compared to DLC after 6-8 weeks (12). Despite these studies suggesting that ELC is associated with more favourable clinical outcomes, rates of ELC in practice remain low (13-15). This study reviews the clinical outcomes of patients undergoing either an ELC or DLC for acute symptomatic gallstone disease at a secondary-care surgical centre over a two-year period.

MATERIAL and METHODS

All cholecystectomies performed at a secondary-care surgical centre in the United Kingdom between 2011-2013 were reviewed. Cholecystectomies for non-acute presentations, such as elective referrals from other centres, were excluded. ELC was defined as cholecystectomy performed within the timeframes for each gallstone presentation based on the current recommendations shown in Table 1. DLC was any cholecystectomy after these recommended time frames.

Pre-operative parameters measured included demographic data, symptomatic presentation (biliary colic, acute cholecystitis, gallstone pancreatitis and obstructive jaundice secondary to choledocholithiasis), and time between index presentation and cholecystectomy. Intra- and post-operative complications data were collected for both ELC and DLC groups. Further analysis in the DLC group included recurrence of gallstone-related symptoms, repeat gallstone-related re-admissions, repeat gallstone-related imaging and length of re-admission hospital stay. The study received approval from the University College London Hospitals NHS Foundation Trust local audit department board (UCLH Audit Committee GIS/06.03.2012).

Statistical Analysis

In statistical analysis, for baseline variables in the ELC and DLC groups, mean and standard error were calculated for continuous variables. For peri-operative outcomes, time to surgery was defined as the time between index presentation and date of cholecystectomy in days. Index hospital stay was defined as the time from index gallstone-related presentation to date of discharge for the first hospital admission. Post-operative stay was the time from cholecystectomy to hospital discharge. Repeat admission days was the total number of days a patient was re-admitted for gallstone-related disease, after the initial index admission. Mean and standard error for peri-operative outcomes were calculated for ELC and DLC groups.

RESULTS

A total of 105 patients were reviewed in the study (Table 2). The mean age (± standard error) of patients in the study was 52.2±1.7 years (range 18-84 years), with 65.7% of the patients being female. Only 7 patients (6.7%) had ELC within the recommended time period (3 cases of acute cholecystitis, 2 cases of biliary colic, 1 case of gallstone pancreatitis, 1 case of obstructive jaundice). The frequency of presentations for acute gallstone disease is shown in Table 2.

The time from index presentation to cholecystectomy was longer in the DLC cohort compared to ELC (119.6±13.3 days vs. 3.4±1.1 days) (Table 3). In the DLC group, eight patients experienced complications. Four patients experienced a bile leak, with one case requiring laparoscopic wash-out. There were 3 cases of choledocholithiasis, all requiring ERCP for biliary decompression.

In the DLC group, 38 patients (38.8%) experienced further gallstone-related symptoms while awaiting laparoscopic cholecystectomy from the time of index presentation. Twenty-five patients (25.5%) returned to the hospital acutely, with five patients returning twice following their initial presentation, and one patient returning three times. The total additional acute hospital presentations was 33, with the breakdown shown in Table 4. The majority of re-presentations were biliary colic, but more serious complications included five cases of gallstone pancreatitis and one case of gallbladder perforation and empyema. Seventeen patients seen in the outpatient clinic between index presentation and DLC reported having biliary colic.

Total additional hospital stay length due to gallstone-related readmissions was 172 days (mean 3.3±7.9 days). Additional gallstone-related imaging was required in 30 patients

Table 1. A summary of recommendations for the timing of early laparoscopic cholecystectomy for different presentations of acute symptomatic gallstones based on European Association for the Study of Liver Diseases (10)

Presentation	Recommendation
Biliary colic	Early <24 hrs of diagnosis
Acute cholecystitis	Early <7 days of onset of symptoms
Acute pancreatitis	Within same admission unless a clear plan is made for definitive Rx within 2 weeks
Obstructive jaundice	± Complications: Within same admission/10 days

Table 2. Demographical data for patients with acute presentations of gallstone-related disease between 2011-2013		
	Early laparoscopic cholecystectomy (n=7)	**Delayed laparoscopic cholecystectomy (n=98)**
Age	41.1±3.6	52.9±1.8
Female	4 (57.1%)	65 (66.3%)
Gallstone presentation		
Acute cholecystitis	3 (42.9%)	33 (33.7%)
Biliary colic	2 (28.6%)	43 (43.9%)
Gallstone pancreatitis	1 (14.3%)	17 (17.3%)
Obstructive jaundice	1 (14.3%)	5 (5.1%)
All values shown are mean ± standard error for continuous variables and frequency with (%) shown for categorical variables		

Table 3. Peri-operative outcomes for patients undergoing ELC and DLC for gallstone-related disease		
	Early cholecystectomy (n=7)	**Late cholecystectomy (n=98)**
Timing of cholecystectomy from index presentation (days)	3.4±1.1	119.6±13.3
Index hospital stay (days)	6.0±0.8	6.0±0.6
Post-operative stay (days)	2.1±0.5	2.2±0.4
Surgical complications	0	8 (8.2%)
Bile Leak[†]	0	4 (4.1%)
Retained Stone[‡]	0	3 (3.1%)
Pancreatitis	0	1 (1.0%)
All values shown are mean ± standard error for continuous variables and frequency with (%) shown for categorical variables, [†]: 1 case of Bile Leak required Laparoscopic washout, 1 case required ERCP and 2 cases required drain insertion [‡]: All 3 cases of retained stones required ERCP, ERCP: Endoscopic retrograde cholangiopancreatography, ELC: Early laparoscopic cholecystectomy, DLC: Delayed laparoscopic cholecystectomy		

Table 4. Re-presentations of gallstone-related disease in patients awaiting delayed laparoscopic cholecystectomy	
	Delayed laparoscopic cholecystectomy (n=98)
Acute cholecystitis	6 (6.1%)
Biliary colic	17 (17.4%)
Gallstone pancreatitis	5 (5.1%)
Obstructive jaundice	2 (2.0%)
Empyema	1 (1.0%)
Perforated gallbladder	1 (1.0%)
Cholecystostomy Leak	1 (1.0%)
Total	**33 (33.7%)**

having DLC (30.3%), including 13 ultrasound scans (13.3%), 5 computed tomographys (5.1%) and 12 magnetic resonance cholangiopancreatographys (MRCPs) (12.2%). Table 5 summarizes the outcomes of the ELC and DLC groups and the additional presentations and imaging for the DLC cohort.

DISCUSSION

In this retrospective study, we found over one-third of patients experienced a recurrence of gallstone-related symptoms while awaiting DLC, with over one-quarter re-presenting to hospital. DLC was associated with an average additional 3.3-day hospital stay due to re-admission, with 30.3% of patients requiring repeat imaging. This study highlights that DLC is associated with increased morbidity and the use of additional healthcare resources.

ELC for symptomatic gallstone-related disease is supported by a growing body of evidence. Though high-quality randomised studies for ELC in biliary colic and gallstone pancreatitis are lacking, the general consensus is the benefits of ELC include reduced hospital stay and reduced re-admissions without increase in intra-operative or post-operative complications (3-5,7,11). In this study, we have observed no increase in surgical complication rate after ELC. Several other studies have shown that ELCs do not have an increased intra- or post-operative complication rate (3-5,7,11). However, surgeons remain reluctant to perform cholecystectomy acutely, citing a lack of experienced surgeons and emergency theatre availability (2).

This study has shown that a delay in cholecystectomy is associated with increased patient morbidity. Over one third of patients experienced gallstone related disease while awaiting cholecystectomy, with significant morbidity, including acute pancreatitis, empyema, and a perforated gallbladder observed.

Table 5. Summary of outcomes of early laparoscopic cholecystectomy and delayed laparoscopic cholecystectomy

	Early cholecystectomy (n=7)	Late cholecystectomy (n=98)
Timing of cholecystectomy from index presentation (days)	3.4±1.1	119.6±13.3
Index hospital stay (days)	6.0±0.8	6.0±0.6
Post-operative stay (days)	2.1±0.5	2.2±0.4
Surgical complications	0	14 (14.3%)
Repeat gallstone symptoms	-	38 (38.8%)
Repeat hospital admissions	-	25 (25.5%)
Repeat hospital stay (days)	-	3.3±0.8
Additional imaging -Ultrasound -CT -MRCP	- - - -	30 (30.6%) 13 (13.3%) 5 (5.1%) 12 (12.2%)

All values shown are mean ± standard error for continuous variables, CT: Computed tomography, MRCP: Magnetic resonance cholangiopancreatographys

In addition to health implications, recurrence of gallstone-related disease generates numerous additional costs in DLC patients. Approximately one quarter of patients were re-admitted to hospital with recurrence of gallstone-related symptoms, associated with, on average, an extra 3.3-day inpatient stay per patient. This additional requirement for acute medical resources, including repeat imaging to re-confirm gallstone related disease, would not be seen in ELC patients.

With the increasing pressures in the current economic climate, the financial benefit of ELC may be the biggest driver for change. Costing analysis has shown ELC is less expensive with a gain in quality adjusted life years (QALYs) (16). Furthermore, a cost-utility model for the NHS predicted that ELC is £820 cheaper per patient than DLC, with a 0.05 QALY gained per patient, amounting to an overall saving of £8.5 million per annum for the NHS (17).

A potential reason for the poor rates of ELC demonstrated here and in other studies (18), is the difficulty accommodating these cases in overbooked emergency theatre operating lists. Mild gallstone disease, in particular biliary colic, could be perceived as low priority when compared to acute presentations from other surgical specialties such as orthopaedics, trauma, and gynaecology. However, this study demonstrates that a delay in cholecystectomy can result in significant morbidity for the patient.

There are several strategies that can be adopted to accommodate ELC into practice. A quality improvement initiative from a district general hospital showed how a multi-disciplinary approach can successfully add ELC onto acute surgical lists (15). The availability of dedicated radiological slots for morning diagnosis of acute gallstone disease, and theatre and anaesthetic staff for afternoon slots, meant rates of ELC increased from 10% to 58% in just 6 months. Alternatively, it has been proposed that ELC cases can be managed on a "Semi-Acute" list. A model from Cockbain et al. (19) proposed a twice weekly-dedicated ELC list. Under this model, patients presenting with an acute gallstone diagnosis would be stabilised and discharged, with a date to return for ELC within one week. This model was associated with significant savings from reduced bed occupancy and less pressure on shared emergency lists.

Study Limitations

Our study has several limitations. Due to its retrospective design, there is a risk of selection bias. Furthermore, there may be underlying unrecorded patient factors influencing the choice of ELC and DLC. As only seven cases of ELC were performed, the true rate of peri-operative complications may be underestimated in this cohort. Additionally, there may be longer- complications in the ELC and DLC groups not captured in the study.

CONCLUSION

Our study demonstrates that delayed laparoscopic cholecystectomy has an impact on patients' health due to the recurrence of gallstone morbidity, as well as an adverse financial impact due to the use of additional acute hospital resources. These findings advocate the use of early laparoscopic cholecystectomy, which is associated with favourable health and financial benefits without affecting surgical complication rates.

Ethics

Ethics Committee Approval: The study received approval from the University College London Hospitals NHS Foundation Trust local audit department board (UCLH Audit Committee GIS/06.03.2012).

Informed Consent: Retrospective study.

Acknowledgments

We would like to thank the general surgery department at the secondary-care hospital for their support in the study.

Footnotes

Author Contributions

Concept - M.V., C.Y., K.D.; Supervision - K.D.; Fundings- K.D.; Design - M.V., C.Y., K.D.; Data Collection or Processing - K.D.; Analysis or Interpretation - M.V., C.Y.; Literature Search - M.V., C.Y.; Critical Review - M.V., C.Y., K.D.; Writing - M.V., C.Y., K.D.

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

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

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ORIGINAL ARTICLE
Turk J Surg 2025;41(1):24-30

Cholecystectomy associated vasculobiliary injuries: Incidence and impact on surgical repair outcomes

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ABSTRACT

Objective: Bile duct injury with concomitant vascular injury is a common complication of cholecystectomy. The influence of concomitant vascular injury on the presentation and management of bile duct injury remains debatable. This study aimed to determine the incidence of concomitant vascular injury in patients with post-cholecystectomy bile duct injury and its impact on presentation and short-term outcomes following biliary repair.

Material and Methods: This prospective study was done between November 2019 and December 2022. Patients presenting with post-cholecystectomy bile duct injury were investigated to detect vascular injury using computed tomography angiography. A comparative analysis of clinical presentation, and results of biliary reconstruction was performed on patients with and without concomitant vascular injury. McDonald criteria were used to grade the outcome of biliary reconstruction in these patients.

Results: We studied 48 patients with bile duct injury of which 19 (39%) patients had concomitant vascular injury on imaging. Concomitant vascular injury was found in 87% and 42% of patients with Strasberg type 4 and type 3 injury, respectively. At presentation, the incidence of liver abscesses was significantly higher in patients with concomitant vascular injury. After two years of biliary repair, 75% of patients had McDonald Grade A status, irrespective of whether vascular injury was present.

Conclusion: Approximately 39% of patients with biliary injury had concomitant vascular injury. A higher grade of biliary injury was associated with increased chances of concomitant vascular injury. The presence of vascular injury did not correlate with increased operative morbidity, prolonged hospital stay, or inferior outcomes of delayed biliary repair.

Keywords: Cholecystectomy, vasculobiliary injury, biloma, liver abscess, McDonald grade

INTRODUCTION

Bile duct injury (BDI) is a devastating complication of cholecystectomy. Studies suggest that between 12% and 61% of cases of BDI, particularly those involving proximal ducts, are associated with concomitant vascular injuries (1-7). Among the affected vessels, the right hepatic artery is the most commonly damaged, whereas injury to the portal vein is rare (8). The consequences of concurrent vascular injury can vary widely, ranging from asymptomatic conditions to potentially life-threatening complications (1-3). Despite standardized surgical techniques and safety measures adopted in cholecystectomy, vasculobiliary injuries (VBI) continue to occur, leading to significant morbidity and mortality (9-11).

The impact of concomitant vascular injury on the outcomes of biliary repair remains uncertain (3-7). Additionally, the appropriate timing for biliary repair in the presence of vascular injury is subject to debate (5-6,12-15). In resource-constrained settings, it is not cost-effective to routinely screen every biliary injury for concurrent vascular damage. Only a limited number of studies have prospectively investigated the incidence, presentation, and impact of concurrent vascular injury on the outcomes of biliary reconstruction.

This study aimed to determine the incidence of concomitant VBI and evaluate its impact on the outcomes of biliary repair surgery.

MATERIAL and METHODS

This prospective observational study was conducted at a tertiary-care hospital in Northern India between November 2019 and December 2022. Approval for conducting the study was obtained from the Institutional Ethics Committee of Indira

Cite this article as: Singla S, Singh RK, Kumar S, Prasad U, Mandal M, Kumar S. Cholecystectomy associated vasculobiliary injuries: Incidence and impact on surgical repair outcomes. *Turk J Surg.* 2025;41(1):24-30

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Received: 11.09.2024
Accepted: 29.01.2025
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2025.6577

Available at www.turkjsurg.com

Gandhi Institute of Medical Sciences (date: 14/12/2019, number: 1205/IEC/IGIMS/2019). Patients with documented BDI sustained during cholecystectomy were included in the study. Patients who did not undergo computed tomography (CT) angiography due to pregnancy or a contrast allergy were excluded. Additionally, patients with incidentally diagnosed gallbladder carcinoma on postoperative histopathology were excluded.

The demographic characteristics of patients, operative details of index cholecystectomy (obtained either through discharge card or telephone communication with the operating surgeon), presenting features, and details of biliary repair surgery were collected prospectively. During the study period, 61 patients with BDI were managed in our department. CT angiography to detect associated vascular injury was performed in 48 patients. These patients were enrolled in the study and were divided into two groups based on associated vascular injury on CT angiography: Patients with VBI and those with isolated bile duct injury (IBDI).

The management of patients with BDI followed standard protocol. Patients presenting with peritonitis or biloma were managed with intravenous fluids, broad-spectrum antibiotics and ultrasound-guided percutaneous drainage of collected bile. Patients presenting with cholangitis were managed with antibiotics and percutaneous transhepatic biliary drainage in selected cases.

These patients were given adequate time for resolution of biliary fistula, sepsis, and dyselectrolytemia. Any complication occurring during the follow-up was recorded. The patients were investigated for potential vascular injury and aberrant vascular anatomy, classified and they were classified according to Michel's classification (Supplementary Material 1), using CT angiography before definitive reconstruction. Preoperative magnetic resonance cholangiopancreatography (MRCP) was routinely performed to classify BDI using the Strasberg classification (Supplementary Material 2) (16). Patients were planned for delayed biliary reconstruction, usually 6-8 weeks after control of sepsis/cholangitis. The duration of injury was defined as the time from cholecystectomy to the day of repair.

Surgical Procedure: After careful adhesiolysis, a healthy segment of proximal bile duct was obtained for mucosa-to-mucosa anastomosis. Thirty-six patients underwent Roux-en-Y hepaticojejunostomy (HJ) with Hepp-Coiunaud technique using 4-0 absorbable monofilament sutures (17). Length of hospital stay was taken as the number of days after surgery.

Follow-up: Post-operative follow-up was performed every three months for a minimum of 18 months. At each follow-up, clinical examination, liver function tests, and, if required, imaging studies (ultrasound abdomen/MRCP) were done. After the last follow-up at 18 months, patients were classified according to McDonald criteria (Supplementary Material 3) to assess the operative results (18).

Statistical Analysis

Data are described in terms of range, mean ± standard deviation, frequency (number of cases), and relative frequency (percentages), as appropriate. To compare categorical data, the chi-square (χ^2) test was performed. Statistical significance was set at a p-value less than 0.05. All statistical calculations were performed using (Statistical Package for the Social Science) SPSS 21version (SPSS Inc., Chicago, IL, USA) for Microsoft Windows.

RESULTS

The study included 48 patients (36 men and 12 women) with post-cholecystectomy BDI. The median age of the patients was 41 years (range, 13-66 years). Indication for cholecystectomy was chronic calculous cholecystitis in 46 patients, whereas 2 patients were operated on for acute cholecystitis. In our study, open cholecystectomy was performed in 24 patients; 20 patients had undergone laparoscopic cholecystectomy; whereas laparoscopic cholecystectomy converted to open surgery was performed in 4 patients.

Vascular injury was detected in 19 (39%) patients, with the right hepatic artery being the most common injured vessel, followed by the middle hepatic artery injury (Figure 1a). No case of portal vein injury was observed in our study. On CT angiography, 84% (16/19) of patients with VBI had evidence of collateral formation (Figure 1b).

Five patients (10.5%) had a history of blood transfusion during the index cholecystectomy, of whom 3 (6.3%) had VBI. The duration of hospital stay following the index cholecystectomy did not show a significant difference between patients with VBI and IDBI. A hospital stay exceeding 3 days was observed in 23 (79%) patients with IDBI, in comparison to 17 (90%) in the VBI group (p=0.646). Re-exploration with peritoneal lavage and abdominal drain placement was required in 10 (21%) patients. The need for re-exploration was higher in patients with VBI than in patients with IBDI (26% vs. 17%). The demographic profile of

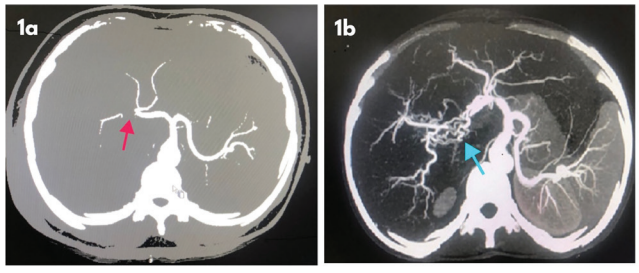

Figure 1. Computed tomography angiographic image showing (1a) showing right hepatic artery injury (red arrow), (1b) showing formation of web of collaterals after right hepatic artery injury (blue arrow).

patients, clinical presentation, and details of management have been provided in Table 1.

Overall, Strasberg type E2 BDI (48%) was seen in the majority of patients, followed by Type E3 (25%), Type E4 (17%), and Type E5 (2%). Strasberg type A injury was encountered in two patients. In our study, the incidence of vascular injury correlated with the complexity of bile duct injury. The concomitant vascular injury was present in 87% of patients with type E4 injury, whereas only 26% of patients with type E2 biliary injury had associated vascular injury (Table 2). On CT angiography, aberrant vascular anatomy was detected in six patients. Five patients had Michels' Type 3 configuration, while one patient had Michels' Type 2 configuration (19). Among patients with aberrant anatomy, only two had associated vascular injury.

The incidence of liver abscess, transaminitis, and cholangitis in the VBI and IBDI groups has been detailed in Table 3.

Four patients in our study did not undergo biliary repair surgery. Two of these patients had developed secondary biliary cirrhosis with portal hypertension by the time they presented to us and were deemed unfit for surgery. The other two patients had Strasberg type A injuries and were managed non-surgically. Biliary reconstruction was performed in 36 patients (23 patients with IBDI and 13 patients with VBI). Overall, the median interval between injury and repair was seven months (interquartile range, 5-14 months). There was no statistical significance (p=0.23) between two groups with regard to injury-to-repair duration.

In patients undergoing reconstructive surgery (n=36), five had a bile leak in the postoperative period. Three of these patients belonged to the IBDI group, while two belonged to the VBI group. In the IBDI group, one patient required multiple PCDs to control the anastomotic leak. The bile leak was managed conservatively in four other patients. A sepsis-related death occurred on post-operative day 2 in a patient with VBI.

The mean duration of hospital stay after definitive repair was 6.5±3.6 days. There was no statistically significant difference regarding the duration of hospital stay between the two groups (p=0.38) (Table 4).

Overall, patients had a mean follow-up of 26±10 months (range, 18-36 months). There was no statistically significant distinction between the two groups regarding the duration of their follow-up (p=0.14).

Table 1. Demographic and clinical characteristics of respective groups

Parameters	IBDI (29)	VBI (19)	p-value
Age (years)	41.38± 12.78	44.26± 12.92	0.66
Females: Males	21: 8	15:4	0.60
Multiple stones	20	14	0.72
Chronic cholecystitis	27	19	0.07
Acute cholecystitis	2	0	0.07
Laparoscopic approach	13	7	0.81
Open cholecystectomy	14	10	0.81
Duration of index surgery (<2 hours)	15	13	0.47
Intra operative bile duct injury detection	0	2	0.15
Blood transfusion	2	3	0.37
Hospital stay after index cholecystectomy (>3 days)	23	17	0.64
Bile leakage	15	13	0.25
Biliary stricture	14	6	0.35
Re-exploration before definitive surgery	5	5	0.12
Percutaneous drainage	16	10	0.97
Percutaneous transhepatic biliary drainage	4	5	0.27

IBDI: Isolated bile duct injury, VBI: Vasculobiliary injury

Table 2. Distribution of level of biliary injury (Strasberg-Bismuth) by surgical approach and injury type (isolated bile duct injury or vasculobiliary injury)

Biliary injury-type (Strasberg-Bismuth)	Laparoscopic cholecystectomy		Open cholecystectomy		Laparoscopic to open conversion	
	IBDI	VBI	IBDI	VBI	IBDI	VBI
Type 2	8	1	8	5	1	0
Type 3	5	3	2	2	0	0
Type 4	0	3	1	2	0	2
Type 5	0	0	0	0	1	0
Total	13	7	11	9	2	2

IBDI: Isolated bile duct injury, VBI: Vasculobiliary injury

Table 3. Comparison between IBDI and VBI with respect to complications and surgical results

Parameters	IBDI (n=29)	VBI (n=19)	p-value
Hemorrhage	2	1	0.82
Liver abscess	2	5	0.06
Cholangitis	14	10	0.76
Transaminitis	14	7	0.43
Type 2	17	6	0.11
Type 3	7	5	0.86
Type 4	1	7	0.01
Aberrant vascular anatomy	4	1	0.03
Repair within 1 year	14	9	0.40
Post operative bile leak	3	2	0.49

IBDI: Isolated bile duct injury, VBI: Vasculobiliary injury

Table 4. Follow-up of patients after biliary repair		
	IBDI (n=23)	**VBI (n=13)**
Lost to follow-up	3	2
Death	0	1
McDonald Grade A	15	8
McDonald Grade B	3	2
McDonald Grade C	1	0
McDonald Grade D	1	0
IBDI: Isolated bile duct injury, VBI: Vasculobiliary injury		

DISCUSSION

BDI is a potentially lethal complication of cholecystectomy. Concomitant vascular injury may further complicate the situation. Damage to vessels can impair blood supply to the bile ducts and liver, resulting in ischemia and tissue damage.

In the present study, concomitant vascular injury was detected in 39% of patients with bile duct injury. The most commonly involved vessel was the right hepatic artery. The incidence of VBI varies significantly across different studies, with reported rates ranging from 12% to 61%. This divergence is attributed to the selective utilization of preoperative angiography for identifying vascular injuries. Studies that incorporate routine angiography tend to report higher incidences (3,6). According to the literature, the laparoscopic approach is associated with a higher incidence of VBI compared to open cholecystectomy (6). In our study, the majority of patients underwent open cholecystectomy, which could account for the lower incidence of vascular injury (39%). Bismuth and Lazorthes (20) reported a comparable incidence of vascular injury among patients with post-open cholecystectomy bile duct injuries.

In this study, we found a correlation between the occurrence of vascular injury and the type of biliary injury. Specifically, vascular injury was detected in 87% of patients with Strasberg E4 BDI, whereas only 26% of patients with Strasberg E2 injury had associated vascular injury. Prior studies have also reported an association between the severity of biliary injury (Strasberg E3, E4) and the likelihood of concomitant arterial injury (6,12,21). In our analysis, 60% of patients with concomitant vascular injury exhibited a high type (E3 or E4) biliary injury, whereas only 40% of patients exhibited high type injury in the IBDI group. Buell et al. (12) reported a similar correlation between the incidence of arterial injury and the grade of biliary injury. In our study, a higher grade of biliary injury was more common in patients who underwent a laparoscopic procedure (n=11, 55%) than in those who underwent an open surgery (n=7, 29%). Other researchers have also observed a similar association between the laparoscopic approach and the grade of BDI (10,22).

The hepatic artery serves as a primary source of blood supply to the biliary system, and its injury may result in ischemic injury to the liver and the bile ducts. In our investigation, we observed that 26.3% of individuals with VBI developed liver abscesses, contrasting with 6.9% among those with IBDI. Among the patients who present with liver abscess (n=7): 72% (5) belonged to the VBI group. This observation is in accordance with Bilge et al. (6), who reported a 75% incidence rate of hepatic abscess in their study. However, the incidence of liver abscesses reported by Stewart et al. (21) was lower at 31% among VBI patients. The variation in the incidence of liver abscesses may be related to the grade of BDI and the interval between injury and definitive repair.

In our study, 50% (n=24) of patients had presented with episodes of cholangitis. This high incidence of cholangitis can be partly attributed to the fact that the majority of these patients underwent delayed repair. The delay in treatment was due to the Coronavirus disease-2019 pandemic, which necessitated the postponement of elective surgeries at our institute.

The impact of concomitant vascular injury on the outcomes of biliary repair remains debatable. Initially, it was reported that vascular injury could lead to a complicated postoperative course, marked by an increased incidence of anastomotic leaks, recurrent cholangitis, and anastomotic stricture formation in the long-term (4,12,23,24). However, some recent studies have shown that concomitant vascular injury does not significantly increase mortality rates or negatively impact the success of biliary repair, especially when adequate collateral circulation has been established (3,21). In our study, 36 patients underwent delayed definitive repair after resolution of sepsis and healing of biliary fistula. This approach allowed sufficient time for the injury to stabilize, and for collateral circulation to be established through the hilar vascular collaterals, which could explain the equivalent long-term results observed in the IBDI and VBI groups.

We observed a similar postoperative hospital stay in both the IDBI and VBI groups, which is consistent with the findings of Alves et al. (3). Several studies have reported higher postoperative complications and prolonged hospital stays in patients with vascular injury (6,12). Our findings could be attributed to the delayed approach that we employed in this study. The delayed surgery allowed inflammation to subside and adequate collateralization to develop, mitigating the potential complications of concomitant vascular injury.

The perioperative morbidity and mortality rates associated with the HJ procedure typically range from 20% to 35% and 1% to 4%, respectively (25,26). In our study, one patient died on the second postoperative day due to fulminant sepsis, resulting in a mortality rate of 2%. The incidence of mortality in our study aligns with the findings of Stewart et al. (21), who reported a mortality rate of 2.4%. Postoperative bile leak occurred in 5 patients (17%) in our study. Among these patients, three belonged to the IBDI group,

while two belonged to the VBI group. Our study did not identify any significant differences in terms of hospital stay or the rate of postoperative complications between the two groups.

After 18 months of biliary reconstruction, 75% of the patients had McDonald's Grade A outcome, regardless of the presence of vascular injury. At a follow-up of 26±10 months, both the VBI and IDBI groups showed excellent to good repair outcomes, ranging from 88% to 90%. In the literature, the success rate of biliary repair varies from 84% to 98% (29). In our study, collateral circulation arising from hilar shunt was observed in 84% of patients with VBI, serving as a compensatory mechanism for the injured hepatic artery. The good outcomes observed in our study, irrespective of vascular injury, could be attributed to delayed repair, which allowed healing of biliary fistula and resolution of sepsis. Additionally, some patients developed a spontaneous hepatico-duodenal fistula, providing temporary relief of symptoms (Figure 2).

Study Limitations

Our study had several limitations that should be acknowledged. Firstly, the standard technique of cholecystectomy, which includes delineating the critical view of safety, may not have been consistently employed in all cases studied. This inconsistency could have affected the incidence of vascular injury. Secondly, the experience of the primary operating surgeon was neither documented nor verified. Additionally, the higher incidence of vascular injury observed in our study population could be attributed to referral bias. It is possible that patients with more complex or severe biliary injuries, including those with concomitant vascular involvement, were preferentially referred to our institution. Consequently, the incidence of vascular injury in our study may not be representative of the general population undergoing cholecystectomy. Another important limitations of our study is the small sample size and short follow-up period, which may have restricted our ability to capture the long-term consequences of vascular biliary injury. It is important to consider these limitations when interpreting the findings of our study.

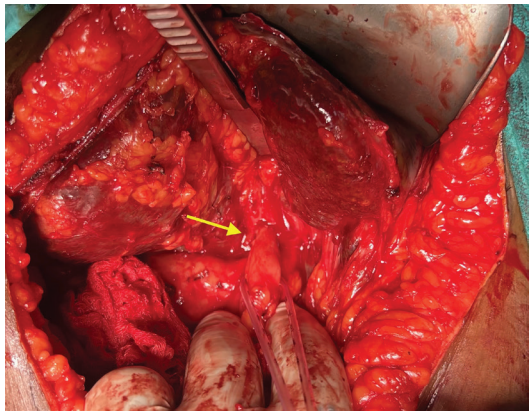

Figure 2. Intraoperative image showing spontaneous hepatico-duodenal fistula in a patient with type 3 bile duct injury.

CONCLUSION

Patients with post-cholecystectomy BDI have a high incidence of concomitant vascular injury. The laparoscopic approach is associated with complex biliary injuries and a higher likelihood of VBI compared to the open approach. The incidence of vascular injury correlates with the severity of biliary injury. Patients with VBI are more susceptible to developing hepatic abscesses than those with IBDI. Delayed Roux-en-Y HJ provided excellent functional outcomes regardless of the presence of vascular injury. In cases where delayed repair (>6 weeks) is contemplated, omitting CECT to detect concomitant vascular injury may be acceptable, as it does not alter the management plan or the surgical result.

Ethics

Ethics Committee Approval: Approval for conducting the study was obtained from the Institutional Ethics Committee of Indira Gandhi Institute of Medical Sciences (date: 14/12/2019, number: 1205/IEC/IGIMS/2019).

Informed Consent: Prospective study.

Footnotes

Author Contributions

Concept – S.S., S.K., R.K.S.; Design – S.S., M.M., San.K.; Materials – S.S., S.K., R.K.S.; Data Collection or Processing – S.S., S.K., R.K.S.; Analysis or Interpretation – M.M., S.K., R.K.S.; Literature Search – U.P., M.M., R.K.S.; Critical Review – S.S., S.K, R.K.S.; Writing - San.K., S.S., R.K.S.

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

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

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Supplementary Material 1. Michel's classification of hepatic artery anatomical variations	
Type	
1	Normal anatomy
2	Replaced left hepatic artery from left gastric artery
3	Replaced right hepatic artery from superior mesenteric artery
4	Replaced right hepatic and left hepatic artery
5	Accessory left hepatic artery
6	Accessory right hepatic artery
7	Accessory right hepatic and left hepatic artery
8	Replaced right hepatic artery and accessory left hepatic artery or Replaced left hepatic artery and accessory right hepatic artery
9	Common hepatic artery from superior mesenteric artery
10	Common hepatic artery from left gastric artery

Supplementary Material 2. Bismuth-Strasberg classification for bile duct injury	
A	Bile leak from cystic duct or duct of Luschka
B	Occlusion of part of biliary tree, commonly a right segmental duct
C	Bile leak from divided right segmental duct
D	Lateral injury to the extrahepatic bile ducts
E	Circumferential injury of major duct
E_1	Common hepatic duct stump more than 2 cm from the confluence
E_2	Common hepatic duct stump less than 2 cm from the confluence
E3	Hilar injury with intact confluence
E4	Confluence is involved, right and left bile ducts are separated
E5	Injury of aberrant right sectoral duct with concomitant injury of main bile duct

Supplementary Material 3. McDonald's grading system for assessment of results of biliary reconstruction	
Grade A	Normal liver function test results, asymptomatic
Grade B	Mild elevation liver function test results, asymptomatic
Grade C	Abnormal liver function test results, cholangitis, pain
Grade D	Surgical revision or dilation required

ORIGINAL ARTICLE
Turk J Surg 2025;41(1):31-41

Double jeopardy: The aortic-diaphragmatic injury complex

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ABSTRACT

Objective: Concurrent traumatic diaphragmatic hernia (TDH) and blunt thoracic aortic injury (BTAI) are rare but critical injury complexes that result from high-energy trauma mechanisms. This study analyzed the epidemiology, diagnostic approaches, risk factors, and outcomes of concurrent TDH and BTAI and proposed a structured treatment algorithm.

Material and Methods: A retrospective analysis was performed using trauma records from a level 1 trauma center (2004-2024). Four male patients with confirmed concurrent TDH and BTAI were included in the study. Data on demographics, injury characteristics, diagnostic methods, treatment, and outcomes were collected. Statistical analyses were conducted using appropriate tests.

Results: All injuries were caused by high-energy traumas. Mean injury severity score was 38 and the revised trauma score was 6.58. A massive transfusion protocol was activated in 75.0% of cases. Diagnostic imaging showed varying accuracies, with computed tomography demonstrating superior sensitivity for both injuries. All TDH were left-sided posterolateral and BTAI predominantly involved the isthmus. Management followed a sequential approach, with 75.0% of diaphragmatic repairs preceding the aortic intervention. Mean hospital stay was 33 days, with complications including infections, deep vein thrombosis, and atelectasis. Despite the high severity of the injury, all patients survived.

Conclusion: Concurrent TDH and BTAI are rare, but critical injury complexes. Early recognition through structured diagnostic protocols and sequential management guided by institutional capabilities can achieve favorable outcomes despite high injury severity.

Keywords: Wounds and injuries, diaphragmatic hernia, traumatic, abdominal injuries, aortic rupture, thoracic injuries

INTRODUCTION

Traumatic diaphragmatic hernia (TDH) and blunt thoracic aortic injury (BTAI) present unique challenges in trauma management. Diaphragmatic herniation following blunt trauma occurs in a small proportion of cases, predominantly affecting the left hemidiaphragm, whereas BTAI, although uncommon, has a devastating immediate mortality rate (1,2). Although both injuries have been extensively studied individually, their concurrent occurrence has been infrequently discussed in the literature. This injury complex has gained increasing recognition with the advent of high-speed vehicular crashes, improved pre-hospital care systems, and enhanced diagnostic capabilities. Patients with TDH have a six-fold increased risk of BTAI, reflecting shared high-energy injury mechanisms, primarily motor vehicle collisions. Despite their clinical significance, there is limited literature examining these concurrent injuries, with the last major series reporting only seven cases (3). Although TDH and BTAI have been extensively studied as independent entities, their concurrent presentations remain poorly understood. We hypothesize that this injury complex occurs more frequently than is recognized in high-energy trauma, is followed by predictable injury patterns, and that outcomes can be improved through standardized diagnostic and treatment protocols.

This study aimed to analyze the epidemiology, diagnostic approaches, and outcomes of concurrent TDH and BTAI, focusing of developing an evidence-based treatment algorithm based on institutional capabilities.

MATERIAL and METHODS

A descriptive retrospective analysis was performed using the medical records from the trauma database of the Division of Trauma Surgery at the University of

Cite this article as: Kruger VF, Langoni ML, Meneses CJ, Calderan TA.R, Hirano ES, Fraga GP. Double jeopardy: The aortic-diaphragmatic injury complex. *Turk J Surg.* 2025;41(1):31-41

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Received: 17.01.2025
Accepted: 12.02.2025
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2025.6720

Available at www.turkjsurg.com

Campinas, covering the years 2004 to 2023. The facility serves as a level 1 trauma center for a metropolitan area of 3.9 million inhabitants, featuring a dedicated 16-bed trauma floor and 10-bed trauma intensive care unit (ICU). Of the 40 cases of blunt TDH and 47 cases of BTAI, we only included patients with confirmed concurrent injuries. The exclusion criteria were grade I diaphragmatic injuries, congenital defects, deaths before imaging, and incomplete medical records.

Data collection included demographics, trauma bay presentation, injury characteristics (diaphragmatic grade/location and aortic classification/position), herniated organs, and associated injuries. Injury severity score (ISS) and revised trauma score (RTS) were calculated for all patients.

Prior to 2008, whole-body computed tomography (CT) scanning was strictly limited to selected cases, with most trauma patients undergoing selective radiography or segmental CT. Since then, our diagnostic protocol has standardized contrast-enhanced whole-body CT scanning for all hemodynamically stable patients with high-energy trauma mechanisms, when immediate surgery is not indicated.

Treatment documentation covered diagnostic methods, surgical timing, approach selection, and repair techniques. Our protocol for diaphragmatic injuries favors laparotomy or laparoscopy using interrupted non-absorbable sutures with chest drainage. Aortic repair primarily employs endovascular approaches when anatomically suitable, with open repair reserved for specific indications. The timing of aortic intervention was determined based on the associated injuries, patient stability, and prosthesis logistics.

Injuries were classified using standardized criteria. The American Association for the Surgery of Trauma organ injury scale (4) was used for diaphragmatic injuries (grades II-V) and the Society for Vascular Surgery (5) grading system was used for aortic injuries (grades I-IV). Postoperative care followed a standardized protocol, including routine imaging and appropriate anticoagulation therapy. Outcome measures included length of hospital stay, complications, reinterventions, mortality, and follow-up data.

Statistical Analysis

To address the limitations of our small sample size (n=4), statistical analysis included descriptive statistics with median and range for continuous variables.

Fisher's exact test was used for categorical data, and bootstrap resampling was used for confidence intervals. Detailed individual case analyses were performed to strengthen clinical correlations. The analysis was performed using SPSS (version 25.0; IBM Corp., Armonk, NY, USA) was considered statistically significant at $p<0.05$. The study received approval from the Ethics in Research Committee of University of Campinas (CAAE: 78780517.4.0000.5404 and 66498422.9.0000.5453).

RESULTS

Four male patients with concurrent TDH and BTAI were analyzed. The mean age was 32.0±8.4 years. All injuries were caused by high-energy trauma mechanisms. Initial assessment revealed hemodynamic instability in 75.0% of patients, with a mean ISS of 38.0±9.8 and a mean RTS of 6.58±1.2. Glasgow Coma scale scores were distributed bimodally: 50.0% severe and 50.0% mild. Epidemiological data are shown in Table 1.

Table 1. Epidemiological and clinical characteristics of trauma patients

Parameters	Patient 1	Patient 2	Patient 3	Patient 4	Mean ± SD (range)
Trauma severity scores					
ISS	38	38	50	26	38.0±9.8 (26-50)
RTS	4.95	7.84	5.68	7.84	6.58±1.2 (4.95-7.84)
Pre-hospital					
Rescue type	Ground	Ground	Ground	Air	-
Trauma mechanism					
Mechanism	Collision	Rollover	Struck	Rollover	-
Vehicle type	Motorcycle	Car	Car	Car	-
Position	Driver	Passenger	Pedestrian	Driver	-
Safety device	Helmet	No seatbelt	Out of lane	Seatbelt	-
Injury grade					
TDH grade	IV	IV	IV	IV	-
BTAI grade	III	III	III	III	-
Clinical course					
Positive blood culture	Y	Y	Y	Y	100.0%
Length of stay (days)	40	40	42	12	33.0±8.4 (12-42)
ICU stay (days)	34	20	22	9	21.0±6.8 (9-34)
Rehabilitation (days)	90	120	150	100	128.0±24.6 (90-150)

ISS: Injury severity score, RTS: Revised trauma score, TDH: Trauma diaphragmatic hernia, BTAI: Blunt traumatic aortic injury, ICU: Intensive care unit, SD: Standard deviation

Most patients (75.0%) required massive transfusion protocol (MTP) activation, receiving an average of 4 units of packed red blood cells, 4 units of fresh frozen plasma or cryoprecipitate (1 U/10 kg), and 1 g of tranexamic acid. Microperfusion parameters showed significant derangements, with initial lactate levels >6.0 mmol/L and base excess <-5 mmol/L, indicating 100% sensitivity for the MTP requirement. The microperfusion parameters showed significant derangements, and are expressed in Table 2.

Diagnostic imaging has shown varying accuracies. Chest radiography (CXR) demonstrated 50.0% and 75.0% sensitivity for TDH and BTAI, respectively. CT angiography achieved 100% sensitivity and specificity for BTAI, whereas contrast-enhanced CT showed a sensitivity of 75.0% for TDH. Table 3 and 4, Figures 1-3.

Three cases were diagnosed within 2 hours of admission, with one TDH diagnosed at 47 days. All patients with TDH had left-

Table 2. Hemodynamic and microperfusion status in trauma room

Parameters	Patient 1	Patient 2	Patient 3	Patient 4
Vital signs				
SBP <90 mmHg	Y	Y	Y	N
HR >120 bpm	Y	Y	Y	N
RR >20 rpm	Y	Y	Y	Y
Shock index	2.0	1.5	1.5	0.8
Laboratory values				
Base excess (mmol/L)	-12.1	-14.3	-8.9	-2.1
Lactate (mmol/L)	6.8	7.6	6.5	3.6
Ionic calcium (mmol/L)	0.90	0.95	1.1	1.2
Other parameters				
Massive transfusion protocol	Y	Y	Y	N
FAST	Pos	Pos	Neg	Neg
Urine output <1.5 mL/kg/h	Y	Y	Y	N
Tranexamic acid	Y	Y	Y	Y

SBP: Systolic blood pressure, HR: Heart rate, RR: Respiratory rate, FAST: Focused assessment with sonography in trauma

Table 3. Initial chest X-ray findings in trauma patients

Findings	Patient 1	Patient 2	Patient 3	Patient 4
Mediastinal				
Mediastinal widening	Y	Y	Y	Y
Obscured aortic contour	Y	Y	Y	Y
Pleural/rib/parenchymal				
Left hemothorax	Y	Y	N	Y
Left rib fractures	Y	Y	N	Y
Pulmonary opacity	Y	Y	Y	N
Additional				
Right tracheal deviation	Y	Y	Y	Y
Intrathoracic bowel loop	N	Y	N	N
Left main bronchus depression	N	N	Y	Y
Blurring of the diaphragm contour	Y	Y	Y	Y
Atelectasis	N	Y	Y	Y

Table 4. Initial chest CT findings in trauma patients

Findings	Patient 1	Patient 2	Patient 3	Patient 4
Vascular/mediastinal				
Pseudoaneurysm	Y	Y	Y	Y
Mediastinal hematoma	Y	N	N	N
Pneumothorax left	Y	Y	N	Y
Pneumothorax right	N	N	N	Y
Hemothorax left	Y	Y	Y	Y
Hemothorax right	Y	Y	N	N
Pulmonary				
Pulmonary contusion left	Y	Y	N	Y
Pulmonary contusion right	Y	N	N	N
Left rib fractures	Y (1-8)	Y (2-5)	N	Y (1-10)
Right rib fractures	N	N	N	Y (3-7)
Clavicle fracture left	Y	N	N	N
Intrathoracic structure	Y	Y	Y	N
Pneumomediastinum	Y	N	N	N
Atelectasis	Y	Y	Y	Y
Subcutaneous emphysema	Y	Y	N	Y

CT: Computed tomography

sided posterolateral injuries. Herniated organs included the isolated stomach (50.0%), transverse colon with spleen (25.0%), and liver with stomach (25.0%). BTAI predominantly involved the isthmus (75.0%), with one case affecting the anterior wall of the descending aorta (25.0%). The associated injuries are listed in Table 5.

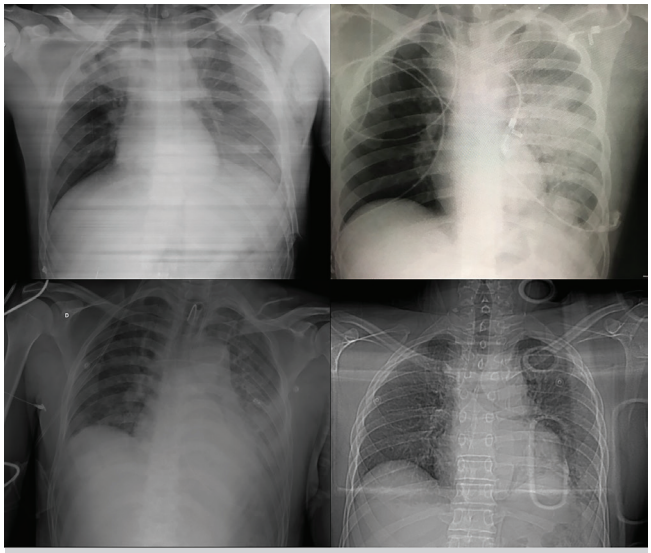

Figure 1. CXR demonstrating mediastinal widening and blurred diaphragmatic contour in patients 1-4, suggestive of BTAI and TDH.

CXR: Chest radiography, BTAI: Blunt thoracic aortic injury, TDH: Traumatic diaphragmatic hernia

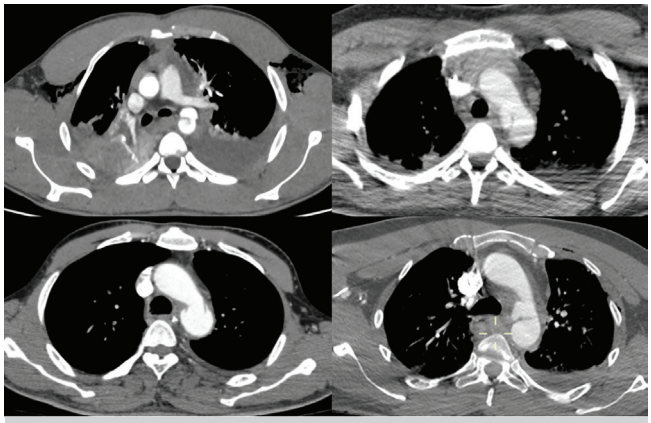

Figure 2. Axial CT angiography showing BTAI grade III in patients 1-4.

CT: Computed tomography, BTAI: Blunt thoracic aortic injury

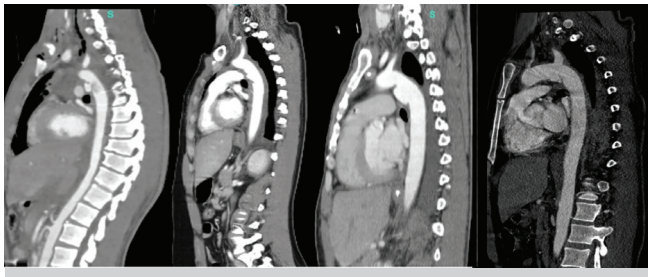

Figure 3. Sagittal CT angiography showing BTAI grade III in patients 1-4.

CT: Computed tomography, BTAI: Blunt thoracic aortic injury

Management followed a sequential approach, with 75.0% of diaphragmatic repairs preceding aortic intervention. Most diaphragmatic repairs (75.0%) were performed via laparotomy, with one laparoscopic repair in a case of delayed diagnosis. All aortic injuries underwent endovascular repair between 3 and 28 days post-injury.

The mean hospital stay was 33.0±8.4 days, with a median ICU stay of 20 days. Early complications included bloodstream infections

Table 5. Associated injuries in trauma patients

Body region/ injuries	Patient 1	Patient 2	Patient 3	Patient 4
Thoracic				
Pneumothorax	Y	Y	N	Y
Hemothorax	Y	Y	Y	Y
Rib fractures	Y	Y	N	Y
Clavicle fracture	Y	N	N	N
Pulmonary contusion	Y	Y	N	Y
Abdominal				
High-grade liver laceration	Y	N	N	N
Low-grade liver laceration	N	Y	N	N
Low-grade kidney injury	Y	N	N	N
Abdominal wall hematoma	Y	N	N	N
Extraperitoneal bladder injury	N	Y	N	Y
Head				
Subarachnoid hemorrhage	Y	N	Y	N
Subdural hematoma	Y	N	Y	N
Skull fracture	Y	N	N	N
Spine				
Unstable fractures	N	N	N	N
Stable fractures	Y	N	N	N
Long bones				
Open fracture lower limb	Y	N	Y	N
Open fracture upper limb	N	Y	N	N
Pelvis				
Ischio-pubic fracture	N	Y	N	Y
Open book fracture	N	N	N	N
Sacral fracture	N	Y	N	Y

(100%), pneumonia (75.0%), deep vein thrombosis (50.0%), and atelectasis requiring prolonged ventilation (25.0%). Procedure-related complications included femoral artery pseudoaneurysms following thoracic endovascular aortic repair (TEVAR). Long-term follow-up (1-5 years) demonstrated favorable outcomes in three patients with no endoleak, migration, or graft-related complications. One patient required reintervention at six months for stent graft migration, causing partial left subclavian artery occlusion, which was successfully managed with secondary stent deployment. All the patients achieved complete functional recovery and returned to their previous activities. Annual CT angiography surveillance confirmed stable graft positions.

Analysis revealed that a shock index >1.4 correlated to longer ICU stay (25 vs. 9 days) and increased hospital length of stay (40 vs. 12 days). ISS was correlated with length of stay. Despite the high injury severity, all patients survived and returned to work after rehabilitation [mean 128.0±24.6 days (90, 150)].

DISCUSSION

Over the past two decades, trauma surgeons have encountered an increasing incidence of complex injury patterns. This evolution reflects multiple factors: higher-energy vehicular crashes, improved pre-hospital care systems, and enhanced trauma center capabilities. Advancements in diagnostic technologies, particularly the widespread implementation of computed tomography as a screening tool, combined with structured trauma training programs, have significantly improved injury detection rates.

Diaphragmatic injuries, particularly blunt ruptures which are rare, are now more frequently diagnosed (3). Blunt thoracic aortic injuries, although uncommon, have shown high detection rates. This parallel increase in TDH and BTAI appears to be linked to shared injury mechanisms during high-energy trauma (6,7). Both conditions, although historically underdiagnosed, are being identified with increasing frequency in modern trauma practice, highlighting the importance of early recognition and standardized protocols.

Teixeira et al. (8) demonstrated that BTAI is present in one-third of motor vehicle crash fatalities and remains the second most common cause of death following blunt mechanisms. Fox et al. (9) reported that 80.0% of BTAI patients die before reaching a trauma center, with an additional 50.0% mortality within 24 hours of hospital arrivals, largely due to severely associated injuries. While our experience at Campinas confirmed the substantial injury burden, with a mean ISS of 38±9.8 (range 26-50), our series demonstrated markedly improved early survival outcomes.

The predominance of motor vehicle collisions (MVC) in concurrent TDH and BTAI has been consistently documented over the past three decades. For TDH, the authors (10-12) reported MVC rates of 63.0% and 65.0%, respectively, which are consistent with the National Data Bank (1) showing 63.0% MVC and 17.0% motorcycle crashes. Regarding BTAI, the multicenter study by the Aortic Trauma Foundation (13) demonstrated a 72.8% prevalence of MVC, with additional injury mechanisms including motorcycle collisions (14.0%) and pedestrian injuries (9.0%). Similarly, Fox et al. (9) found a 70.0% association with MVC. Notably, in the only previous series of concurrent TDH/BTAI, Rizoli et al. (3) reported that all seven cases resulted from MVC. Our series demonstrated a comparable distribution, with 75.0% of cases involving MVC. The specific mechanisms include two frontal fixed-object collisions with a subsequent rollover and one pedestrian struck. Although motorcycle collisions were underrepresented in our study, the increasing prevalence of motorcycle accidents in Brazil warrants particular attention from surgeons.

There is a lack of literature regarding the impact of safety devices on these injuries. In our series, 50.0% of the vehicle occupants were unrestrained by seatbelts. Although safe device use did not appear to affect mortality or injury grade, restrained victims demonstrated lower ISS and RTS scores, reduced length of stay in the ICU, and no activation of the MTP, suggesting a potential mitigating effect.

In our series, 75.0% of the patients presented with shock on admission, requiring MTP activation. This rate is notably higher than that previously reported for isolated TDH, in which Boulanger et al. (6) found a 34.0% overall incidence of shock admissions, with right-sided injuries showing a higher prevalence (56.0% vs. 22.0%). Other investigators have reported admission hypotension rates ranging from 30 to 66.0% in cases of TDH, while DuBose et al. (13) observed an incidence of isolated BTAI at 14.7% (10-15).

Our experience suggests that hemodynamic instability on admission is primarily caused by associated injuries rather than by TDH or BTAI alone. This observation aligns with that of Shah et al. (16), who found that early mortality in TDH predominantly results from associated injuries. All patients with a shock index >1.4 in our series demonstrated significant associated injuries. Two patients presented with similar injury patterns: Both had liver lacerations, hemothorax (>500 mL), and open fractures, with one additionally sustaining pelvic and renal injuries and the other experiencing extraperitoneal bladder injury. Interestingly, patient three presented with shock despite the absence of abdominal bleeding. In this case, we hypothesized that shock resulted from a combination of significant blood loss from open fractures and hemothorax, with hypotensive effects of sedative medications administered for emergency intubation (Glasgow Coma scale score <8 at the scene).

MTP activation in our series followed two distinct patterns: Patients 1 and 2 met the traditional assessment of blood consumption score triggers (systolic blood pressure <90 mmHg, heart rate >120, positive FAST) (17), whereas Patient 3's activation was based on metabolic derangement (base excess -8.9 mmol/L) and surgeon experience. Notably, we observed that a combination of lactate >5.0 mmol/L and calcium consumption demonstrated 100% sensitivity for massive transfusion requirements. Our findings expand upon those of Meyers and McCabe (10), who identified TDH as a marker of serious occult injuries. We observed an average of 4.2 associated injuries per patient, including concurrent injuries, suggesting that both TDH and BTAI may serve as markers of severe multisystem trauma.

Gelman et al. (18) reported distinct differences in CXR sensitivity between left (64%) and right (17.0%) diaphragmatic injuries. Common findings included an elevated hemidiaphragm (61.0%) and intrathoracic air-containing viscera (45.0%). In our TDH cases, CXR demonstrated limited diagnostic reliability with 25.0% sensitivity: Detecting intrathoracic viscera in only one case and missing three others. Diagnostic optimization strategies include pre-imaging nasogastric tube placement and serial radiographic examination. The most sensitive and specific finding in our series was the blurring of the diaphragmatic contour present in all cases. We consider this sign to be the most reliable early indicator of TDH because anatomical disruption of the diaphragmatic outline invariably precedes visceral herniation. While the intrathoracic hollow viscus is traditionally emphasized, this sign may be absent in early presentations. Therefore, trauma surgeons should maintain a high suspicion of TDH when encountering diaphragmatic contour irregularity, even in the absence of obvious herniation.

Despite the relatively low reported sensitivity of 41.0% for BTAI (19), several valuable radiographic findings warrant attention. While classical findings include mediastinal widening, aortic knob obliteration, deviation of the trachea to the right side, and apical pleural cap, these signs often lack specificity. Moreover, in patients with concurrent TDH, these findings can be obscured by pulmonary contusions, herniated viscera, hemothorax, pneumothorax, or atelectasis. Mediastinal widening [mean 8.75±0.5 cm (8.5-9.6)] and right tracheal deviation were present in all cases. Additional findings included an obscured aortic contour, left hemothorax (75.0%), and left main bronchus depression in two patients. These observations reinforce that CXR serves as an important initial screening tool but is insufficient for a definitive diagnosis.

Contrast-enhanced CT (CECT) demonstrated superior diagnostic capability for delineating injury patterns in both TDH and BTAI. Our institutional experience with whole-body CT revealed 100% sensitivity and specificity for BTAI and 75.0% sensitivity for TDH, showing a complete correlation with the intraoperative findings. These results align with those of previous studies that reported sensitivities of 61-100% and specificities of 76-99.0% (20,21). CT features proved particularly valuable, demonstrating higher sensitivity for left-sided injuries, enhanced diagnostic accuracy with coronal and sagittal reformations, and specific signs including the collar sign, dangling diaphragm, and intrathoracic visceral herniation.

For BTAI, CT angiography (CTA) has emerged as the primary diagnostic tool, demonstrating 98-100% sensitivity and specificity with near-perfect negative predictive value (22,23). Our cases showed 100% diagnostic accuracy, with CTA precisely characterizing the type and extent of vascular injury, identifying pseudoaneurysm in all cases, and associated periaortic hematoma in one case. CTA also provides superior detection of associated thoracic injuries, including hemopneumothorax, pneumomediastinum, and rib fractures. Although conventional angiography remains a potential diagnostic modality, it has been largely superseded by CTA. Our findings highlight two critical considerations in trauma imaging assessments. CXR and CECT should not be viewed as competing modalities. Although CECT offers superior diagnostic details, CXR plays an essential role as a screening tool. These imaging approaches are complementary, rather than substitutive. Second, CECT interpretation requires a broader perspective beyond identifying single injuries. Trauma surgeons must actively search for associated injuries that often require more urgent attention than initially suspected.

All BTAI cases and three TDH cases were diagnosed within 2 hours post-trauma, with one notable exception: A TDH case diagnosed at 47 days. This delayed diagnosis occurred in a patient with complex thoracic trauma including multiple bilateral rib fractures, atelectasis, hemothorax (>500 mL), pneumothorax, and splenic herniation. Overlapping injuries create a challenging radiological picture that compromises the sensitivity of CT imaging. Early diagnosis and surgical repair are crucial to prevent catastrophic outcomes in patients with TDH. This case highlights one of the three potential diagnostic pitfalls cited by Kruger et al. (11): Misinterpretation of initial imaging.

A high index of suspicion is mandatory for trauma surgeons, focusing on trauma mechanisms. Reiff et al. (24) demonstrated that combining specific crash parameters (frontal/near-side lateral compartment intrusion ≥30 cm, or delta-V ≥40 kph) with associated organ injuries provides high sensitivity (68-89.0%) for TDH prediction (Figure 4). Notably, BTAI showed a strong association with TDH (odds ratio 5.2, 95.0% confidence interval 2.2-12.5), exhibiting high specificity (96.6%) despite low sensitivity (15.4%). This suggests that although aortic injury strongly indicates potential TDH, its absence does not exclude the diagnosis. All the patients in our series had posterolateral left-sided grade IV TDH. Left-sided injuries predominate in hospital settings owing to three factors: Anatomical weakness at the left posterolateral embryonic fusion point, protective effect of the

Figure 4. High-energy trauma mechanism: (Top) Fixed barrier impact with severe deformation before rollover; (Bottom) lateral impact against barrier followed by rollover, resulting in extensive structural damage.

liver on the right hemidiaphragm, and detection bias. This bias becomes evident when comparing clinical and autopsy findings. While hospital studies show left-side predominance, autopsy studies reveal a more balanced distribution (right-sided injuries: 50.0% in autopsy vs. 14.0% in hospitalized patients), suggesting that right-sided TDH carries higher pre-hospital mortality (25).

Nikolic et al. (26) described two distinct patterns of BTAI mechanisms. Drivers sustain injury through thoracoabdominal compression during steering wheel impact, whereas front passengers experience aortic injury through hyperextension when sudden deceleration causes opposing forces between the forward-moving carotid vessels and fixed intercostal arteries. The aortic isthmus, anatomically located at the ligamentum arteriosum, represents the most vulnerable segment, accounting for 60.0 - 66.0% of injuries in the literature and 75.0% of cases in our series (8,9,13,26). This predominance is explained by the distortion of the aorta and vertebral column during rapid deceleration in frontal collisions (27). BTAI manifests as a spectrum of lesions, with Grade III injuries (pseudoaneurysm) representing the most prevalent form, both in the literature and in our four cases (8,13).

Our cases demonstrated distinct mechanisms of injury. The driver (Patient 4) showed extensive thoracic injuries from steering wheel compression during deceleration, whereas the front passenger (Patient 2) presented with fewer thoracic injuries but a significant hematoma near the left subclavian artery, reflecting the typical passenger injury pattern of caudorostral hyperextension.

TDH requires more urgent surgical management than BTAI because of the associated injuries that can cause hemodynamic shock or ventilatory impairment. Patients who required laparotomy demonstrated a higher ISS (42 vs. 26). In our series, except for one missed diagnosis, all patients underwent laparotomy with diaphragmatic repair before aortic intervention. The timing of diagnosis and repair was consistently less than 4 hours. In contrast, TEVAR procedures were significantly delayed (3-28 days post-injury). This timing differs from contemporary literature: In 2008, Demetriades et al. (28) reported a mean intervention time of 67 h; DuBose et al. (13) recently demonstrated shorter intervals from admission to repair of 36 h (within 6 h, 49.1%; within 24 h, 78.7%; within 48 h, 80.3%). Our extended timeline reflects several challenges: The need for custom endografts in young trauma patients with smaller, non-atherosclerotic aortas, public healthcare system constraints, the institutional learning curve, and complex team coordination. However, improved endograft availability, established supply chains, and streamlined team protocols have significantly reduced the treatment intervals in recent cases.

The management of BTAI has undergone changes over the last two decades, primarily driven by the development of minimally invasive endovascular techniques. The current treatment strategy begins with impulse control (IC). Multiple studies have validated beta-blocker-based anti-impulse therapy with additional agents to achieve target parameters. Jacob-Brassard et al. (29) meta-analysis of 8,606 patients confirmed the safety and feasibility of medical management, while recent studies by Arbabi et al. (30), established the following specific targets: systolic blood pressure <120 mmHg and HR 60-80 bpm.

DuBose et al. (31) recommend expectant management with blood pressure control for grade I lesions, as most heal spontaneously. Anti-impulse therapy dramatically reduced the risk of rupture from 12.0% to 1.5%. TEVAR has emerged as the dominant therapeutic approach for higher-grade injuries, accounting for 76.4% of cases in the largest multicenter analysis (32). While SVS guidelines (23) recommend urgent repair (<24 h), evidence suggests that delayed intervention may improve outcomes, with one study showing that delayed repair (>24 h) of BTAI is associated with improved survival (33). In our series, none of the patients presented with low-grade BTAI, which would have been suitable for non-operative management. All patients were admitted to the ICU with strict IC until endograft placement, managed with esmolol, with two cases additionally requiring nitroprusside. All four BTAI cases were treated with TEVAR by cardiac surgeons, whereas three TDH cases underwent exploratory laparotomy with reduction of herniated contents and diaphragmatic repair. One case of TDH was laparoscopically managed (Figure 5). This patient had a delayed diagnosis, was beyond the acute trauma phase, and lacked associated intra-

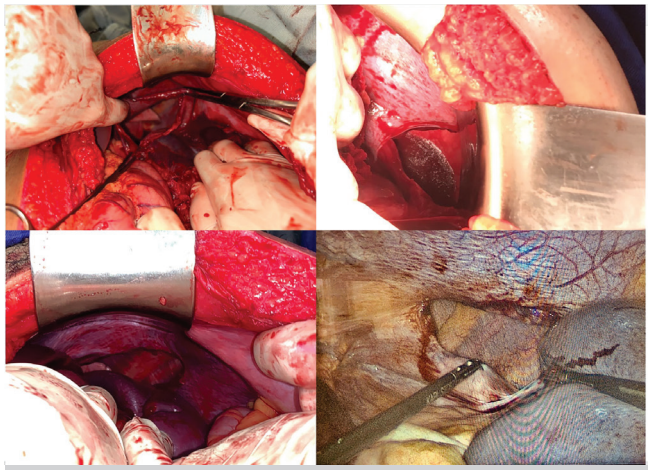

Figure 5. Intraoperative findings during TDH repair: 1-3: Direct visualization of diaphragmatic rupture 4: Laparoscopy view during diaphragmatic repair.

TDH: Traumatic diaphragmatic hernia

abdominal injuries or hemodynamic instability, supporting the suitability of a minimally invasive approach. Although most surgeons in our series were more experienced in open surgery, this case highlights the potential role of minimally invasive techniques in selected TDH cases, but success depends on surgeon expertise and patient stability.

Teixeira et al. (8) demonstrated that BTAI significantly increased the risk of concurrent injuries compared to patients without BTAI, particularly affecting solid organs such as the liver (55.0% vs. 34.0%, p<0.001), spleen (36.0% vs. 22.0%, p=0.009), and kidneys (18.0% vs. 9.0%, p=0.023). They also noted increased rates of thoracic trauma, including rib fractures, hemothorax, (86.0% vs. 56.0%, p<0.001), and pelvic fractures (40.0% vs. 26.0%, p=0.014). A landmark study (10) on diaphragmatic rupture revealed similar patterns, with high rates of musculoskeletal injuries (pelvic 52.0% and long bone fractures 48.0%) and solid organ trauma (splenic injury 48.0% and hepatic lacerations 16.0%). Their series also documented significant thoracic involvement, including rib fractures (52.0%), pulmonary contusions (20.0%), BTAI (8.0%), and cardiac contusions (4.0%). Studies have reported concurrent injury rates ranging from 3.0% to 14.0% (8,12).

Our findings align with this pattern; specifically, all cases presented with thoracic injuries including hemothorax, pulmonary contusion, and rib fractures. Abdominal injuries followed a distribution similar to that of common liver and pelvic injuries. Notably, both patients with pelvic trauma had extraperitoneal bladder injury. In our TDH cases, the stomach was the most herniated organ, consistent with the literature.

Demetriades (32) reviewed 125 patients and reported 43.5% systemic complications, including paraplegia (1.7%), pneumonia (30.7%), acute respiratory distress (16.1%), sepsis (12.4%), urinary tract infection (17.9%), deep vein thrombosis (4.5%), and renal failure (4.5%). TEVAR-specific complications occurred in 18.4% of cases, predominantly endoleaks (13.6%). More recently, lower rates of endovascular complications have been observed, as reported in (13), including endograft malposition (3.0%), endoleaks (2.5%), paralysis (0.5%), and stroke (1.0%).

Respiratory complications have historically been dominant in patients with blunt TDH. Rodriguez-Morales et al. (14) reported atelectasis in 65.0% of patients, whereas pneumonia rates varied from 32.0% in the Boulanger series (6) to 14.8% in the Fair analysis (12). Beyond respiratory issues, infectious complications significantly impact outcomes, with Boulanger reporting intra-abdominal abscess in 32% and Rodriguez-Morales et al. (14) documenting systemic sepsis in 28.0% of cases (6,12).

In our series, complications were predominantly related to prolonged hospitalization (mean, 33 days) and ICU stay (21 days for the first three cases), rather than directly linked to TDH or BTAI repair. Systemic complications included DVT requiring anticoagulation in two patients and pneumonia with septic complications in three patients. Procedure-related complications occurred in two cases: endograft malposition causing partial left subclavian artery occlusion requiring secondary stent graft deployment, and a femoral artery pseudoaneurysm after puncture. Three patients required tracheostomy due to prolonged ICU stay and extended mechanical ventilation requirements. Notably, no cases of paralysis, myocardial infarction, renal failure requiring hemodialysis, multiple organ failure, or chest tube complications were observed. Our experience suggests that complications are primarily associated with the severity of the associated injuries rather than with TDH or BTAI. Experts (34) have recommended lifelong imaging surveillance after endovascular repair. Our follow-up CTA results at six months are shown in Figure 6.

Compared to the Rizoli et al. (3) series, which reported 14.0% mortality in seven cases, our four patients survived, although recovery time was significantly impacted in our cases.

Study Limitations

Our study had several important limitations that warrant caution. This retrospective study has inherent limitations in terms of data collection and analysis. More significantly, despite our status as a high-volume trauma center, we identified and treated only four cases over the past 20 years. This small sample size severely limits our statistical power and ability to draw robust conclusions. Nevertheless, given the extreme rarity of combined BTAI and TDH injuries, with the last report published over 30 years ago, which was reporting only seven cases, we believe our detailed case series adds valuable information to the current literature.

Based on our institutional experience and literature review, we propose a structured treatment algorithm for concurrent TDH

and BTAI, according to institutional capabilities. For centers without surgical capabilities, immediate transfer to tertiary trauma centers is recommended. For institutions with surgical but lacking endovascular resources, we suggest first addressing TDH and associated injuries, maintaining strict IC, and then transferring the patient to an endovascular-capable facility. For fully capable trauma centers, we recommend initial TDH repair and any associated injuries, followed by a TEVAR procedure within the first 3-5 days, allowing for patient stabilization and custom endograft availability. For suspected TDH with negative initial imaging, follow-up CT at 5-7 days with nasogastric tube, thin-slice acquisition, and multiplanar reconstruction is recommended. In concurrent BTAI cases, TEVAR is performed before chest drainage to minimize complications with post-drainage CT follow-up. For a retained hemothorax, video-assisted thoracoscopy enables both diaphragmatic inspection and evacuation (Figure 7).

Given the rarity of these concurrent injuries, establishing a global trauma registry is recommended, as even high-volume trauma centers encounter too few cases to generate robust evidence-based recommendations.

CONCLUSION

Concurrent TDH and BTAI present a challenging injury complex that requires a structured diagnostic and therapeutic approach. Sequential management through diaphragmatic repair and endovascular intervention guided by institutional capabilities can achieve favorable outcomes despite high injury severity. A global trauma registry is essential to develop evidence-based protocols for these rare injuries.

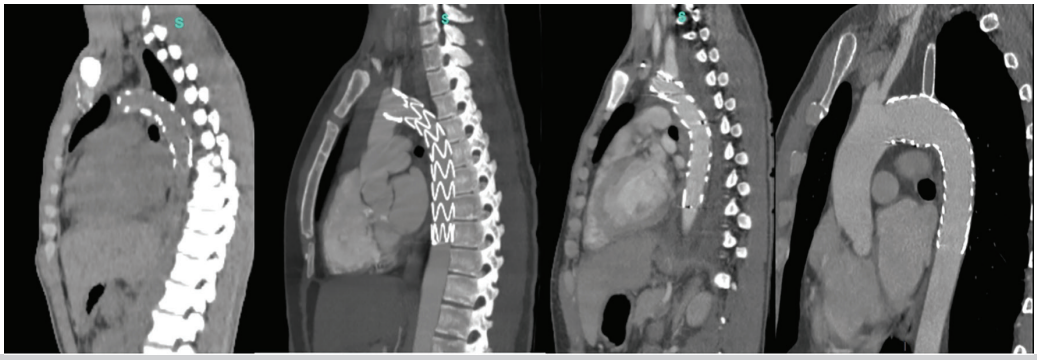

Figure 6. Sagittal CT angiography showing grade III BTAI post-TEVAR in patients 1-4.
CT: Computed tomography, BTAI: Blunt thoracic aortic injury, TEVAR: Thoracic endovascular aortic repair

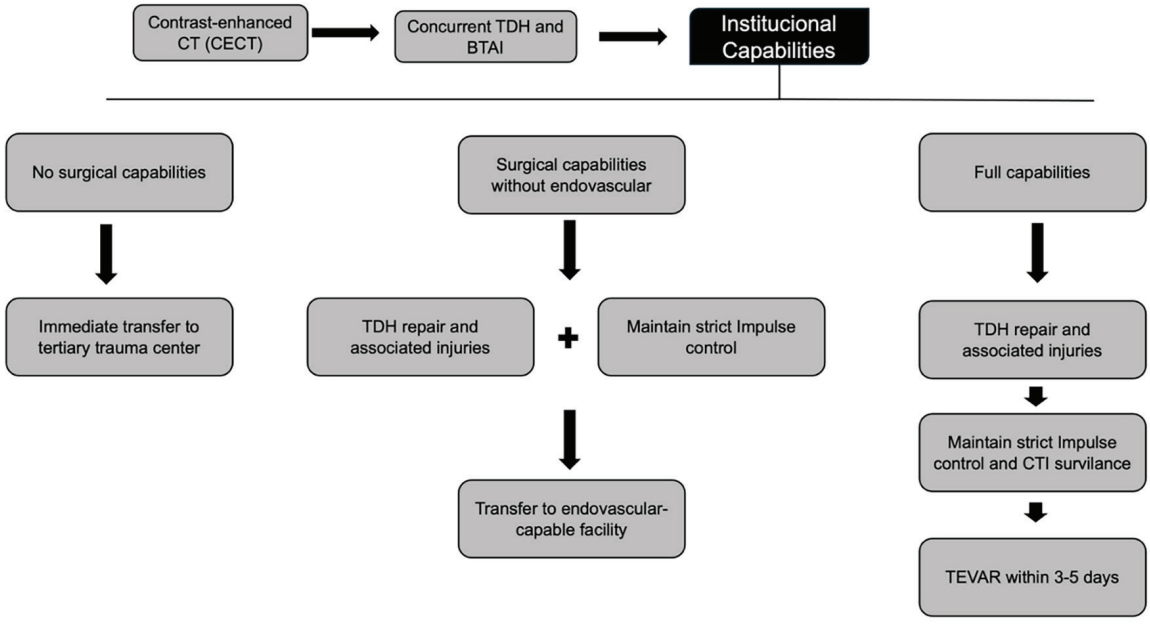

Figure 7. Treatment algorithm for concurrent TDH and BTAI, according to institutional capabilities.
CT: Computed tomography, BTAI: Blunt thoracic aortic injury, TEVAR: Thoracic endovascular aortic repair, TDH: Traumatic diaphragmatic hernia

Ethics

Ethics Committee Approval: The study received approval from the Ethics in Research Committee of University of Campinas (CAAE: 78780517.4.0000.5404 and 66498422.9.0000.5453).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Concept - V.F.K., C.J.M.; Design - V.F.K., G.P.F.; Supervision - V.F.K.; Data Collection or Processing - M.L.L., C.J.M.; Literature Search - V.F.K.; Writing - V.F.K., G.P.F.

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

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

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ORIGINAL ARTICLE
Turk J Surg 2025;41(1):42-46

Pathologic results of laparoscopic cholecystectomy specimens with 8148 patients in a single center

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ABSTRACT

Objective: The aim of this study was to investigate the frequency of incidental pathologies detected in the surgical specimens of patients who underwent laparoscopic cholecystectomy in high-volume referral center, which accepts patients from different regions of our country, and to contribute to epidemiological studies.

Material and Methods: Male and female patients over 18 years of age who underwent laparoscopic cholecystectomy between July 2010 and May 2019 were included in the study. All surgical specimens were taken for pathologic examination. The pathology results were classified into three categories: Benign pathologies (including cholecystitis, non-neoplastic lesions and benign tumors), premalignant pathologies and malignant pathologies.

Results: The study included a total of 8148 patients. The mean age was 49.74±14.51 years (minimum 18, maximum 94) and 72.2% of the patients were female. Benign pathologies included cholecystitis in 1742 (21.4%), non-neoplastic lesions in 6203 (76.1%) and benign tumors in 12 (0.1%), premalignant pathologies in 173 (2.1%) and malignant pathologies in 18 (0.2%). Although no statistically significant gender difference was observed between benign, premalignant and malignant pathologies, the incidence of premalignant and malignant pathologies increased with age (p=0.273, p<0.001, respectively).

Conclusion: In this study of 8148 patients, incidental premalignant and malignant pathologies were identified in 2.1% and 0.2% of cases, respectively, which is consistent with the findings of literature. These results may be instructive for epidemiologic studies.

Keywords: Gallbladder, histopathology, cancer, dysplasia

INTRODUCTION

Gallbladder surgeries are one of the most common procedures performed by general surgery clinics in daily practice. Cholecystectomy, together with inguinal hernia surgery, appendectomy, and hemorrhoidectomy, constitutes approximately 25% of daily practice (1). Gallbladder surgery may be indicated for a number of conditions, including cholecystitis, symptomatic cholelithiasis, biliary dysfunction, gallstone pancreatitis, polyps, and gallbladder masses. In cases where no pathological findings are present before or during surgery and the macroscopic characteristics appear benign, further management and follow-up may be required due to the presence of underlying pathologies. While the guidelines recommend routine pathological examination, there is still a debate surrounding the necessity of performing this examination on all cholecystectomy specimens, as it is a labor-intensive and costly process (2-5). Gallbladder cancers are rare and have a poor prognosis. The diagnosis of gallbladder cancer is made preoperatively in symptomatic patients, intraoperatively with macroscopic findings, or incidentally during routine pathologic examination after surgery (6). Gallbladder pathologies can be classified as benign, premalignant and malignant. In the 5th edition of the World Health Organization's (WHO) classification of tumors of the digestive system, three types of premalignant pathology of the gallbladder were defined: pyloric gland adenoma (PGA), biliary intraepithelial neoplasm (BilIN) and intracholecystic papillary neoplasm (ICPN) (7). Gallbladder cancer is responsible for 7% of cancer-related deaths, only 20% of which are early diagnoses. Furthermore, the incidental diagnosis of gallbladder cancer is increasing worldwide as more laparoscopic cholecystectomies for symptomatic gallbladder disease are safely performed (8). The aim of this study was to analyze the prevalence of incidental gallbladder pathologies in patients with no suspicion of malignancy in the preoperative or intraoperative period, at a surgical center that

Cite this article as: Pehlevan Özel H, Dinç T. Pathologic results of laparoscopic cholecystectomy specimens with 8148 patients in a single center. *Turk J Surg.* 2025;41(1):42-46

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Received: 24.11.2024
Accepted: 22.01.2025
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2025.6529

Available at www.turkjsurg.com

performs as a high-volume referral center and accepts patients from different regions of our country. Additionally, this study aimed to contribute to epidemiological studies.

MATERIAL and METHODS

The study was approved by the Institutional Review Board University of Health Sciences Türkiye, Ankara Bilkent City Hospital (date: 04.04.2024 and number: 2-24-131) and conducted in accordance with the Declaration of Helsinki. The study included cholecystectomies performed between 2010 and 2019 in the hospital, which is a high-volume referral center and accepts patients from different regions of our country. A total of 9.259 patients who underwent cholecystectomy for gallbladder disease (cholecystitis, stones, polyps, etc.) were analyzed for the study. 8.148 patients were eligible for the study.

Inclusion Criteria: Male and female patients over 18 years of age were included in the study, and only those who underwent standard laparoscopic cholecystectomy for benign causes were investigated.

Exclusion Criteria: Those who did not undergo laparoscopic surgery, those who underwent cholecystectomy simultaneously while having surgery for another reason, those with suspected malignancy in the gallbladder and patients already diagnosed with any type of cancer.

Pathological Classification

Patients were divided into three groups: Benign pathologies, premalignant pathologies, and malignant pathologies. The benign pathologies were categorized into three main groups: Cholecystitis, non-neoplastic lesions, and benign tumors, and then these three groups were divided into subgroups. Cholecystitis was classified as acute, chronic, erosion, follicular, eosinophilic, gangrenous, xanthogranulomatous, and porcelain gallbladder. Non-neoplastic lesions were classified as cholelithiasis, cholesterolosis, cholesterol polyp, adenomyoma, and metaplasia (gastric antral metaplasia, pyloric metaplasia, intestinal metaplasia, osseous metaplasia). Benign tumors were classified as biliary adenoma, tubulovillous adenoma, hyperplastic polyp, papillomatosis, fibroepithelial polyp, and mucinous cystadenoma. Premalign pathologies were classified as PGA, ICPN, and BillN. BillN was divided into grade 1, 2, and 3. Malignant pathologies were classified as neuroendocrine tumors and adenocarcinomas.

Statistical Analysis

IBM Statistical Package for the Social Sciences (SPSS) version 21 software (SPSS Inc., Chicago, IL, USA) was used for the study. Frequency (n) and percentage values were used in the evaluation of categorical variables, and mean, standard deviation, and minimum-maximum values were used in the evaluation of numerical variables. The chi-square test was used for categorical variables, while the t-test and the ANOVA test were used for numerical variables. Receiver operating characteristic (ROC) curve was generated to determine the relationship between malignancy and age. The whole study was evaluated with a 95% confidence interval (CI).

RESULTS

A total of 8.148 patients were included in the study. 5.885 (72.2%) were female and 2263 (27.8%) were male. The mean age of the patients was 49.74±14.51 years with a minimum age of 18 years and a maximum age of 94 years. The mean age was 49.10±14.52 years in women and 51.42±14.34 years in men (p<0.001).

7957 (97.7%) of the patients had benign pathologies, 173 (2.1%) patients had premalignant pathologies and 18 (0.02%) had malignant pathologies (Table 1). When male and female genders were compared, there was no statistically significant difference between benign, premalignant and malignant pathologies (p=0.249) (Table 1).

The mean age was 49.63±14.50 years for benign patients, 52.86±13.48 years for premalignant patients and 69.55±9.82 years (minimum 51 years old and maximum 86 years old) for malignant patients (Table 2, Figure 1). When the ROC curve was constructed for the age of malignant patients, the cut-off age was 50 years [area under the curve 0.868, sensitivity 100%, specificity 51.1%, 95% CI (0.806-0.930)]. In this patient group, all patients with a malignant diagnosis were over 50 years of age, and the frequency of patients with premalignant conditions also increased over 50 years of age (Table 3).

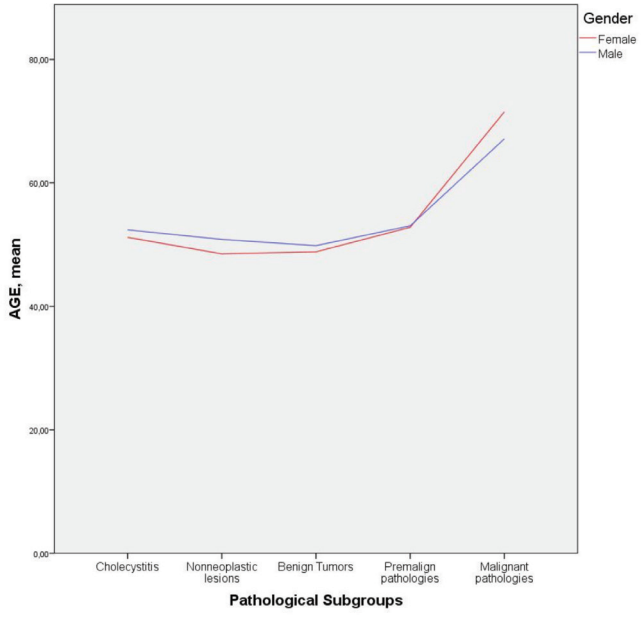

Figure 1. Age distribution according to pathologies.

Table 1. The incidence of gallbladder pathologies according to gender

Pathology		Female, n (%)	Male, n (%)	Total, n (%)	p-value
Benign pathologies		5.748	2.209	7.957 (97.7%)	0.273
	Cholecystitis	**1.040 (59.7%)**	**702 (40.3%)**	**1.742 (21.4%)**	
	Acute	273 (49.6%)	277 (50.4%)	550 (6.8%)	
	Chronic	618 (61.1%)	289 (31.9%)	907 (11.1%)	
	Follicular	34 (58.6%)	24 (41.4%)	58 (0.7%)	
	Erosyone	52 (56.5%)	40 (43.5%)	92 (1.1%)	
	Eosinophilic	2	0	2	
	Gangrenous	38 (48.7%)	40 (51.3%)	78 (1.0%)	
	Xanthogranulomatous	22 (40.7%)	32 (59.3%)	54 (0.7%)	
	Porcelain gallbladder	1	0	1	
	Non-neoplastic lesions	**4.702 (75.8%)**	**1.501 (42.2%)**	**6.203 (76.1%)**	
	Adenomyoma	52 (61.1%)	33 (38.8%)	85 (1%)	
	Cholelithiasis	2.958 (74%)	1.040 (26%)	3.998 (49.1%)	
	Choleterol polyp	154 (70%)	66 (30%)	220 (2.7%)	
	Cholesterellosis	1.367 (81.2%)	316 (18.8%)	1.683 (2.7%)	
	Metaplasia				
	Gastric antral metaplasia	6	0	6	
	Pyloric metaplasia	61 (78.2%)	17 (21.8%)	78 (1.6%)	
	Intestinal metaplasia	104 (78.8%)	28 (21.2%)	132 (1.6%)	
	Osseous metaplasia	1	2	3	
	Benign tumors	**6 (0.1%)**	**6 (0.3%)**	**12 (0.1%)**	
	Biliary adenoma	2	1	3	
	Tubulovillous adenoma	0	1	1	
	Hyperplastic polyp	1	2	3	
	Papillomatosis	2	1	3	
	Fibroepithelial polyp	0	1	1	
	Mucinous cystadenoma	1	0	1	
Premalign pathologies		**127**	**46**	**173 (2.1%)**	
	Pyloric gland adenoma	4	2	6	
	Intracholecystic papillary neoplasm	1	1	2	
	BilIN	122 (73.9%)	43 (26.1%)	165 (2.0%)	
	BilN 1	105 (75.0%)	35 (25.0%)	140	
	BilN 2	10 (62.5%)	6 (37.5%)	16	
	BilN 3	7 (77.8%)	2 (22.2%)	9	
Malignant pathologies		**10**	**8**	**18 (0.2%)**	
	NET Grade 1	2	0	2	
	Adenocancer	8	8	16 (0.2%)	
	Poorly differentiated	1	2	3	
	Moderately differentiated	5	3	8	
	Good differentiated	1	2	3	
	Musinous	1	1	2	
Total		5.885 (72.2%)	2.263 (27.8%)	8.148	

BilIN: Biliary intraepithelial neoplasia, NET: Neuroendocrine tumor

DISCUSSION

Gallbladder surgeries are common procedures in general surgery practice. It is a generally accepted approach to operate laparoscopic surgery primarily. The growing number of laparoscopic cholecystectomy procedures has led to an increased prevalence of incidental pathologies. This study analyzed cholecystectomies performed over a nine-year period in a high-volume referral center that accepts patients from diverse regions within the country. The objective was to investigate the frequency of incidental pathologies encountered during these procedures.

The development of premalignant lesions of the gallbladder is typically attributed to a sequence of injury, inflammation,

Table 2. Distribution of pathologies by age

	Age average	p-value	Female age average	p-value	Male age average	p-value
Benign pathologies	49.63±14.51	<0.001	48.98±14.52	<0.001	51.33±14.33	0.006
Premalign pathologies	52.86±13.48		52.79±13.27		53.04±14.21	
Malignant pathologies	69.55±9.82		71.50±9.31		67.12±10.53	

Table 3. Pathology results are classified as over and under 50 years of age

		Pathologies			p-value
		Benign pathologies	Premalign pathologies	Malignant pathologies	
Female	<50 years old	2.877 (98.5%)[a]	44 (1.5%)[b]	0[b]	<0.001
	≥50 years old	2.871 (96.9%)[a]	83 (2.8%)[b]	10 (0.3%)[b]	
Male	<50 years old	1.006 (98.2%)[a]	18 (1.8%)[a,b]	0[b]	0.016
	≥50 years old	1.203 (98.2%)[a]	28 (2.3%)[a,b]	8 (0.6%)[b]	
Totally	<50 years old	3.883 (97.6%)[a]	62 (1.6%)[b]	0[c]	<0.001
	≥50 years old	4.074 (96.9%)[a]	111 (2.6%)[b]	18 (0.4%)[c]	

[a,b,c]: Each superscript letter denotes a subset of pathology categories whose column ratios are not significantly different from each other at the 0.05 level

regeneration, and neoplastic transformation (9). One hundred seventy-three patients had premalignant pathology, of which 6 were PGA, 2 were ICPN, and 165 (2%) were BilIN. There was no statistical difference between male and female patients; however, the incidence of these pathologies increased with increasing age (p=0.273, p<0.01, respectively).

BilIN is a microscopic, non-invasive, micropapillary premalignant lesion with atypical features similar to those seen in cancer but confined to the bile duct. As such, requiring examination of the entire tissue to differentiate it from cancer (10). In countries where BilIN gallbladder cancer is endemic, Grade 1-2 disease is seen in 15% and Grade 3 disease in 1-3.5%, whereas in North America, Grade 1-2 disease is seen in <5% and <0.1% (11). In this patient group, the number of patients with BilIN was 165 (2%) and only 9 (0.005%) patients were diagnosed with grade 3, which is consistent with the literature.

PGA is a polypoid non-invasive epithelial lesion of the gallbladder classified as a premalignant lesion by WHO as of 2019 (12). PGA is a pathology found in 0.2-0.5% of patients operated for chronic cholecystitis or cholelithiasis, and is mostly seen in women and adults (11). In this study, the condition was observed in 6 patients (<0.01%), and 4 of them were women.

ICPN is a preinvasive neoplasm of the gallbladder, and studies have reported that ICPN is found in 4% of cholecystectomies and is associated with approximately 6% of gallbladder carcinomas (12). In this study, ICPN was found in two patients only.

Gallbladder cancer is the fifth most common cancer among cancers of the gastrointestinal tract. Less than 10% of patients are resectable; half of these patients have lymph node metastases. Five-year survival is less than 5% (13). It is commonly found in women, increases in frequency in older ages, and is common in Chile, Japan, and India (13). Incidental gallbladder cancer is identified in 0.2% to 2.9% of all cholecystectomies performed for gallstone disease surgery (8,14). While cholecystectomy is sufficient in patients diagnosed with stage Tis and T1a cancer in gallbladder examinations, stage T1b and above require further surgical treatment (6). In this study, the incidental gallbladder cancer rate was found to be 0.2%, consistent with the literature. Unlike the literature, there was no difference between genders; however, the incidence increased with age in accordance with the literature (p=0.273, p<0.001, respectively).

CONCLUSION

Although most gallbladder specimens obtained after cholecystectomy are benign, a small number are incidentally detected as malignant or potentially malignant. This study examined the occurrence of incidental gallbladder pathologies in our country, confirming the presence of such unexpected lesions in accordance with the literature. The findings underscore the importance of routine pathological examination to ensure timely intervention and improve patient outcomes.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Review Board University of Health Sciences Türkiye, Ankara Bilkent City Hospital (date: 04.04.2024 and number: 2-24-131) and conducted in accordance with the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all patients before treatment.

Footnotes

Author Contributions

Concept - H.P.Ö., T.D.; Design - H.P.Ö.; Supervision - T.D.; Data Collection or Processing - H.P.Ö.; Analysis or Interpretation - H.P.Ö.; Literature Search - H.P.Ö.; Critical Review - T.D.; Writing - H.P.Ö.

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

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

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ORIGINAL ARTICLE
Turk J Surg 2025;41(1):47-55

Self-confidence, communication skills, and a solution-focused approach in organ transplantation coordinators: Descriptive study

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ABSTRACT

Objective: The acquisition of communication skills, which form the basis of solution-focused thinking, also develops self-confidence in organ transplantation coordinators, enabling them to plan appropriate care in the organ donation process. The aim of this study was to determine the levels of self-confidence, communication skills, and solution-focused approaches in organ transplantation coordinators.

Material and Methods: A descriptive and correlational study. The study was conducted with 203 organ transplantation coordinators in Türkiye between August and September 2023. The data were collected using a personal information form, the self-confidence scale, the communication skills scale, and the solution-focused inventory.

Results: A positive, weak correlation was determined between the solution-focused inventory and communication skills ($r=0.261$, $p<0.001$) and self-confidence ($r=0.269$, $p<0.001$), and a positive high-level correlation was determined between communication skills and self-confidence ($r=0.811$, $p<0.001$). Self-confidence ($\beta=0.614$) and the solution-focused approach inventory ($\beta=0.076$) explained 65.6% of the communication skills (corrected $R^2=0.656$).

Conclusion: The solution-focused approach and self-confidence were found to increase the communication skills of the organ transplantation coordinator.

Keywords: Organ transplantation coordinator, self-confidence, communication skills, solution-focused approach

INTRODUCTION

Organ donation is an extremely complex and specific process requiring multidisciplinary communication in which nurse transplantation coordinators (NTC) have an important role (1). The donation process starts with the identification of a potential donor during mechanical ventilation, and includes various components such as the diagnosis of brain death, obtaining informed consent, organ transplantation coordination, the harvesting operation, and providing support to the family throughout the process (2).

The NTC makes daily visits to the intensive care unit to follow-up on patients who may be potential cadaver organ donors meeting the brain death criteria (1,3). In addition, the NTC manages the clinical planning of cadaver donors, coordinates laboratory tests, organizes the health records, evaluates the needs of patients for organ transplantation, and establishes communication with many doctors and members of the multidisciplinary team associated with care of the patients. The NTC functions as a bridge between the surgical team and the organ donor (or family members) and communicates with the patient and hospital for the planning of the operating theatres (4). In addition, it is the NTC who communicates with the families of patients in whom brain death has occurred to persuade them to agree to organ donation (1,3).

The organ donation process includes crisis management. In a family experiencing shock after trauma, it can be extremely difficult for the NTC to communicate with the family and request organ donation (5). In the interviews with the family for organ donation, it is emphasized that brain death is actual death and that organ donation is important (6). NTCs are working in a fast-paced environment in the

Cite this article as: Soylu D. Self-confidence, communication skills, and a solution-focused approach in organ transplantation coordinators: Descriptive study. *Turk J Surg.* 2025;41(1):47-55

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Received: 14.11.2024
Accepted: 23.01.2025
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2025.6606

Available at www.turkjsurg.com

donation process, and are often exposed to work stress factors. All these stress factors, and the effort of coping with pressure, can be overwhelming for NTCs (7). In this process, NTCs must be extremely patient, decisive, and calm when providing coordination (5).

Solution-focused thinking is a strategy that develops communication skills and thereby supports the problem-solving skills of nurses. Solution-focused thinking is a communication strategy that focuses on the strengths of both the nurse and the patient despite the problems, and trains nurses to be future and goal-oriented by developing optimism. Nurses who have developed solution-focused thinking and problem-solving skills can motivate themselves as well as those to whom they are providing care, and can help them to be aware of their strengths and overcome problems (8). Moreover, a solution-focused approach allows the person to be aware of their strengths and the available resources in exceptional circumstances. It has been emphasized that when a person reaches a solution to a problem using their own abilities, it has a positive effect on the self-confidence of that individual (9).

By developing solution-focused communication skills, NTCs can increase their self-confidence and maintain better patient care in the difficult and complex process of organ donation. However, no study could be found in the literature that has investigated the levels of self-confidence, communication skills and solution-focused approaches together in organ transplantation co-ordinators. Therefore, the aim of this study was to determine the levels of self-confidence, communication skills, and solution-focused approaches in organ transplantation co-ordinators. To meet this aim, the answers were sought to the following questions:

1. What are the levels of communication skills, solution-focused approach and self-confidence of organ transplantation co-ordinators?

2. Do the levels of communication skills, solution-focused approach and self-confidence of organ transplantation coordinators change according to socio-demographic characteristics?

3. Are there correlations between the levels of communication skills, solution-focused approach and self-confidence of organ transplantation co-ordinators?

4. Does the level of communication skills predict the levels of solution-focused approach and self-confidence of organ transplantation co-ordinators?

MATERIAL and METHODS

Research Design

This research was designed as a descriptive study to evaluate the levels of communication skills, solution-focused approach, and self-confidence of organ transplantation co-ordinators. The sampling method used was chain referral sampling/snowball sampling. In this method, the first participants included identify other potential participants who meet the study inclusion criteria, and as this process is repeated, the sample is expanded. The use of this sampling method has been shown to be appropriate when it is difficult to reach potential participants (10). It was considered that a homogeneous sample group would be formed with respect to its characteristics, and that the other characteristics of the sample would have no specific effect on the subject examined.

The study inclusion criteria were defined as age ≥18 years, completion of all the questions on the data collection form, and agreement to participate in the study.

Location and Time of the Study

The study was conducted with organ transplantation coordinators in Türkiye between August and September 2023. It was conducted as a descriptive, cross-sectional, and correlation-seeking study.

Data Collection

The study sample was obtained using the snowball sampling method. The starting point was a researcher working as an organ transplantation coordinator in a university hospital. The participants were requested to complete the data collection forms and then send them on to other organ transplantation coordinators known to them. The researchers invited the organ transplantation coordinators to participate in the study through a mobile phone message containing information about the study and the data collection tools.

The questionnaire was created on Google forms. After the participants provided informed consent for participation and confirmed that they met the study inclusion criteria, they completed the questionnaire. All the questions were defined as mandatory. Thus, informed consent was provided, the appropriateness of the age criteria was evaluated, and the questionnaire was fully completed.

Study Universe and Sample

Power analysis was performed based on the mean scores derived from the solution-focused approach concerning gender,

obtained from the results of a study by Karasu et al. (11). The sample size calculated with G*power analysis was determined to be 114 subjects with effect size d=0.7081244, α err prob=0.05, and power (1-β err prob)=0.95. This study included 203 subjects.

Data Collection

Personal Information Form

This form included questions to obtain information about age, gender, profession, marital status, education level, years of working in the profession, and years of working as a co-ordinator.

Self-confidence Scale (SCS)

The SCS, developed by Akın (12), is a 5-point Likert-type scale consisting of a total of 33 items. The scale has two subscales: Internal and external self-confidence. Items 4-25-32-17-10-30-12-3-19-5-21-27-9-23-1-7-15 are in the internal self-confidence subscale and items 6-31-20-29-16-14-22-11-18-33-2-28-26-13-8-24 refer to external self-confidence. There are no negative items on the scale. The points scored range from a minimum of 33 to a maximum of 165, with higher points indicating a higher level of self-confidence. In the original study, the Cronbach alpha coefficient was 0.94 in general, 0.97 for the internal self-confidence subscale, and 0.87 for the external self-confidence subscale (12). In the current study, the Cronbach alpha coefficient was calculated as 0.953.

Communication Skills Scale-adult Form (CSS-AF)

The CSS-AF was developed by Korkut Owen and Bugay (13) to measure communication skills. Adaptation studies were conducted by Korkut Owen and Bugay (13) to use the scale for adults. The scale includes 25 items with 5-point Likert-type responses graded from "always" to "never". There are no reverse-scored items. The total score obtained ranges from a minimum of 25 to a maximum of 125, with higher scores indicating a higher level of communication skills. The scale has a five-factor structure. The first factor consists of 9 items and is named basic skills and self-expression. The second factor consists of 5 items and refers to the importance given to communication, the third factor, consisting of 3 items, is the willingness to establish relationships, and the fourth factor, consisting of 5 items, is named effective listening and non-verbal communication. The fifth factor consists of three items and represents compliance with communication principles. The Cronbach alpha coefficient was found to be 0.94 (13,14). The Cronbach's alpha coefficient in this study was calculated as 0.939.

Solution-focused Inventory (SFI)

The SFI was developed by Grant et al. (15) and adapted to Turkish by Şanal Karahan and Hamarta (14). It is a 12-item inventory based on short-term solution-focused therapy, which measures solution-focused thinking. The SFI is composed of 3 subscales. Correlations between the Turkish and the original form were examined: and the problem disengagement subscale was found to be 0.92, the goal orientation subscale was 0.94, and the resource activation subscale was 0.91.

The responses to the items on the SFI are scored as 6-point Likert-type responses from 1=I definitely disagree to 6=I definitely agree. Items 1, 2, 4, and 5 are reverse-scored. Higher points obtained from the scale are interpreted as a sign of a high level of solution-focused thinking. The internal consistency coefficients were found to be 0.77 for problem disengagement, 0.84 for goal orientation, and 0.70 for resource activation.

Items 1, 2, 4, and 5 correspond to problem disengagement; 9, 10, 11, and 12 correspond to goal orientation; 3, 6, 7, and 8 correspond to resource activation. The subscales are scored separately, and a total score is also obtained, from a minimum of 12 points to a maximum of 72. Higher points show a greater change towards solution-focused thinking (14). In this study, the Cronbach alpha coefficient was calculated as 0.650.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS vn.20.0 software (IBM Corpn., Armonk, NY, USA). In the evaluation of the conformity of the data to normal distribution, skewness and kurtosis coefficients were used [(-2, +2)] (10). In the comparisons between two groups, the Independent Samples t-test was used for quantitative variables, and for 3 or more groups, One-Way ANOVA and the Kruskal-Wallis test were used. Bonferroni-corrected multiple comparison tests were applied to the "a, b, c" columns. Relationships between quantitative variables were examined with Pearson correlation analysis. Multivariate linear regression analysis was performed to determine the level of communication skills. In calculating the reliability coefficients of the scale, the Cronbach alpha coefficient was used. Values of $p<0.01$ and $p<0.05$ were accepted as statistically significant.

Ethics Committee Approval

The necessary permission conduct the study was obtained from the Medical Research Ethics Committee of the Kahramanmaraş Sütçü İmam University (decision no: 06, session no: 2022/23, dated: 06.09.2022). Written informed consent was provided by all the study participants.

RESULTS

The Mean Scale Points

The mean points of the participants obtained from the scales were analyzed. The mean points of the SCS (142.94±14.77), CSS-AF (107.91±11.37), and SFI (50.95±6.97) were considered high.

Relationships Between the Socio-demographic Characteristics and Experience of Working in the Coordination System

The socio-demographic characteristics of the study participants are shown in Table 1. The participants comprised 73.4% females and 26.6% males with a mean age of 42.14±7.50 years; 59.1% were aged ≥42 years. 77.3% were nurses, 83.3% were married, and 53.7% had a university degree. Fifty-four percent stated that their duration of working in the profession was ≥21 years, and 50.2% had been working as an organ transplantation coordinator for ≥8 years. The mean duration of working in the profession was 20.64±7.58 years, and the mean time as organ transplantation coordinator was 8.41±5.98 years. Of the total participants, 58.6% reported that they held an organ transplantation coordinator certificate, and 32% worked in a transplantation centre. Additionally, 44.8% had made a declaration of brain death, 44.8% had obtained family consent for organ donation, 50.2% had participated in the preparation for organ transplantation from a living donor, and 39.4% had participated in the preparation for organ transplantation from a cadaver.

Findings Related to the Comparisons of the Socio-demographic Characteristics and the Scale Mean Points

The comparisons of the mean scale points across the participant socio-demographic characteristics are shown in Table 2. In the comparison of age and scale points, a statistically significant difference was found in the mean SCS points according to age (p=0.001) but not in the other scale points (p>0.05). No significant difference was seen in the mean scale points according to marital status (p>0.05). When examined according to education level, statistically significant differences were determined in the SCS mean points (p=0.023) and the CSS-AF mean points (p<0.001). The difference between the groups was determined to be due to university degree level education status. The mean scale points were compared according to the professional group of the participants, and the differences in the CSS-AF and SFI mean points were statistically significant (p=0.009, p=0.001). The difference was determined to be due to the midwife group. The participants who had been working for ≥21 years were determined to have statistically significant higher SCS (p=0.001) and CSS-AF (p=0.039) mean points compared to those with shorter work experience. When the scale points were compared based on years of work experience, statistically significant differences were identified in the SCS (p=0.034) and CSS-AF (p=0.039) mean points.

Findings Related to the Comparisons of the Experience of Working in the Coordination System and the Scale Mean Points

Comparisons of the mean scale points based on participants' experience in the coordination system are shown in Table 3.

Table 1. Socio-demographic and the experience of the participants working in the co-ordination system

Characteristics		Number	%
Age (years)	≤41	83	40.9
	≥42	120	59.1
Gender	Female	149	73.4
	Male	54	26.6
Profession	Nurse	157	77.3
	Doctor	20	9.9
	Midwife	12	5.9
	Health technician	14	6.9
Marital status	Married	169	83.3
	Single	34	16.7
Education level	Associate degree	24	11.8
	University degree	109	53.7
	Postgraduate	70	34.5
Years of working in the profession	≤20 years	93	45.8
	≥21 years	110	54.2
Years of working as coordinator	≤7 years	101	49.8
	≥8 years	102	50.2
Do you have an organ transplantation co-ordinator certificate?	Yes	119	58.6
	No	84	41.4
In which area of coordination do you work?	Transplant centre	65	32.0
	Intensive care	44	21.7
	Donor hospital	60	29.6
	Regional coordination centre	30	14.8
	National coordination centre	4	2.0
Have you ever made a brain death declaration?	Never	44	21.7
	A few times	91	44.8
	Many times	68	33.5
Have you received consent from the family for organ donation?	Never	44	21.7
	A few times	91	44.8
	Many times	68	33.5
Have you participated in the preparation of organ transplantation from a living donor?	Never	102	50.2
	A few times	36	17.7
	Many times	65	32.0
Have you participated in the preparation of organ transplantation from a cadaver?	Never	62	30.5
	A few times	61	30.0
	Many times	80	39.4

The SCS mean points were high for the participants with an organ transplantation co-ordinator certificate, and this was determined to create a statistically significant difference between the groups. No significant difference was determined between the CSS-AF and SFI mean points of the groups (p>0.05). In the participants working as a co-ordinator in a donor hospital, the SCS (p<0.001), CSS-AF (p=0.002), and SFI (p=0.003) mean points were determined to be statistically significantly higher than those of the other groups. The SCS mean points were low for the participants who reported having made a declaration of brain death only a few times, creating a statistically significant difference between the groups (p=0.048). No significant difference was determined in the CSS-AF and SFI mean points according to the frequency of brain death declarations (p>0.05). The mean SFI points were low for the participants who reported having obtained family consent for organ donation only a few times, creating a statistically significant difference between the groups (p=0.029). The SCS (p<0.001), CSS-AF (p=0.21), and SFI (p=0.032) mean points were determined to be low for the respondents who had participated in the preparation of organ transplantion from a cadaver many times. Those who had participated many times in the preparation of organ transplantion from a living donor were also determined to have lower mean SCS (p<0.001), CSS-AF (p<0.001), and SFI (p=0.019) points.

Correlation Analyses of the Scales

The results of the correlation analyses between the scales are given in Table 4. There was determined to be a positive weak correlation between the CSS-AF (r=0.261, p<0.001) and the SCS (r=0.269, p<0.001), and a positive strong correlation between the CSS-AF and SCS (r=0.811, p<0.001).

Table 2. Comparisons of the socio-demographic characteristics of the participants according to the mean scale points

Characteristics		**SCS Mean/SD Mean Rank (Min-max)**	**CSS-AF Mean/SD Mean Rank (Min-max)**	**SFI Mean/SD Mean Rank (Min-max)**
Age (years)	≤41	138.69±17.04	50.83±5.86	50.83±0.64
	≥42	145.88±12.21	51.03±7.67	51.03±0.70
Test/p		-3.498/0.**001***	-0.202/0.832*	-0.212/0.832*
Gender	Female	144.02±12.09	109.82±10.70	51.18±7.54
	Male	139.96±12.09	102.62±11.59	50.29±5.11
Test/p		1.386/0.170*	4.140/0.**000***	0.958/0.340*
Marital status	Married	143.53±15.29	108.43±10.85	50.85±6.87
	Single	140.00±11.64	105.29±13.55	51.41±7.56
Test/p		1.526/0.132*	1.273/0.210*	-0.395/0.695*
Education level	Associate degree	138.00±13.53[b]	71.25 (86-125)[b]	49.83±7.06
	University degree	145.46±13.31[a]	120.71 (85-123)[a]	51.29±7.61
	Postgraduate-doctorate	140.71±16.65[b]	83.41 (83-125)[b]	50.80±5.88
Test/p		3.833/0.**023****	24.708/0.**000*****	0.453/0.636**
Profession	Nurse	100.96 (111-165)	100.30 (85-125)[b]	106.94 (37-66)
	Doctor	89.70 (93-157)	93.80 (83-117)[b]	103.40 (44-61)[b]
	Midwife	127.50 (137-159)	155.83 (112-123)[a]	33.67 (30-49)[a]
	Health technician	109.36 (133-153)	86.64 (96-112)[a,b]	103.14 (49-57)[b]
Test/p		3.413/0.332***	11.589/0.**009*****	17.483/0.**001****
Years of working in the profession	≤20 years	139.18±16.55	104.64±11.76	51.02±5.98
	≥21 years	146.12±12.30	110.67±10.29	50.89±7.74
Test/p		-3.423/0.**001***	-3.849/0.**000***	0.135/0.892*
Years of working as a coordinator	≤7 years	140.73±15.67	106.25±10.80	50.22±6.228
	≥8 years	145.13±13.55	109.54±11.73	51.66±7.61
Test/p		-2.140/0.**034***	-2.080/0.**039***	-1.475/0.142*

*: Independendent Samples t-test, **: One-Way ANOVA test, ***: Kruskal-Wallis test. p<0.05, [a, b]: The difference between the groups expressed by the letters is statistically significant at p<0.05 after Bonferroni correction, SD: Standard deviation, SFI: Solution-focused inventory, SCS: Self-confidence scale, CSS-AF: Communication skills scale-adult form

Multiple Linear Regression Analysis

The regression analysis results are given in Table 5. According to the results, the model explains 65% of the variance in the regression analysis and is statistically significant (F=193.771, p<0.001). It was determined that the change in SFI has no effect (β=0.076, p>0.05); that a one-unit change in SCS has a positive effect (β=0.614, p<0.001) and significantly affects CSS-AF.

DISCUSSION

In this study, the self-confidence, communication skills, and solution-focused approach levels of organ transplantation coordinators were investigated. As no other study could be found in the literature evaluating these factors together, the current study findings were discussed with those of similar studies.

When the SCS mean points of the current study participants were examined, the level of self-confiidence was determined to be high. In a study of nursing students, Yalnızoğlu Çaka et al. (16) determined that the students' self-confidence levels were high. Another study of nursing students also reported high levels of self-confidence (17). The current study results showed that the communication skills of the participants were assessed to be high. In a study by Alan et al. (18), the emotional intelligence and communication skills levels of organ transplantation coordinatorswere seen to be above the average expected. Tiryaki Şen et al. (19) investigated the communication skills of nurses in in-service training and determined that the communnication skills of the nurses were at a high level. In a study that examined the effect of communication skills on the resilience of nursing degree students in Türkiye, Yıldırım et al. (20) reported high

Table 3. Comparisons of the characteristics of the experience of the participants working in the co-ordination system according to the mean scale points

Characteristics		SCS Mean/SD Mean Rank (Min-max)	CSS-AF Mean/SD Mean Rank (Min-max)	SFI Mean/SD Mean Rank (Min-max)
Do you have an organ transplantation coordinator certificate?	Yes	144.77±12.08	108.28±11.15	51.21±6.25
	No	140.35±17.67	107.38±11.71	50.57±7.91
Test/p		1.986/0**.049***	0.557/0.578*	0.650/0.517*
In which area of coordination do you work?	Transplant centre	84.45 (117-159)[b]	80.95 (86-123)[b]	89.23 (38-61)[b]
	Intensive care	100.86 (93-164)[b]	102.39 (83-125)[a]	87.75 (30-60)[b]
	Donor hospital	129.17 (132-165)[a]	121.43 (93-125)[b]	122.83 (44-66)[a]
	BKM	89.09 (111-152)[b]	107.44 (85-115)[b]	108.09 (37-59)[a,b]
Test/p		20.333/0**.000****	15.247/0**.002***	13.664/0**.003****
Have you ever made a brain death declaration?	Never	110.56 (122-164)[b]	115.78 (96-125)	52.44±5.95
	A few times	85.84 (93-161)[a]	89.91 (83-123)	49.45±8.45
	Many times	107.57 (117-165)[b]	103.75 (86-125)	51.23±6.33
Test/p		6.077/0**.048****	4.505/0.105**	2.252/0.108***
Have you received consent from the family for organ donation?	Never	120.64 (133-161)	120.64 (96-123)	53.27±6.54[a]
	A few times	96.18 (93-165)	96.18 (83-125)	49.87±7.38[b]
	Many times	97.74 (111-159)	97.74 (85-123)	50.88±6.39[a,b]
Test/p		5.692/0.058**	5.948/0.051**	3.603/0**.029****
Have you participated in the preparation of organ transplantation from a cadaver?	Never	112.92 (93-164)[b]	112.02 (83-125)[b]	52.54±7.79[b]
	A few times	118.48 (121-165)[b]	110.41 (92-125)[a,b]	51.22±7.27[a,b]
	Many times	80.98 (11-157)[a]	87.83 (85-123)[a]	49.50±5.758[a]
Test/p		17.220/0**.000****	7.733/0**.021****	3.487/0**.032****
Have you participated in the preparation of organ transplantation from a living donor?	Never	145.62±15.09[a]	118.68[a]	51.0196±7.55[a]
	A few times	147.44±13.54[a]	102.86[a]	53.50±6.67[a]
	Many times	136.24±12.68[b]	75.35[b]	49.43±5.77[b]
Test/p		11.019/0**.000*****	21.665/0**.000****	4.070/0**.019*****

*: Independendent t-test, **: Kruskal-Wallis test, ***: One-Way ANOVA test, p<0.05, [a,b]: The difference between the groups expressed by the letters is statistically significant at p<0.05 after Bonferroni correction

Table 4. Comparison of cadaveric organ donation and some characteristics of organ transplantation coordinators

		Years of working in the profession		Years of working as a coordinator		In which area of coordination do you work?				Profession				Do you have an organ transplantation coordinator certificate?	
		≤20 years n (%)	≥21 years n (%)	≤7 years n (%)	≥8 years n (%)	Transplant centre n (%)	Intensive care n (%)	Donor hospital n (%)	RCC n (%)	Nurse n (%)	Doctor n (%)	Midwife n (%)	Health technician n (%)	Yes n (%)	No n (%)
Have you ever made a brain death declaration?	Never	20 (55.6)	16 (44.4)	30 (83.3)	6 (16.7)	8 (22.2)	14 (38.9)	0 (0.0)	14 (38.9)	34 (77.3)	4 (9.1)	4 (9.1)	2 (4.5)	10 (27.8)	26 (72.2)
	A few times	35 (61.4)	22 (38.6)	37 (64.9)	20 (35.1)	19 (33.3)	26 (45.6)	8 (14.0)	4 (7.0)	73 (80.2)	6 (6.6)	4 (4.4)	8 (8.8)	19 (33.3)	38 (66.7)
	Many times	38 (34.5)	72 (65.5)	34 (30.9)	76 (69.1)	38 (34.5)	4 (3.6)	52 (47.3)	16 (14.5)	50 (73.5)	10 (14.7)	4 (5.9)	4 (5.9)	90 (81.8)	20 (18.2)
Have you received consent from the family for organ donation?	Never	28 (63.6)	16 (36.4)	34 (77.3)	10 (22.7)	12 (27.3)	18 (40.9)	4 (9.1)	10 (22.7)	34 (77.3)	4 (9.1)	4 (9.1)	2 (4.5)	12 (27.3)	32 (72.7)
	A few times	45 (49.5)	46 (50.5)	59 (64.8)	32 (35.2)	31 (34.1)	26 (28.6)	26 (28.6)	8 (8.8)	73 (80.2)	6 (6.6)	4 (4.4)	8 (8.8)	39 (42.9)	52 (57.1)
	Many times	20 (29.4)	48 (70.6)	8 (11.8)	60 (88.2)	22 (32.4)	0 (0.0)	30 (44.1)	16 (23.5)	50 (73.5)	10 (14.7)	4 (5.9)	4 (5.9)	68 (100)	0 (0.0)
Have you participated in the preparation of organ transplantation from a cadaver?	Never	38 (61.3)	24 (38.7)	42 (67.7)	20 (32.3)	8 (12.9)	34 (54.8)	10 (16.1)	10 (16.1)	48 (77.4)	6 (9.7)	4 (6.5)	4 (6.5)	6 (9.7)	56 (90.3)
	A few times	29 (47.5)	32 (52.5)	41 (67.2)	20 (32.8)	19 (31.1)	10 (16.4)	28 (45.9)	4 (6.6)	53 (86.9)	2 (3.3)	0 (0.0)	6 (9.8)	39 (63.9)	22 (36.1)
	Many times	26 (32.5)	54 (67.5)	18 (22.5)	62 (77.5)	38 (47.5)	0 (0.0)	22 (27.5)	20 (25.0)	56 (70.0)	12 (15.0)	8 (10.0)	4 (5.0)	74 (92.5)	6 (7.5)

levels of communication skills of the students. As the SFI mean points were high in the current study, it indicates that the participants had a high tendency to solution-focused thinking. Selçuk Tosun et al. (21) conducted a study with midwives and nurses and determined high levels of solution-focused approaches. In another study of nursing students in Türkiye, the points obtained on the SFI were determined to be above average (8). The findings previously reported in the literature support the results of the current study.

In the current study, a significant difference was determined in the mean points of the SCS according to age, of the CSS-AF according to gender, and of the SCS and CSS-AF according to education level. Significant differences were determined in the mean points of the CSS-AF and SFI according to profession, the SCS and CSS-AF according to the duration of working in the profession, and the SCS and CSS-AF according to the duration of working as a co-ordinator (Table 2). In a previous study that examined self-confidence, gender, and academic success in nursing degree students, the female students were determined to have lower levels of self-confidence than the male students (22). Abu Sharour et al. (23) examined the self-efficacy, self-confidence, and interaction with Coronavirus disease-2019 patients in nurses, and reported that self-confidence was high in nurses with a high level of education and longer professional experience. Hendekci (24) determined that female nursing students had higher levels of communication skills than male students. However, another study reported that socio-demographic characteristics had no effect on communication skills (19). In another study, a solution-focused approach and anxiety levels were investigated in nurses and midwives, and it was determined that socio-demographic characteristics (gender, marital status, education level,

Table 5. Determinants of CSS-AF

Model	β_0 (95% CI)	S. error	β_1	t	p	VIF
(Constant)	16.220 (6.154-26.287)	5.105		3.177	**0.002**	
SFI	0.076 (-0.062-0.214)	0.070	0.047	1.089	0.278	1.078
SCS	0.614 (0.549-0.679)	0.033	0.798	18.641	**0.000**	1.078

CSS-AF, F=193.771, *: p<0.001, Adjusted R^2=0.656, multivariate linear regression analysis, SFI: Solution-focused inventory, SCS: Self-confidence scale, CSS-AF: Communication skills scale-adult form, CI: Confidence interval

profession) did not have an effect on the SFI total mean points (21). In contrast, Akgül-Gündoğdu and Selçuk-Tosun (8) reported a difference between the SFI and gender, whereas Kaya and Guler (25) found no statistically significant difference in mean SFI points according to the demographic characteristics of midwifery students. These differences in results can be attributed to different sample sizes and/or the data collected from groups.

In the current study, there were seen to be differences in the mean points of the SCS according to the status of having an organ transplantation co-ordinator certificate, of the SCS, CSS-AF and SFI according to the area of working in the coordination system, of the SCS according to declaration of brain death, of the SFI according to the status of having obtained family consent for organ donation, and of the SCS, CSS-AF, and SFI according to participation in the preparation of organ transplantation from a cadaver or from a living donor (Table 3). Fernández-Alonso et al. (5) examined the factors facilitating and obstructing NTC in the organ donation process, and the participants in that study reported that transplantation coordinator was not a job for an inexperienced nurse. In a study by Chuang et al. (26), it was determined that coordinators who had attended organ donation courses and were experienced in obtaining organ donation showed better performance on the subject of requesting organ donation. Simonsson et al. (2) investigated the care-giving experiences of nurses with little intensive care experience during the organ donation process. As a result of the study, it was reported that the care of an organ donor is complex, and nurses experienced difficulties especially on the subject of informing relatives of the loss of a loved one and providing support for them (2). Karabilgin et al. (27) evaluated the effect of a course on simulated donor family interviews on the organ donation process and reported that the course had a positive effect on the communication skills of organ transplantation coordinators. Coordinators being experienced in the organ donation process can affect communication skills, self-confidence, and solution-focused approach skills.

Self-confidence is a strong factor affecting the effective nursing interventions in emergency conditions and in the care of critical patients. Nurses with high self-confidence show greater competence in correct decision-making, developing appropriate and safe interventions, and providing better quality care for patients (23). Solution-focused thinking can help nurses to more easily manage concerns, and can aid patient recovery. This is because an individual's strengths, along with the discovery and development of resources, enable them to be motivated, optimistic, and focused on the future (21). This perspective encourages the nurse, whose aim is to manage the crisis well, to use communication skills in dealing with the problems of her patients (28).

However, there is no other study in literature that has examined self-confidence, communication skills, and solution-focused thinking skills together of organ transplantation co-ordinators. Therefore, the relationship between these variables has been discussed based on the results of the current study. A positive correlation was found between the mean points of the SCS, CSS-AF, and SFI. This finding suggests that communication skills in organ transplantation coordinatorscan be affecteed by self-confidence and solution-focused thinking skills. Moreover, it also shows that nurse organ transplantation coordinatorsneed solution-focused thinking skills to integrate professional knowledge into patient care and to activate external resources.

Study Limitations

From the starting point of an organ transplantation co-ordinator in a public hospital, organ transplantation coordinators in private and public hospitals were contacted. The organ transplantation coordinators in all the hospitals in Türkiye could not be reached. Therefore, the study results cannot be generalised to all the organ transplantation coordinators in Türkiye. The research data were collected on the basis of self-reporting, which could have led to response bias or social desirability bias as the respondents might have wished to show themselves in a good light. These points constitute limitations to this study.

CONCLUSION

The study's results indicated that a solution-focused approach and self-confidence enhanced the communication abilities of organ transplantation coordinators. Organ transplantation coordinators can increase their confidence and provide better patient care during the difficult and complex organ donation procedure by enhancing their solution-focused communication skills.

Ethics

Ethics Committee Approval: The necessary permission conduct the study was obtained from the Medical Research Ethics Committee of the Kahramanmaraş Sütçü İmam University (decision no: 06, session no: 2022/23, dated: 06.09.2022).

Informed Consent: Written informed consent was provided by all the study participants.

Footnotes

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

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ORIGINAL ARTICLE
Turk J Surg 2025;41(1):56-60

Comparative evaluation of P-POSSUM and NELA scores in predicting 30-day mortality following emergency laparotomy: A prospective observational study

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ABSTRACT

Objective: Emergency laparotomy carries a 10-18% mortality risk, influenced by factors such as age, medical conditions, and sarcopenia. Scoring models like the Portsmouth physiological and operative severity score (P-POSSUM) and the National Emergency Laparotomy Audit (NELA) have been developed to predict outcomes and assist decision-making. Both models are widely used, but their effectiveness in predicting outcomes, particularly in the Indian context, requires further evaluation. This study aimed to compare the P-POSSUM and NELA scores in predicting 30-day mortality for patients undergoing emergency laparotomy.

Material and Methods: This single-institution prospective observational study included 238 adult patients of age ≥18 years undergoing emergency laparotomy for acute abdominal conditions, following ethical approval. P-POSSUM and NELA scores were calculated preoperatively, and their predictive accuracy was evaluated by comparing predicted versus observed mortality using sensitivity, specificity, positive and negative predictive values, and the area under the receiver operating characteristic curve.

Results: The NELA area under the curve was 0.699, while the P-POSSUM area under the curve was 0.687. NELA demonstrated higher sensitivity (73.9%) and specificity (45.6%) than P-POSSUM, which had a sensitivity of 52.2% and specificity of 27.4%. P-POSSUM and NELA scores were significantly higher in patients requiring intensive care unit admission than in those who did not.

Conclusion: Our study found that the NELA score outperforms the P-POSSUM score in predicting 30-day mortality in emergency laparotomy patients, indicating that NELA is a more reliable tool for preoperative risk stratification and clinical decision-making.

Keywords: Emergency laparotomy, P-POSSUM, NELA, mortality

INTRODUCTION

The average incidence of mortality after emergency laparotomy varies from 10% to 18% in different studies (1,2). The mortality-related risks in emergency laparotomies are much higher than any major gastrointestinal surgeries (2). The outcomes of emergency laparotomy are impacted by several factors, including the patient's age, medical comorbidities, general condition, presence of contamination, sarcopenia, etc. We need to focus on pre-operative considerations and associated factors to estimate the survival probability of patients undergoing emergency laparotomy. Prediction scores like the National Emergency Laparotomy Audit (NELA) and the Portsmouth-physiological and operative severity score for enumeration of mortality and morbidity (P-POSSUM) aid clinicians in predicting patient outcomes and supplement decision-making (3,4).

Given the rise in emergency laparotomies, it is crucial to identify reliable risk assessment tools to recognise high-risk patients early and allocate resources appropriately. A comparative analysis in India found that the P-POSSUM score effectively predicted mortality preoperatively in emergency laparotomy cases (5). A study conducted in Sweden demonstrated that P-POSSUM scores are highly accurate in predicting mortality among geriatric patients undergoing laparotomy in emergency settings (6). A study in New Zealand concluded that the NELA score is the most predictive tool for assessing mortality risk among emergency laparotomy patients (7). A UK study found that the P-POSSUM score moderately predicts mortality in elderly patients undergoing emergency abdominal surgery (8). Few studies have shown that both

Cite this article as: Lodha M, Khoth K, N K, Badkur M, Meena SP, Banerjee N, et al. Comparative evaluation of P-POSSUM and NELA scores in predicting 30-day mortality following emergency laparotomy: A prospective observational study. *Turk J Surg.* 2025;41(1):56-60

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Received: 21.11.2024
Accepted: 29.01.2025
Publication Date: 27.02.2025
DOI: 10.47717/turkjsurg.2025.6645
Available at www.turkjsurg.com

P-POSSUM and NELA scores tend to overestimate mortality in patients undergoing emergency laparotomies (9,10). While some studies found no significant differences between the two scores in estimating mortality, others found that NELA outperformed P-POSSUM in clinical practice (11-15).

A study highlighted that while P-POSSUM and APACHE-II are often used to predict mortality in emergency laparotomy patients, no scoring system currently provides highly accurate or easily calculable risk predictions (16). Due to the rising number of emergency laparotomies in India, both P-POSSUM and NELA scoring models are widely used. However, their validity in predicting mortality and morbidity in emergency laparotomy patients, particularly in the Indian population, still requires further evaluation. Most of the studies are retrospective, and there is a lack of well-designed prospective observational studies in the Indian population that establish the effectiveness of both scoring models (17). This study compares the NELA and P-POSSUM scoring systems in estimating thirty-day mortality for patients undergoing emergency laparotomies.

MATERIAL and METHODS

Study Design and Patients

This single-centre, prospective observational study was conducted at our tertiary care hospital from July 2022 to January 2024. The Institutional Ethics Committee approved the study All India Institute of Medical Sciences, Jodhpur (IEC/2022/4135). All patients who underwent emergency laparotomy in the department of general surgery were enrolled. Eligibility criteria included adults aged 18 years or older who had undergone emergency laparotomy for any acute abdominal aetiology through a midline incision of 5 cm or longer. Patients undergoing trauma laparotomies were excluded.

Study Procedure and Outcomes

All the patients admitted to our department of surgery underwent comprehensive medical evaluations as a part of standard practice. Through convenience sampling, patients who met the inclusion criteria were selected and given detailed explanations of the study format using a patient information sheet. Written informed consent was taken from the patients willing to participate. The NELA and P-POSSUM mortality risk scores were calculated for each patient in the preoperative room based on the respective scoring algorithms. The primary objective was to compare the effectiveness of both scores in predicting thirty-day mortality. The predictive accuracy of both mortality risk scores was assessed by comparing predicted mortality rates with observed mortality rates using metrics such as specificity, sensitivity, area under the receiver operating characteristic curve, and positive and negative predictive values. Secondary objectives included assessing the length of postoperative hospital stay and redo surgeries within 30 days. Demographic details, comorbid conditions, and substance use information were collected. All the patients were followed up until discharge.

Sample Size

Using the mean and standard deviation values from Lai et al.'s (15) study -16.3±21.4 for P-POSSUM and 9.8±12.7 for NELA- the sample size was calculated through OpenEpi software. The required sample size was 238, accounting for 80% power, a 95% confidence interval, and a 10% contingency.

Statistical Analysis

Data were analysed using the IBM Statistical Package for Social Sciences version 29.0. Descriptive data were reported for each variable. Data for continuous variables were expressed as mean or median, and compared using the Student's t-test or Mann-Whitney U test, depending on the distribution. The analysis focused on evaluating discrimination and calibration for each risk prediction tool selected. Discrimination of a risk prediction tool refers to its ability or inability to correctly classify patients with or without mortality following an emergency laparotomy, as determined by the area under the curve (AUC)- receiver operating characteristic (ROC) curve. The AUC provides a quantitative assessment of the discrimination of a risk prediction tool, enabling comparison between different tools. The observed thirty-day mortality rate was compared with the predicted thirty-day mortality rate for each risk prediction tool using the chi-square test. A p-value greater than 0.05 indicated that the expected and observed mortality rates were similar, suggesting good calibration of the risk prediction tool.

RESULTS

A total of 238 patients were enrolled during the study period. It was observed that the patients' mean age was 50.2 years. Almost 45% of cases in the study group were aged between 36 and 55. The mean postoperative hospital stay was 9.94 days. Notably, 85.7% of cases in the study group did not need postoperative intensive care unit (ICU). Of the 34 cases requiring postoperative ICU care, 21 patients were admitted for less than three days, while 5 were admitted for more than a week. The patient characteristics are detailed in Table 1.

It was observed that 23 cases died within 30 days of surgery, while 215 cases survived. It was observed that the P-POSSUM score in cases needing ICU admission was 15.15, while it was 11.00 in cases not needing ICU admission. The NELA score was 12.41 in cases requiring ICU admission and 5.18 in cases not requiring ICU. the scores were significantly higher in cases ICU admission.

It was observed that the P-POSSUM score in cases that did not survive was 17.61, while it was 10.97 in cases that survived.

Additionally, the NELA score was 13.61 in cases that did not survive, while it was 5.4 in cases that survived. The difference in P-POSSUM and NELA scores between cases categorized by mortality was statistically significant. A comparison of both scores in predicting the 30-day mortality and postoperative ICU care is shown in Table 2.

In our study on predicting 30-day mortality for patients undergoing laparotomy in emergency settings, we analysed the effectiveness of both scores using ROC curve analysis. It was observed that NELA AUC was 0.699, while P-POSSUM AUC was 0.687. AUC NELA (73.9%) indicates significantly higher sensitivity than P-POSSUM (52.2%). NELA (45.6%) also has higher specificity than P-POSSUM (27.4%). A comparison of both scores in predicting thirty-day mortality based on ROC curve analysis is shown in Table 3 and Figure 1.

DISCUSSION

Our study compared the effectiveness of NELA and P-POSSUM scores in estimating thirty-day mortality for patients undergoing an emergency laparotomy. In our study, mean patient age was 50.2±18.3 years, with nearly half aged 36-55 years. Comparable studies by Rinisha et al. (14) and Hunter Emergency Laparotomy Collaborator Group (18) reported mean ages of 66.0±17 years and 45.48±15.75 years, respectively. Contrary to our findings, Naidoo et al. (19) reported a mean age of 38.2 years for non-trauma emergency laparotomy patients. In Singapore, Lai et al. (15) found a higher mean age of 65.9 years ±14.7, likely due to differences in demographics, ethnicity, and patient severity. With 64% male patients in our study, this aligns with findings from Naidoo et al. (19) and Lai et al. (15), reporting a higher proportion of male patients. In contrast to our findings, Sharma et al. (20) in Birmingham, Barghash et al. (11), and Rinisha et al. (14) in Karnataka reported more female patients, with 78.4% female patients (11,20). This difference may reflect variations in study locations and populations. In our study, ICU-admitted cases had significantly higher scores. P-POSSUM averaged 15.15 (vs. 11.00 for non-ICU cases), and NELA averaged 12.41 (vs. 5.18 for non-ICU cases). This indicates that both scores effectively identified patients requiring ICU admission. Of 34 ICU cases, 21 stayed under 3 days, 8 stayed 4-7 days, and 5 stayed more than a week. Rinisha et al. (14) reported a mean postoperative ICU stay of 1.5±0.3 days for emergency laparotomy patients. In our study, 9.7% (23 cases) died during a 30-day follow-up. Hunter Emergency Laparotomy Collaborator Group (18) reported 10.5% mortality within 30 days for emergency laparotomy patients. NELA predicted 25.4% deaths (52 cases) in high-risk patients, compared to 18.8% (46 cases) with P-POSSUM.

Our study found that P-POSSUM and NELA scores were significantly higher in patients who did not survive, suggesting these scores may effectively differentiate mortality risk in emergency laparotomy cases. Lai et al. (15) found that NELA and P-POSSUM over-predicted mortality, with NELA demonstrating superior performance compared to P-POSSUM. In the Rinisha et al. (14) study, the prediction of mortality using NELA scores was found to correspond better to observed mortality data than the P-POSSUM scores at 30 and 60-day mortality (14). In a retrospective study, Darbyshire et al. (9) concluded that the NELA prediction score was better-calibrated than P-POSSUM, which over-estimated the mortality risk of more than 20% among emergency laparotomy patients. Both the scoring systems

Table 1. Characteristics of patients (n=238)

Patient characteristics		**Total (%)**
Mean age in years ± SD		50.2±18.3
Sex (%)	Male	152 (63.9%)
	Female	86 (36.1%)
Median operative duration in minutes (IQR)		180 (160-192)
Diagnosis (%)	Perforation peritonitis	105 (44.1%)
	Acute intestinal obstruction	116 (48.7%)
	Miscellaneous	17 (7.1%)
Mean duration of postoperative hospital stay in days ± SD		9.9±5.0
Duration of ICU stay (34)	1-3 days	21 (8.8%)
	4-7 days	8 (3.4%)
	>7 days	5 (2.1%)
Redo surgeries within 30 days (%)	Needed	22 (9.2%)
	Not needed	216 (90.8%)

SD: Standard deviation, IQR: Interquartile range, ICU: Intensive care unit

Table 2. Comparison of P-POSSUM and NELA scores in predicting 30-day mortality and postoperative ICU care

Outcome		**P-POSSUM (mean ± SD)**	***p-value**	**NELA (mean ± SD)**	***p-value**
30-day mortality	Death (n=23)	17.6±13.3	0.005	13.6±15.5	<0.01
	Recovered (n=215)	11.0±10.4		5.4±6.3	
Postoperative ICU care	Needed (n=34)	15.2±12.9	0.039	12.4±8.8	<0.01
	Not needed (n=204)	11.0±10.4		5.2±7.4	

*: p-value is calculated using the independent t-test, P-POSSUM: Portsmouth physiological and operative severity score, NELA: National Emergency Laparotomy Audit, SD: Standard deviation, ICU: Intensive care unit

Table 3. Comparative analysis of P-POSSUM and NELA scores in predicting 30-day mortality based on ROC curve analysis

ROC curve in the prediction of mortality	P-POSSUM	NELA
Ideal cut-off value	13.30	3.77
AUC	0.687	0.699
Sensitivity	52.2%	73.9%
Specificity	27.4%	45.6%

AUC: Area under curve, P-POSSUM: Portsmouth physiological and operative severity score, NELA: National Emergency Laparotomy Audit, ROC: Receiver operating characteristic

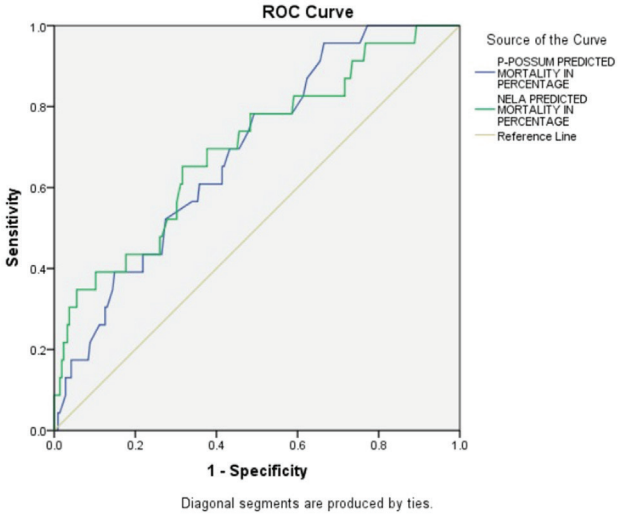

Figure 1. Receiver operating characteristics curve for P-POSSUM and NELA in the mortality prediction in emergency laparotomy cases.

P-POSSUM: Portsmouth physiological and operative severity score, NELA: National Emergency Laparotomy Audit, ROC: Receiver operating characteristic

showed good discrimination with slight variation between operative approaches, over-predicting mortality for laparoscopy (9). Thahir et al. (12) also reported that P-POSSUM over-predicted the risk of mortality, while NELA underestimated the same risk. Alabbasy et al. (21) found 30-day and 90-day mortality rates of 10.3% and 13.1%, respectively, among 670 patients undergoing emergency laparotomy, with AUCs of 0.774 preoperatively for the NELA score and 0.763 for the P-POSSUM score. Their findings, corroborated by Barghash et al. (11), indicated no statistically significant difference in mortality prediction between the two scoring models.

In our study, we found, using the ROC curve, that the NELA model is more specific and sensitive, in the 30-day mortality analysis. The AUC of 0.873 in NELA revealed its better predictive value than the P-POSSUM score (AUC 0.544) in predicting thirty-day mortality in a study conducted by Rinisha et al. (14). In contrast to our findings, Lai et al. (15) found that the area under the receiver operating characteristics curve was similar for the NELA (0.86) and the P-POSSUM score models (0.84). Linganathan et al. (22) in 2024 found that the NELA scoring method had lesser accuracy in predicting 30-day mortality among emergency laparotomy patients aged above 80 years; they found that the ROC graph analysis of NELA showed that the AUC was 0.78 in the age group of above 80 years and 0.89 in the age group of below 80 years, however, the score was not well-calibrated. This difference was due to different inclusion criteria and age groups. Overall, the findings of this retrospective study noted that the NELA tool performs better, supporting other findings in the literature.

The NELA and P-POSSUM scores have demonstrated discrimination, irrespective of the pre- or post-operative approach, to be preferred as one of the most effective risk-adjustment tools. The NELA method was well-adjusted and calibrated across all risk bands. However, the P-POSSUM method had limited predicted mortality, beyond which over-predicted risk in comparison. However, both scores concerning open surgery were found to be overestimating the mortality among the patients associated with emergency laparotomies.

The study's prospective design strengthened its ability to establish temporal relationships, reduce recall bias, and provide a reliable assessment of associations between exposures and outcomes. NELA and P-POSSUM scores show moderate predictive value (AUC under 0.7).

Study Limitations

This may suggest that while NELA performs better, both scores have limitations. The operative scores rely on subjective assessments, like peritoneal contamination, and do not account for operative duration, the time of presentation to the healthcare facility, and operative approach. The low specificity in both scores suggests they may overestimate risk in the population. This overestimation aligns with the findings of other studies and could be relevant for discussions on their use in Indian settings. The results align with previous research, showing that while both scores are predictive, NELA may be more useful in assessing 30-day mortality risk in emergency laparotomy patients. Further discussion on the clinical implications of these findings and the limitations of the scores in the Indian context could add valuable insight.

CONCLUSION

Our study demonstrated that the NELA score outperforms the P-POSSUM score in estimating thirty-day mortality for emergency laparotomy patients. NELA's superior accuracy suggests it may be a more reliable tool for preoperative risk stratification and clinical decision-making in this high-risk patient population.

Ethics

Ethics Committee Approval: The Institutional Ethics Committee approved the study All India Institute of Medical Sciences, Jodhpur (IEC/2022/4135).

Informed Consent: Written informed consent was taken from the patients willing to participate.

Footnotes

Author Contributions

Concept - M.L., N.B., A.K.; Design - M.L., N.B., S.P.M.; Data Collection or Processing - A.K., M.B., K.N.; Analysis or Interpretation - K.N., S.W., N.B.; Literature Search - S.P.M., M.L., M.B.; Critical Review - M.L., A.K., K.N., M.B., S.P.M., N.B., S.M.; Writing - K.N., S.M., A.K.

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

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

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ORIGINAL ARTICLE
Turk J Surg 2025;41(1):61-68

The results of the same day and appointment colonoscopy in inadequate bowel cleansing; a randomized controlled trial

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ABSTRACT

Objective: The aim of this study is to compare the results of repeat colonoscopies performed on the same day and by appointment in patients with inadequate bowel cleansing.

Material and Methods: The study was designed as a prospective randomized controlled study. Eighty patients with inadequate bowel cleansing detected in elective colonoscopies were included in the study. Patients were randomly divided into 2 groups: Group I: Same day group and Group II: Appointment day group. Same day colonoscopy group was given day hospitalization, sennoside A+B calcium was given and colonoscopy procedure was repeated. Patients in Group II were rescheduled and standard colonoscopy preparation protocol was applied. Boston bowel preparation scale (BBPS) was used for bowel preparation quality. Cecal intubation time, cecal intubation rate, procedure time, BBPS score and polyp detection rate were compared between the groups.

Results: In the same-day group, 52.5% of the patients were female while 45.9% were female in the appointment group. There was no significant difference between the two groups in terms of age or gender (p>0.05). The rate of cecum intubation was higher in the same-day group than it was in the appointment group (p=0.022). The total BBPS score was 7.9±1.79 in the same-day group and 6.89±2.23 in the appointment group, and the difference was statistically significant (p=0.03). When the two groups were compared in terms of tolerability of the procedure, no difference was detected (p>0.05).

Conclusion: Same-day colonoscopy is an effective method and can be performed safely in patients with inadequate bowel cleansing.

Keywords: Inadequate bowel preparation, same-day colonoscopy, repeat colonoscopy

INTRODUCTION

Colorectal cancer is an important cause of morbidity and mortality worldwide. Approximately 550,000 deaths occur worldwide every year due to this cancer type (1). Screening colonoscopies performed to reduce the incidence of colorectal cancer aim to detect adenomatous lesions at an early stage (2).

Colonoscopy is an invasive imaging method used in the diagnosis of colon cancer. Apart from its role in diagnosis, it is widely used because of its curative properties in cases such as the removal of colon polyps, treatment of lower gastrointestinal system (GIS) bleeding, stenting for stenotic lesions, and volvulus detorsion (3).

Although colonoscopy is considered the gold standard for evaluating the colonic mucosa, its diagnostic accuracy depends on the quality of the bowel preparation (4). However, insufficients bowel preparation is a common problem in colonoscopy practice. It has been reported in approximately 20-25% of all colonoscopies (5). This causes pathological lesions to be overlooked, increases costs, decreases patient satisfaction, and wastes workforce and time (6). In addition, recurrent bowel cleansing may cause fluid, protein and calorie malnutrition in elderly patients (7). Because of all these negative results, the feasibility of same-day colonoscopy has come to the fore, instead of scheduled colonoscopy in patients with inadequate bowel preparation. In their latest guideline, the European Society of Gastrointestinal Endoscopy (ESGE) and the American Society of Gastrointestinal Endoscopy reported, albeit with inconclusive evidence and cautious recommendation, that colonoscopies

Cite this article as: Özsoy U, Yıldırım M, Daldal E, Koca B, Sağlam Aİ, Gül SC, et al. The results of the same day and appointment colonoscopy in inadequate bowel cleansing; a randomized controlled trial. *Turk J Surg.* 2025;41(1):61-68

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Received: 02.09.2024
Accepted: 06.02.2025
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2025.6541

Available at www.turkjsurg.com

performed on the same day or the next day yield better results compared to delayed colonoscopies (8,9).

In this study, we aimed to evaluate the effectiveness and tolerability of repeat colonoscopies, both those performed on the same day and those scheduled at a later time, in patients with insufficient bowel preparation. To the best of our knowledge, our study is the first prospective randomized controlled study on this subject.

MATERIAL and METHODS

This prospective randomized controlled study was conducted at the Department of General Surgery of Tokat Gaziosmanpaşa University. Approval for the study was obtained from the Tokat Gaziosmanpaşa University Ethics Committee (approval no: 20-KAEK-089). Patients who had insufficient bowel cleansing in the colonoscopies performed by the General Surgery Clinic under elective conditions between 19 April 2020 and 19 April 2021, and who agreed to participate in the study, were included. During this period, 826 patients underwent colonoscopy in our clinic. Adequate bowel cleansing was achieved in 730 of these patients. Inadequate bowel cleansing was found in 104 patients. Those who were using antipsychotics or antidepressants, those under the age of 18, those who had previous stomach, colon or rectal surgery, those who underwent emergency colonoscopy, those who red-flag signs and symptoms for cancer and those who did not want to participate in the study were excluded from the study. In addition, since appropriate randomization could not be performed for colonoscopies performed after 13:00, these patients were also excluded from the study. After applying these exclusion criteria, the remaining 80 people were equally divided into groups (Figure 1).

Patients who met the inclusion criteria and gave written informed consent were randomized equally into two groups, a same-day group and an appointment group, usings ealed envelopes. Randomization was performed by a blinded physician who was not present during the study. Eighty pre-preparedand mixeds ealed envelopes were used. The patient's envelope selection was determined by re-mixing each time under the supervision of the same faculty member. Demographic data of the patients, height, weight, body mass index (BMI), and presence of morbidity were recorded. Additional bowel cleansing medication was given to the same-day group and the colonoscopy was repeated for this group. The group was scheduled for a new appointment according to the standard procedure. Colonoscopy is performed on an average of 2,000 patients annually at our department. Colonoscopy appointments are made during outpatient examinations. The patients were informed by the endoscopy nurse verbally and in writing about how bowel preparation would be performed during the colonoscopy appointment. The colonoscopy procedure was carried out by an endoscopist who performs more than 250 colonoscopy procedures per year in the clinic. All patients underwent colonoscopy using the same Olympus device (serial number: CF-H170L).

A low fiber diet was recommended 72 hours before the procedure for bowel cleansing. A sample written form was provided for the recommended diet. As in our routine practice, 2 solutions (150 mL, 300 mg) containing sennoside A+B calcium were prescribed. A written form containing instructions for using the drug was also given. Sennozid A+B calcium should be taken with at least 1.5 liters of water at 6 o'clock in the evening and again at 5 o'clock in the morning, one night before the procedure. The patients with inadequate bowel cleansing in the same-day colonoscopy group were admitted to the clinic. One dose of sennoside A+B calcium, 150 mL (300 mg), was given to be swallowed with 1.5 liters of water after the procedure. The procedure was repeated 4 hours after the last dose (10). In the second group, appointments were scheduled and standard colonoscopy preparation protocol was applied.

The decision of whether the initial colonoscopy could be continued due to inadequate bowel cleansing was made by the physician performing the colonoscopy. The internationally proven Boston bowel preparation scale (BBPS), which has been used in many studies, informed this decision. According to this scale, the right, middle, and left colon segments are scored between 0 and 3. BBPS takes values between 0 and 9. A total value of less than 5 means insufficient colon cleansing, as it affects the polyp detection rate. In our study, re-colonoscopy was recommended for patients with a BBPS less than five. Patients who could not complete the colonoscopy due to difficult anatomy or excessive looping, and those who could not tolerate anesthesia due to comorbidities, were excluded from the study.

Patients who underwent colonoscopy were sedated with 0.05 mg/kg midazolam and 0.5 mg/kg pethidine hydrochloride. In both groups, pulse, blood pressure, and blood glucose levels were measured before the second colonoscopy. In both groups, the indication of the procedure, information about the physician performing the procedure, the drugs used for sedation, the duration of the procedure, the duration of cecum intubation, the location of the detected lesions, and the presence of complications were recorded. Additionally, BBPS, and whether the procedure was incomplete (due to complications, pain, etc.) were noted. Procedure time, cecum intubation rate, adenoma or lesion detection rate, quality of bowel cleansing, and patients' tolerability of the procedure were evaluated for both groups.

Statistical Analysis

Statistical analyses of the data obtained in our study were performed using the SPSS (Version 22.0, SPSS Inc. Chicago, IL, USA) package program. Descriptive statistics were presented

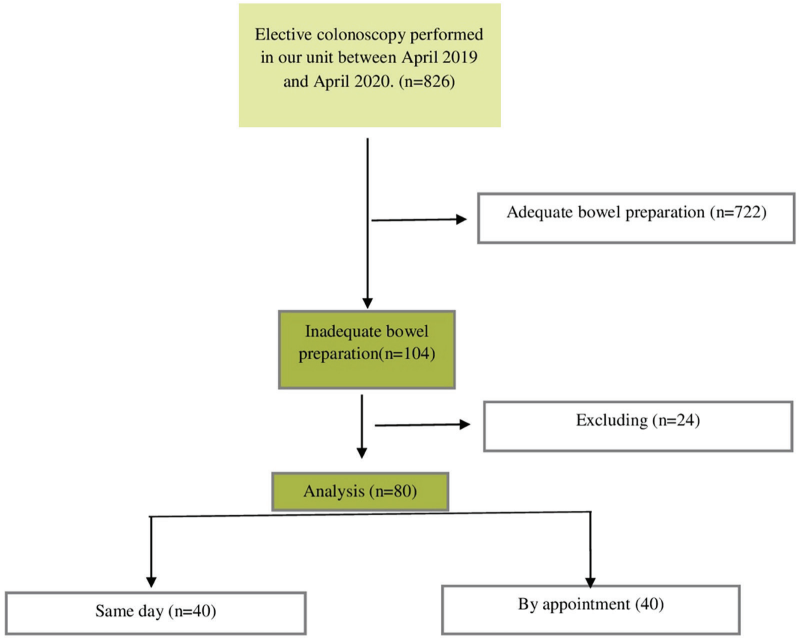

Figure 1. Patient flow diagram.

as numbers (n) and percentages (%) for categorical variables. The quantitative variables that were obtained by measurement were presented as mean ± standard deviation or median (minimum-maximum) values depending on whether the data were normally distributed or not. For the comparison of two independent group data, the Student's t-test was performed. A cross-table and Pearson's chi-square test were used to compare qualitative variables between groups. In the comparison of quantitative data between the groups, a t-test was used when parametric assumptions were met. Inadequate bowel cleansing is seen in from 5% to 30% of studies. Based on the assumption that 10% of patients would have inadequate bowel preparation, we calculated that we needed to include at least 80 patients in the study with 80% power, 5% margin of error, and an effect size of 0.3 (type I error, 5%). P<0.05 was considered statistically significant.

RESULTS

In his study, 80 patients who underwent colonoscopy were found to have inadequate bowel cleansing were included. Patients were divided into two groups, with 40 patients in the same-day group and 40 patients in the appointment group. Since three patients in the appointment group did not attend the control colonoscopy procedure, the second group consisted of 37 patients. Of the patients, 38 (49.4%) were male and 39 (50.6%) were female. The mean age was 57.6±12.99 (20-81). The frequency distributions and descriptive statistics of quantitative variables regarding the age, additional diseases, BMI, education level, and pre-procedure diet compliance status of the participants are given in Table 1.

Table 1. Descriptive statistics of quantitative variables

	Same day n=40	By appointment n=37	p-value
Age (avrg. ± SD)	53.13±14.31	60.7±10.98	0.083
Gender (%)			
Female	21 (52.5%)	17 (45.9%)	0.740
Male	19 (47.5%)	20 (54.1%)	
BMI (avrg. ± SD)	29.10±5.34	26.63±6.12	0.063
Education level (%)			
Not literate	5 (12.5%)	2 (5.4%)	0.129
Primary school	31 (77.5%)	29 (79.3%)	
Middle -high school	1 (2.5%)	4 (10.3%)	
University	3 (7.5%)	4 (10.3%)	
Comorbidity (%)			
Coronary artery disease	5 (12.5%)	12 (32.4%)	0.411
Hypertension	11 (27.5%)	10 (27%)	
Diabetes mellitus	11 (27.5%)	7 (18.9%)	
Asthma/COPD	2 (5%)	1 (2.7%)	
Neurological	2 (5%)	1 (2.7%)	
Diet compliance			
One day	9 (22.5%)	7 (18.1%)	0.919
Two days	5 (12.5%)	9 (24.3%)	
Three days	26 (65%)	21 (56.7%)	

SD: Standard deviation, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease

Of the 40 patients in the same day group, 21 (52.5%) were female, and of the 37 patients in the appointment group, 18 (48.6%) were female. The mean age of the patients was 53.13±14.31 in the same-day group and 60.7±10.98 in the appointment group. BMI was 29.1±5.34 in the same-day group and 26.63±6.12 in the appointment group.

When evaluated in terms of the presence of chronic disease, 20 (50%) of 40 patients in the same-day group and 21 (56.7%) of 37 patients in the appointment group had at least one chronic disease. In the same-day group, 5 patients (12.5%) had coronary artery disease, 11 patients (27.5%) had diabetes mellitus, 11 patients (27.5%) had hypertension, 2 patients (5%) had asthma-chronic obstructive pulmonary disease (COPD), and 2 patients (5%) had neurological disease. In the appointment group, 12 patients (32.4%) had coronary artery disease, 7 patients (18.9%) had diabetes mellitus, 10 patients (27%) had hypertension, 1 patient (2.7%) had asthma-COPD, 1 patient (2.7%) had neurological disease.

In the same-day group, 9 patients (22.5%) followed a low fiber diet for one day, 5 patients (12.5%) for two days, and 26 patients (65%) for three days. In the appointment group, 7 patients (18.1%) followed a low-fiber diet for one day, 9 patients (24.3%) for two days, and 21 patients (56.5%) for three days. There was no statistically significant difference between the two groups in terms of age, gender, BMI, educational status, chronic disease presence, and dietary compliance (p>0.05).

When the groups were examined in terms of procedure indications, in the same-day group, 12 patients (30%) underwent colonoscopy for abdominal pain, 11 (27.5%) for constipation, 6 (15%) for screening, 3 (7.5%) for diarrhea, 2 (5%) for occult blood in the stool, 2 (5%) for anemia, 1 (2.5%) for weight loss, 1 (2.5%) for rectal bleeding, 1 (2.5%) for post-polypectomy follow-up, and 1 (2.5%) for other reasons. In the appointment group, 12 patients (32.4%) underwent colonoscopy for abdominal pain, 9 patients (24.3%) for screening, 8 patients (21.6%) for constipation, 2 patients (5.4%) for anemia, 2 patients (5.4%) for weight loss, 1 patient (2.7%) for post-polypectomy follow-up, 1 patient (2.7%) for diarrhea, and 2 patients (5.4%) for other reasons (Figure 2). There was no statistically significant difference between the two groups in terms of procedure indications (p>0.05).

When the two groups were examined in terms of colonoscopy quality indicators, the cecum was intubated in 37 of 40 patients in the same-day group. In the appointment group, 27 of 37 patients were intubated. There was a statistically significant difference between the two groups in terms of cecum intubation (Table 2, p=0.022). The rate of adenoma detection was 20% in

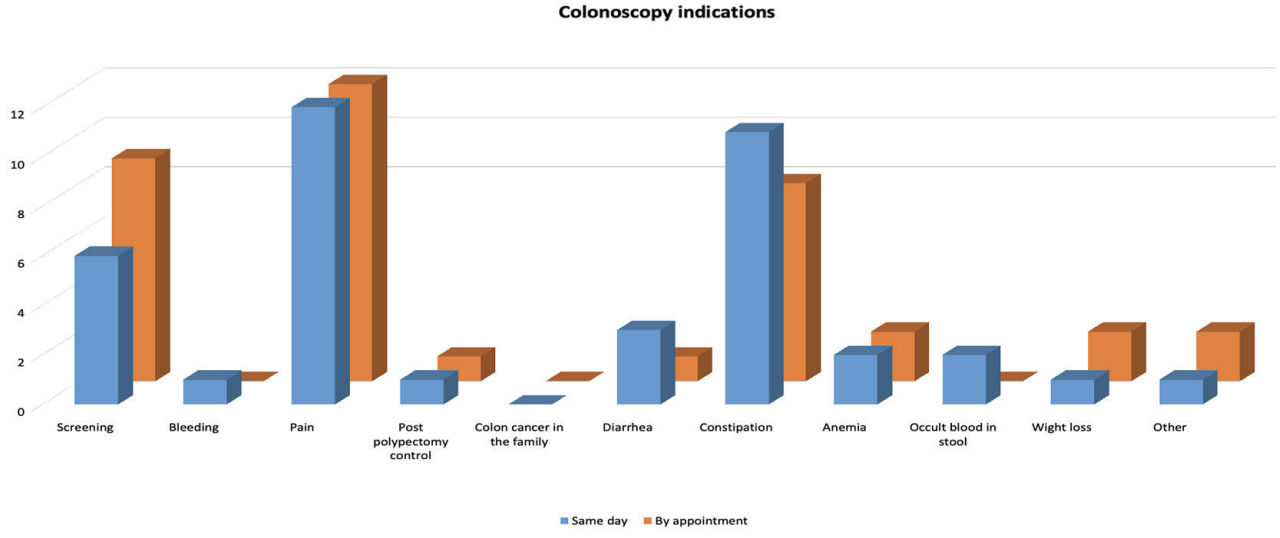

Figure 2. Procedure indications of the patients in the study groups.

Table 2. Colonoscopy quality indicators

Colonoscopy procedure quality parameters n (%)		Same day	By appointment	p-value
		n (%)		
Cecal intubation status	Yes	37 (92.5%)	27 (72.9)	0.022
	No	3 (7.5%)	10 (27.1)	
Causes of unsuccessful cecal intubation	Pain	1 (33.3%)	0 (0%)	
	Inadequate bowel preparation	2 (66.6%)	10 (100%)	
Polyp detection status	Yes	8 (20%)	5 (13.5%)	0.448
	No	32 (80%)	32 (86.5%)	

the same-day group and 13.5% in the appointment group, and no statistically significant difference was found between the two groups (p>0.05).

Cecum intubation times were calculated in the patients. Its time was 9.24±3.35 minutes in the same-day group and 9.78±3.26 minutes in the appointment group. There was no statistically significant difference between the two groups in terms of cecum intubation time (Table 3, p>0.05).

Total processing times were calculated. It was 16.22 ± 4.83 minutes in the same-day group and 14.62±5.81 minutes in the appointment group. There was no statistically significant difference between the two groups in terms of total processing time (Table 3, p>0.05).

The BBPS score was calculated for the total, right colon, transverse colon, and left colon in both groups. The total BBPS score was 7.9±1.79 in the same-day group, and 6.89±2.23 in the appointment group; a statistically significant difference was found (p=0.032). The right colon BBPS score was calculated as 2.6±0.77 in the same-day group and 2.14±1.08 in the appointment group. A statistically significant difference was found (p=0.033). Transverse colon BBPS score was calculated as 2.6±0.74 in the same-day group and 2.32±0.88 in the appointment group, and no statistically significant difference was found between them (p>0.05). The left colon BBPS score was calculated as 2.7±0.56 in the same-day group and 2.42±0.72 in the appointment group; a statistically significant difference was found (p=0.049); Table 4.

The two groups were compared in terms of tolerability of the reintroduced bowel cleansing drug. In the same-day group, 6 (15%) of 49 patients experienced nausea, vomiting, and abdominal pain after the intake. In the appointment group, these symptoms were detected in 5 (13.5%) of 37 patients. When the two groups were compared, no statistically significant difference was found (p>0.05). While 37 (92.5%) of 40 patients in the same-day group could take the full dose, 36 (97.3%) of 37 patients in the appointment group could take all of it. When the two groups were compared, no statistically significant difference was found (p>0.05) as shown in Table 5.

Colonoscopy findings were normal in 25 (62.5%) of the patients in the same-day group. Polyps were detected in 8 patients (20%), diverticula in 4 patients (10%), IBD in 2 patients (5%), and cancer in 1 patient (2.5%). Colonoscopy results were normal in 21 (56.7%) of all 37 patients in the appointment group. Polyps were detected in 5 patients (13.5%), diverticula in 4 patients (10.8%), tumors in 1 patient (2.7%), and intestinal parasites in 1 patient (2.7%) (Figure 3).

Table 3. Procedure and cecum intubation times of the patients in the study groups

Durations (minutes)	Same day (mean ± SD)	By appointment (mean ± SD)	p-value
Cecum intubation time	9.24±3.35	9.78±3.26	0.526
Processing time	16.22±4.83	14.62±5.81	0.191

SD: Standard deviation

DISCUSSION

There are many studies on planning a second colonoscopy in patients with inadequate bowel cleansing (11,12). However, there is no consensus on an ideal bowel preparation method and timing to be recommended for those patients (13). In the split-dose regimen, the morning dose is thought to promote clearance of gastrointestinal and pancreatobiliary secretions that enter the colon in the interim (14). In a retrospective study of Ben-Horin et al. (15), 6,990 colonoscopy procedures were examined. Repeat colonoscopy was planned for 307 patients

Table 4. BBPS scores for colon segments

BBPS (Avrg ± SD)	Same day	By appointment	p-value
Total	7.90±1.79	6.89±2.23	0.032
Right colon	2.60±0.77	2.14±1.08	0.033
Transverse colon	2.60±0.74	2.32±0.88	0.142
Left colon	2.70±0.56	2.42±0.72	0.049

BBPS: Boston bowel preparation scale, SD: Standard deviation

Table 5. Evaluation of study groups in terms of drug tolerability

Tolerance to medicine		Same day n (%)	By appointment n (%)	p-value
Nausea, vomiting, pain after medication	Yes	6 (15%)	5 (13.5%)	0.852
	No	34 (85%)	32 (86.5%)	
Took all the medicine	Yes	37 (92.5%)	36 (97.3%)	0.343
	No	3 (7.5)	1 (2.7)	

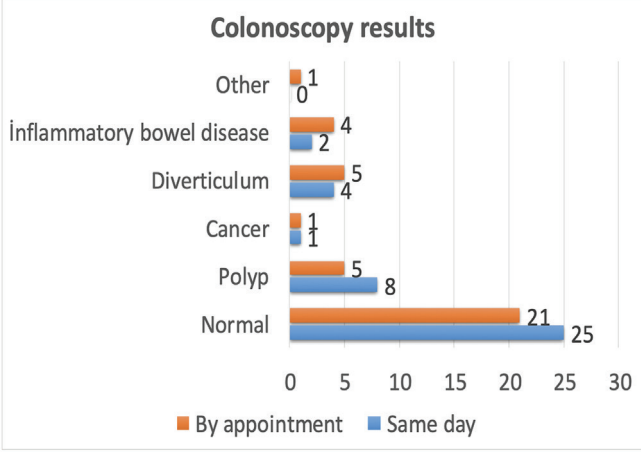

Figure 3. Colonoscopy result.

due to insufficient bowel cleansing. Examination of repeat colonoscopies showed that the success rate of the procedure decreased as it was repeated. When the patients were examined according to the time of the second colonoscopy, the success rate appeared higher in the colonoscopies performed the next day; however, no statistically significant difference was found. As a result of the study, it was recommended to plan a colonoscopy the next day for the patients at risk due to inadequate colon cleansing. In addition, it has been suggested that a randomized controlled study is required to demonstrate the efficacy of next-day colonoscopy in patients with inadequate bowel cleansing (15). In a study by Murphy et al. (16), patients with insufficient bowel cleansing were divided into two groups: The next-day group and the non-next-day group. The rate of unsuccessful control colonoscopy was found to be 29.8% in the next-day group and 23.3% in the non-next-day group, while no statistically significant difference was found between them.

In a prospective study by Akgul et al. (17), 60 patients with inadequate bowel cleansing were given additional bowel laxatives on the same day. The cecum intubation rate was 83.3%. In addition, no complications were observed in 60 patients who were given additional laxative. In the study, it was shown that the second colonoscopy, performed on the same day with additional medication in patients with inadequate bowel cleansing, was effective and safe. However, since there was no control group in the study, no comparison was made with non-same-day colonoscopy results (16).

The two key quality indicators of colonoscopy are cecal intubation rate and polyp detection rate (17). In its guide published in 2017, ESGE reported that the cecum intubation rate should be at least 90% as a colonoscopy quality indicator (18). In our study, the cecum intubation rate was 92.5% in the same-day group and 72.9% in the appointment group. When the two groups were compared in terms of cecum intubation rate, a significant difference was found in favor of the same-day group. We think that the higher-quality preparation and the higher rate of cecum intubation in the same-day group are significant. Furthermore, the administration of additional bowel cleansing agent on the same day to patients who have partial bowel cleansing, therefore, affects the quality of the preparation positively.

Another important colonoscopy quality indicator is the adenoma detection rate. Polyp detection rate has been reported to be more than 25% in many studies (19,20). In the ESGE 2017 guideline, it is suggested that the ADR should be at least 25% (18). The polyp detection rate in our study was found to be lower than it is in these studies. It was 20% in the same-day group and 13.5% in the appointment group. However, there was no significant difference between the two groups in terms of this rate. The polyp detection rate was found to be 19.1% in the study of Park et al. (21) which is similar to the results of our study. In a study conducted by reviewing 10,420 patients in our clinic, a repeat colonoscopy was planned for 522 patients due to insufficient bowel cleansing. Polyp detection rate in the second colonoscopy performed due to insufficient bowel cleansing was 17.8%, which is similar to our study's findings (22).

When the histopathology results of the lesions detected in the colonoscopy were evaluated, one patient in each group was diagnosed with colon cancer. The second colonoscopy procedure was performed on the patient in the appointment group, 74 days after the first procedure. This caused a delay in the diagnosis of the patient's tumor. In addition, it can be assumed that this period may increase due to infectious diseases such as the Coronavirus disease-2019 (COVID-19) pandemic. In our study, 3 patients in the second group could not attend the control colonoscopy procedure because one had a diagnosis of COVID-19, and the others had difficulty visiting the hospital due to pandemic restrictions or long distance. Therefore, we suggest that various factors, such as the distance of patients' homes to the hospital and pandemic conditions, should be taken into consideration when rescheduling colonoscopy for patients with insufficient bowel cleansing. Same-day colonoscopy should be performed on these patients.

In the current study, the BBPS score in the same-day group was found to be higher in all colon segments. When the BBPS scores of both groups were compared, a significant difference was found in favor of the same-day group for the total, right, and left colon. The BBPS score can be used to determine the time of surveillance colonoscopy. A 10-year follow-up is recommended if all segment scores are >2. If inadequate bowel preparation is detected (total BBPS score ≤2), repeat colonoscopy is recommended within the next 1 year (23). Higher BBPS is observed in patients with inadequate bowel cleansing in the same-day group, which increases the rate of polyp detection. Therefore, we recommend rescheduling colonoscopy on the same day for these patients.

When both groups were compared in terms of cecum intubation time and procedure time, there was no significant difference between them. The reason for this, was that control colonoscopy was performed by the same endoscopist in both groups. Better bowel preparation has been known to have shortened the processing time (24). However, the rate of inadequate bowel cleansing was higher in the appointment group. Although the procedure time is very short in patients with completely contaminated bowel, it is thought that there is no significant difference in procedure times between the two groups

When the two groups were compared in terms of tolerability of the procedure, no significant difference was found. In our study, patients were asked whether they had nausea, vomiting, and

abdominal pain, and that the results were found to be similar in both groups. In our study, nausea and vomiting were seen in 15% of the same-day group and 13.5% of the appointment group. In a study, there was no difference in tolerability between the divided-dose regimen administered the same morning and the bowel cleansing regimen spread over two days. In addition, when both groups were evaluated in terms of adherence to the complete drug regimen, the results were found to be similar (25). Before the second colonoscopy procedure, the patients' pulse, blood pressure, and saturation values were measured. The Aldrete score was calculated for discharge. No serious complications were observed in any of the patients. The patients were discharged from the unit on the same day after the procedure. When the regimens using senna and sodium phosphate were compared, senna was better tolerated and had fewer side effects (26). In this study, we used senna in both groups and found that the drug was tolerable. As a result, we recommend using senna as an additional laxative on the same day, but further studies are needed to compare the efficacy of different drugs.

The strength of our study is that it is a randomized controlled prospective study. One limitation of our study is that the higher success rate in the same-day colonoscopy group may have been due to overzealous endoscopists.

Study Limitations

However, this limitation is not unique to our study because, in the absence of widely accepted criteria, even experienced endoscopists often disagree on what constitutes a disqualifying preparation. However, we believe that we have eliminated this bias by using the BBPS to define a dirty colon in our study. It is recommended that the study be supported by multi-center, randomized controlled studies with larger patient numbers.

Conclusion

Today, most of the repeat colonoscopy cases consist of patients with inadequate bowel cleansing. Since colonoscopy is a hardly accessible, and an invasive procedure that requires serious preparation, repeat colonoscopies related to inadequate bowel cleansing should be reduced. In our study, comparing same-day colonoscopies with scheduled colonoscopies in patients with insufficient bowel cleansing, we showed that the quality of bowel preparation and the success rate of the procedure are higher when colonoscopies are performed with additional bowel cleansing medication on the same day, which can be tolerated. We believe this study is a valuable contribution to the literature, as it is the first prospective randomized controlled study on this subject.

Ethics

Ethics Committee Approval: This prospective randomized controlled study was conducted at the Department of General Surgery of Tokat Gaziosmanpaşa University. Approval for the study was obtained from the Tokat Gaziosmanpaşa University Ethics Committee (approval no: 20-KAEK-089).

Informed Consent: Informed consent was obtained.

Footnotes

Author Contributions

Concept - U.Ö., M.Y.; Design - U.Ö., M.Y., E.D.; Supervision - İ.Ö., N.Ö.; Fundings - A.İ.S., S.C.G.; Materials - S.Y., N.Ö., B.K.; Data Collection or Processing - B.K., M.Y.; Analysis or Interpretation -U.Ö., M.Y.; Literature Search - U.Ö., İ.O.; Critical Review - U.Ö., M.Y., E.D., İ.O.; Writing - N.Ö., Aİ.S.

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

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

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ORIGINAL ARTICLE
Turk J Surg 2025;41(1):69-77

A questionnaire on the perception of social and academic discrimination against female general surgeons in Türkiye

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ABSTRACT

Objective: The purpose of this research was to identify the specific prejudices that women in general surgery in Türkiye have to face in their workplace and academic careers. This was achieved by gathering the opinions of both genders on these issues and raising awareness of gender bias to promote a more inclusive environment for future generations of surgeons.

Material and Methods: A total of 202 people, 99 male and 103 female surgeons, participated in the survey. The questionnaire was distributed to people working in general surgery clinics via e-mail and WhatsApp groups of the Turkish Surgical Association and the Turkish Colorectal Association.

Results: The mean age of the participants was 37.65±11.55 years (ranging from 24 to 74 years). Among the partipiciants, 40.4% agreed that surgery is more suitable for males, while 89.3% of women disagreed (p<0.001). 88.3% of the women stated that women are negatively influenced in choosing general surgery because of the male-dominated environment, and 52.5% of men agreed, while 40.4% of men disagreed (p<0.001). 66.7% of men and 65% of women believed that women do not prefer to work in general surgery because it is difficult to balance with family responsibilities (p=0.890). Women are more subjected to humiliating behaviors, while 53.4% of women agree. 85.4% of the women stated that it is important to have a female lecturer as a role model in the institution where they work.

Conclusion: This study shows different views on gender prejudice among male and female surgeons in general surgery. Female respondents, including male and female surgeons, indicated experiencing bias and underrepresentation in academic disciplines, although they had differing perspectives on discrimination. Both genders agreed on the difficulty of work-life balance, with a similar percentage of individuals identifying family responsibilities as an obstacle.

Keywords: Discrimination, gender, women, survey

INTRODUCTION

Gender disparities in medicine have raised concerns over the past century, especially in surgical specialties where the number of female surgeons are notably lower than their male counterparts (1). Despite the significantly increasing number of women in surgery in recent years, female surgeons may still encounter obstacles that can affect their career development, such as lack of support, harassment, and unequal opportunities (2). At the beginning of their careers, women may feel discouraged from pursuing surgery because of the societal norms on family and career balance (3). Additionally, unconscious biases may also affect the evaluation of performance, which may unfairly judging women and limit access to leadership positions, contributing to the so-called "pipeline effect" (4).

The data provided by the Ministry of Health in Türkiye indicate that the percentage of female specialist surgeons is 8.78%, while the percentage of female residents rises to 24% (5). Despite the growing number of women in general surgery, there hasn't been enough research on the challenges faced by women in this traditionally male-dominated field in Türkiye (5).

The purpose of this research is to increase awareness of gender prejudice and create a more inclusive environment for the next generation of surgeons by collecting and evaluating the opinions of both male and female surgeons.

Cite this article as: Bozkurt H, Çolak T, Tuna S, Özcan C, Reyhan E. A questionnaire on the perception of social and academic discrimination against female general surgeons in Türkiye. *Turk J Surg.* 2025;41(1):69-77

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Received: 10.09.2024
Accepted: 04.02.2025
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2025.6578

Available at www.turkjsurg.com

MATERIAL and METHODS

Study Design

After conducting a comprehensive review of the literature, a 32-item questionnaire was created. The questionnaire was created with Google Forms, a widely used and highly secure online survey platform. The questionnaire was subjected to review and revisions by a panel consisting of eight experts, including four male and three female general surgeons, along with one biostatistics faculty member from Mersin University.

The survey was designed to collect demographic information including gender, age, academic rank, years of experience, current working institution, marital status, parental status, and age of first parenthood. In addition, the survey aimed to collect participants' perspectives on three main subjects: Societal bias against female surgeons, gender-related disparities in the workplace, and prejudice against women in academic professions. Participants were given the opportunity to indicate their level of agreement, disagreement, or uncertainty for each statement. Tables 1-4 provide a comprehensive list of all the questions.

Ethical Approval

The Mersin University Clinical Research Ethics Committee approved this study, dated February 21, 2024, and numbered 2024/193.

Data Collection

The questionnaire was tested online by the authors to ensure its clarity before being distributed. It was sent out to general surgeons in February 2024 via WhatsApp groups and email addresses, connected to the Turkish Surgical Association and Turkish Colorectal Association. Before starting the survey, participants received an introduction letter that included the goal, substance, and target audience of the survey. Consent to participate in the study was implied by completing the survey. One week after the initial distribution, reminders were sent out, and three weeks later, the survey was closed to responses. Every response was anonymous and voluntary. Both male and female general surgeons participated in the study. A total of 202 surgeons participated, including 99 males and 103 females.

Table 1. Demographics of partipiciants

Characteristics	Men (n=99)	Women (n=103)	p-value
Age	40.22±12.96 (25-74)	35.18±9.43 (24-64)	0.002
Academic rank			
Research assistant	44 (4.1%)	54 (52.4%)	
Specialist	23 (23.2%)	36 (35%)	
Lecturers	1 (1.0%)	0 (0.0%)	0.024
Assistant professors	2 (2%)	2 (2.9%)	
Associate professors	12 (12.1%)	5 (4.9%)	
Professors	12 (17.2%)	6 (5.8%)	
Years of experience			
0-5	42 (42.4%)	57 (55.3%)	
5-10	16 (16.2%)	17 (16.5%)	0.232
10-20	16 (16.2%)	11 (10.7%)	
20+	25 (25.2%)	18 (17.5%)	
Current working institution			
University hospital	52 (58.6%)	34 (33.0%)	
Training and research hospital	22 (22.2%)	45 (43.7%)	0.001
State hospital	8 (8.1%)	14 (13.6%)	
Private clinic	10 (10.1%)	6 (5.8%)	
Other	1 (1%)	4 (3.9%)	
Marital status			
Married	79 (79.8%)*	42 (40.8%)	<0.001
Single	20 (20.2%)	61 (59.2%)*	
Parental status			
Has children	56 (56.6%)	27 (26.2%)	<0.001
No children	43 (43.4%)	76 (73.8%)	
Age of first parenthood	29.80±3.80 (20-42)	31.72±4.00 (25-46)	0.037
I do not currently or have never worked with female doctors in the general surgery	3 (3%)	4 (3.9%)	1.00

Table 2. Social prejudice in general surgery

Question	Respont	Men (n=99)	Women (n=103)	p-value
I think surgery is more suitable for the male gender.	Agree	40 (40.4%)*	9 (8.7%)	<0.001
	Disagree	46 (46.5%)	92 (89.3%)*	
	Not sure	13 (13.1%)*	2 (1.9%)	
I think women should not choose general surgery because they are physically weaker.	Agree	22 (22.2%)*	2 (1.9%)	<0.001
	Disagree	68 (68.7%)	101 (98.1%)*	
	Not sure	9 (9.1%)	0 (0%)	
I think that women do not prefer to work in general surgery because it is difficult to balance with family responsibilities.	Agree	66 (66.7%)	67 (65%)	0.890
	Disagree	27 (27.3%)	28 (27.2%)	
	Not sure	6 (6.1%)	8 (7.8%)	
I think general surgery is more suitable for men due to long-working hours.	Agree	48 (48.5%)*	6 (5.8%)	<0.001
	Disagree	46 (46.5%)	91 (88.3%)*	
	Not sure	5 (5.1%)	6 (5.8%)	
I think the stress and psychological aspects of general surgery affect women more.	Agree	58 (58.6%)*	38 (36.9%)	0.008
	Disagree	35 (35.4%)	53 (51.5%)*	
	Not sure	6 (6.1%)	12 (11.7%)	
I think that women who want to work in general surgery are negatively influenced by people due to the male-dominated working area in the general surgery.	Agree	52 (52.5%)	91 (88.3%)*	<0.001
	Disagree	40 (40.4%)*	10 (9.7%)	
	Not sure	7 (7.1%)	2 (1.9%)	
I think that female surgeons who are new to a clinic are prejudiced against by their colleagues and other health workers.	Agree	38 (38.4%)	81 (78.6%)*	<0.001
	Disagree	54 (54.5%)*	18 (17.5%)	
	Not sure	7 (7.1%)	4 (3.9%)	

Table 3. Gender bias in workplace

Question	Respont	Men (n=99)	Women (n=103)	p-value
I think there is positive discrimination against female general surgeons.	Agree	40 (40.4%)*	10 (9.7%)	<0.001
	Disagree	47 (47.5%)	88 (85.4%)*	
	Not sure	12 (12.1%)	5 (4.9%)	
I consider it unfair to their colleagues taking maternity leave of female general surgeons	Agree	19 (19.2%)*	6 (5.8%)	0.010
	Disagree	73 (73.7%)	92 (89.3%)*	
	Not sure	7 (7.1%)	5 (4.9%)	
I think there should be separate rest rooms for male and female residents in general surgery clinics.	Agree	59 (59.6%)	54 (52.4%)	0.085
	Disagree	32 (32.3%)	46 (44.7%)	
	Not sure	8 (8.1%)	3 (2.9%)	
I think that the opportunities (training, attendance to congresses, presentations, etc.) given to individuals in the institution where I work are regardless of gender.	Agree	76 (76.8%)*	63 (61.2%)	0.004
	Disagree	16 (16.2%)	37 (35.9%)*	
	Not sure	7 (7.1%)	3 (2.9%)	
I think patients trust male surgeons more than female surgeons.	Agree	52 (52.5%)	57 (55.3%)	0.741
	Disagree	34 (34.3%)	36 (35.0%)	
	Not sure	13 (13.1%)	10 (9.7%)	
I think that female general surgeons are more frequently criticized by their colleagues about their appearance.	Agree	27 (27.3%)	68 (66.0%)*	<0.001
	Disagree	65 (65.7%)*	30 (29.1%)	
	Not sure	7 (7.1%)	5 (4.9%)	

Table 3. Continued

Question	Respont	Men (n=99)	Women (n=103)	p-value
I think the clothes that female general surgeons wear in the hospital should look more masculine.	Agree	11 (11.4%)	4 (3.9%)	0.099
	Disagree	83 (83.8%)	96 (93.2%)	
	Not sure	5 (5%)	3 (2.9%)	
I think that female general surgeons are given fewer cases and responsibilities.	Agree	14 (14.1%)	47 (45.6%)*	<0.001
	Disagree	76 (76.8%)*	48 (46.6%)	
	Not sure	9 (9.1%)	8 (7.8%)	
I think that female general surgeons are more often subjected to humiliating behaviors.	Agree	15 (15.2%)	55 (53.4%)*	<0.001
	Disagree	78 (78.8%)*	40 (38.8%)	
	Not sure	6 (6.1%)	8 (7.8%)	
I think that female general surgeons are more exposed to verbal/physical harassment.	Agree	17 (17.2%)	59 (57.3%)*	<0.001
	Disagree	73 (73.7%)*	33 (33.0%)	
	Not sure	9 (9.1%)	10 (9.7%)	

Table 4. Discirimination in academic career

Question	Respont	Men (n=99)	Women (n=103)	p-value
It is important for me to have a female surgeon in the institution where I will work.	Agree	55 (55.6%)	64 (62.1%)	0.217
	Disagree	26 (26.3%)	29 (28.2%)	
	Not sure	18 (18.2%)	10 (9.7%)	
I think it is important for female residents to have a female lecturer as a role model in the institution where they work.	Agree	58 (58.6%)	88 (85.4%)*	<0.001
	Disagree	34 (34.3%)*	9 (8.7%)	
	Not sure	7 (7.1%)	6 (5.8%)	
I think female lecturers are more successful in training students and residents.	Agree	19 (19.2%)	58 (56.3%)*	<0.001
	Disagree	68 (68.7%)*	23 (22.3%)	
	Not sure	12 (12.1%)	22 (21.4%)	
I think women are rejected more often when applying for a lecturer position.	Agree	22 (22.2%)	64 (62.1%)*	<0.001
	Disagree	66 (66.7%)*	23 (22.3%)	
	Not sure	11 (11.1%)	16 (15.5%)	
I think female surgeons can be more successful in the field of breast-endocrine.	Agree	30 (30.3%)	24 (23.3%)	0.384
	Disagree	58 (58.6%)	70 (68.0%)	
	Not sure	11 (11.1%)	9 (8.7%)	
I think that female surgeons are less self-developed in the field of perianal area diseases.	Agree	26 (26.3%)	29 (28.2%)	0.938
	Disagree	62 (62.6%)	62 (60.2%)	
	Not sure	11 (11.1%)	12 (11.7%)	

Statistical Analysis

In the evaluation of the survey questions, the normality of continuous variables was evaluated with the Shapiro-Wilk test. Since the data conformed to the normal distribution, independent means t-test was used for comparisons according to gender. In the analysis of categorical data, the chi-Square test and the Fisher's exact test were used if more than 20% of the expected values were less than 5. A Z-test (comparison of two ratios) was applied to assess statistical significance in tables larger than 2x2. Data analysis was performed in the TIBCO Statistica program.

RESULTS

Demographic Data

Table 1 presents the demographic characteristics of the study participants. A total of 202 people, 99 male and 103 female doctors, participated in the survey. The mean age of the participants was 37.65±11.55 years (range from 24 to 74). There were no significant differences between male and female surgeons regarding age, academic rank, years of experience, working institution, or age of first parenthood. The duration of experience in general surgery varied from less than 5 years

to over 20 years. Among participants, 48.5% were residents, 29.2% were specialists, 0.5% were lecturers, 2% were assistant professors, 8.4% were associate professors, and 11.4% were professors (Figure 1). The distribution of workplaces was as follows: 10.9% worked in public hospitals, 33.2% in training and research hospitals, 45.5% in university hospitals, and 7.9% in private clinics.

The marriage rate among female participants was 40.8%, and the rate of having children was 26.2%, whereas the marriage rate among male participants was 79.8%, and the rate of having children was 56.6% (Figure 2). The average age of first childbirth for female participants was 31.72±4.00 (25-46), while the average age of first parenthood for male participants was 29.80±3.80 (20-42) (p=0.037). 3% of the males and 3.9% of the female participants had never worked with a female doctor in a general surgery.

Social Prejudice

Table 2 shows the agreement of our participants with some social prejudices against female surgeons. Among the 99 male respondents, 40.4% agreed that surgery is more suitable for males, 46.5% disagreed, and 13.1% were unsure (Figure 3). In contrast, only 8.7% of the 103 female respondents agreed with this statement, while 89.3% disagreed and 1.9% were unsure (p<0.001). Regarding the belief that "women should not choose general surgery because they are physically weaker," 22.2% of men agreed compared to just 1.9% of women (p<0.001). Both male (66.7%) and female (65%) respondents commonly agreed that women do not prefer general surgery due to difficulties in balancing family responsibilities with the demands of a surgical career (p=0.890). Furthermore, 48.5% of men believed that general surgery is more suitable for men because of long working hours, whereas only 5.8% of women agreed (p<0.001). Regarding stress and psychological aspects, 58.6% of men and 36.9% of women felt that these factors affect women more (p=0.008). While 88.3% of women believed that the male-dominated environment negatively influences women's choice to pursue general surgery, only 52.5% of men agreed, with 40.4% disagreeing (p<0.001). Perceptions of prejudice towards female surgeons new to clinics differed significantly, with 54.5% of men disagreeing compared to 78.6% of women (p<0.001).

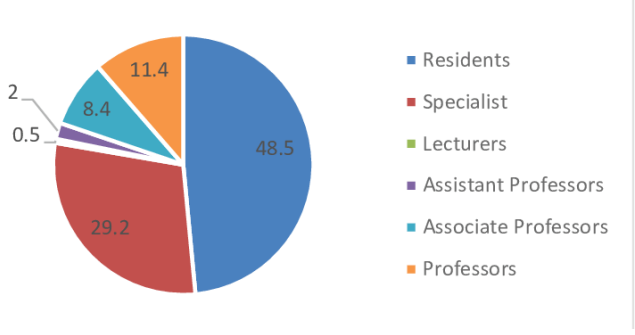

Figure 1. Academic titles of the participants.

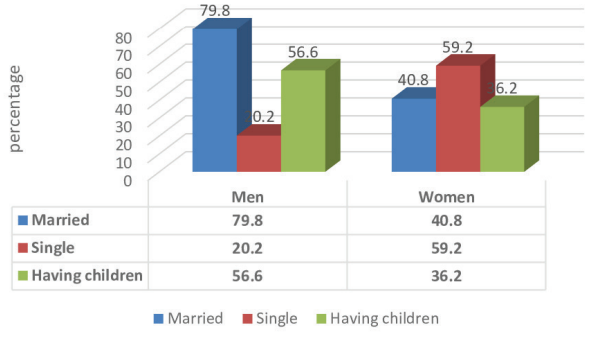

Figure 2. Percentage of marriage and having children among genders.

Gender Bias in Workplace

Table 3 shows a notable gender gap in recognizing disadvantages faced by female surgeons. While 40.4% of male participants agreed that there is positive discrimination towards female general surgeons, 85.4% of female participants disagreed (p<0.001). Additionally, 66% of the women stated that female surgeons are frequently criticized by their colleagues about their appearance, while 65.7% of men disagreed (p<0.001). Regarding case and responsibility distribution, 45.6% of women agreed that female surgeons receive fewer cases and responsibilities, whereas 76.8% of men disagreed. Furthermore, 53.4% of women felt female surgeons were subjected to humiliating behaviors, in contrast to 78.8% of men who disagreed (p<0.001). Similarly, 73.7% of men disagreed that female surgeons face verbal or physical harassment, while 57.3% of women believed they do (p<0.001). Opinions on maternity leave, separate rest rooms, and equal opportunities were more aligned than other issues, with no significant differences noted between genders. Specifically, 73.7% of men and 89.3% of women agreed that maternity leave

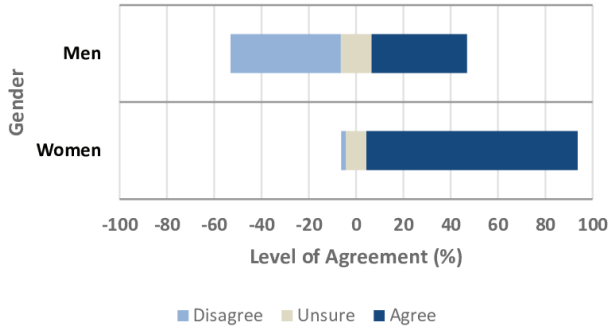

Figure 3. Rurvey respondents' answer to the question "I think surgery is more suitable fort he male gender".

is not unfair to colleagues (p=0.010). Regarding separate rest rooms, 59.6% of men and 52.4% of women supported having similar facilities for both genders (p=0.085). Additionally, 76.8% of men versus 61.2% of women agreed that opportunities are equally given to both genders (p=0.004). Both genders also agreed that patients trust male surgeons more, with 52.5% of men and 55.3% of women expressing this view (p=0.741).

Discirimination in Academic Career

The survey also investigated attitudes towards gender roles and perceptions in academic careers, highlighting varying perspectives between male and female respondents (Table 4). Regarding the importance of having a female surgeon in their institution, 55.6% of men and 62.1% of women agreed, with no statistically significant difference found (p=0.217). Additionally, 85.4% of female participants emphasized the importance of having a female faculty member as a role model.

There was a clear disparity in views on the success of female lecturers. While 56.3% of female respondents stated that female lecturers are more successful in training surgical residents and students, 68.7% of male respondents disagreed (p<0.001). Similarly, 62.1% of the female respondents also expressed that women are more frequently rejected for lecturer positions, while 66.7% of men disagreed (p<0.001). Opinions on the success of female surgeons within specialized fields, such as breast-endocrine and perianal area diseases, were more aligned, with no significant differences between genders.

DISCUSSION

There are several factors contributing to women's lesser inclination to pursue a career in surgery. Female medical students and residents describe numerous barriers when considering a career in surgery, including gender prejudices, the lack of female role models, and concerns about achieving work-life balance (6,7). These issues are directly related to gender-based expectations and instances of bias, which eventually affect women's professional choices. However, gender bias often manifests in subtle and indirect ways, making it challenging to address and rectify. Creating safe spaces for open conversations remains essential, even after recognizing gender prejudice. Women in this predominantly male field consciously avoid addressing gender-related matters in order to avoid being "marked" (8). Because of their fear of being remembered as victims of discrimination, they cannot raise their voices against discrimination so as not to be labeled as "sensitive" or "complaining".

Although the number of female doctors graduating from medical schools in Türkiye has increased by approximately 50% in recent years (9), general surgery has historically been a male-dominated medical specialty, as in other countries. Only 20.6% of surgical physicians in the U.S. are women, compared to 12% in the U.K. and 8.9% in South Korea (10). According to data from the Turkish Ministry of Health, as of January 1, 2024, 8.78% of general surgery specialists (410 out of 4.665) and 24% of general surgery residents (385 out of 1.604) are women (5).

This study takes the first step to explore gender discrimination in general surgery in Türkiye and focuses on the perception of gender bias by both genders throughout the careers of general surgeons. Our study shows that almost half of male surgeons think that surgery is more suitable for men and that women have more difficulty in general surgery because women are both physically weaker and more vulnerable to stress, but a strong majority of women disagree with that statement. This view may be related to gender stereotypes. In contrast to men, who are traditionally more independent, detached, and hierarchical, people perceive women as more sensitive and compassionate (11). Berg (12) explained that positive student evaluations and departmental acceptance reward traditionally feminine behavior but label stronger assertiveness as "pushy" or "bitchy". However, when male colleagues display these same assertive qualities, people view them as signs of high standards and academic rigor (12). According to Bernardi et al. (13), female surgeons revealed that the evaluation process might undervalue their contributions, attributing their success to chance rather than hard work and virtue.

Due to the male-dominated nature of general surgery, the majority of female participants (88.8%) report experiencing negative pressure from their social circles. Being in a male-dominated field alone presents some challenges for female surgeons (14). Bellini et al. (15) revealed that gendered language is a contentious issue in surgery and that the most common recommendation to deal with this issue is to speak out against inappropriate language. The same study shows that women feel restricted by the surgical environment embedded in masculine discourses and make efforts to adapt to it.

Male participants in our study for the most part did not believe that female general surgeons received fewer cases, while female participants disagreed with them on this point. Even after accounting for subspecialties and seniority, Chen et al. (16) found that female surgeons receive fewer complex cases than their male colleagues. Despite performing a lower volume of cases, female surgeons have similar postoperative outcomes or slightly better ones postoperative outcomes compared to male surgeons, according to Wallis et al. (17). Vasey and Mitchell (18) stated that one of the challenges women face in the operating room is that operating equipment such as laparoscopic staplers or colonoscopes are designed for large hands and come in only one size, which might lead to difficulties for female surgeons with smaller hands.

In our survey, more than half of the female respondents stated that female general surgeons are more exposed to humiliating behavior and verbal or physical harassment, while interestingly, the majority of male respondents disagreed. Other studies also support the finding that women are more likely to experience harassment. Schlick et al. (19) stated that common forms of harassment include crude, demeaning comments, unwanted sexual attention, offensive body language, and gender harassment. According to their study, the most common source of verbal harassment experienced by female residents was patients and patient relatives, while the most common source of sexual harassment was co-residents or fellows. Some studies reported that harassment is associated with severe burnout, depression, and suicidal thoughts among female surgeons (20,21). Our study showed that, despite the high prevalence of harassment, unfortunately male participants are not aware of this issue. The reason for the low visibility rate is the inadequacy of reporting due to fears of repercussions, beliefs that nothing positive will come from reporting, and discomfort in identifying as a target, phenomena mentioned in other studies (21-23). These studies suggested that the solution involves better institutional support, including formal condemnation of harassing behavior and the establishment of support groups.

In the questionnaire, 76.8% of male participants said that opportunities (training, congresses, presentations, etc.) given to individuals are gender-independent; 52.5% stated that patients trust male surgeons more; yet, 40% of male participants believed that women face positive discrimination.

This study's limitation lies in its inability to pinpoint specific areas where women face affirmative action advantages in their general surgery careers.

One of the biggest obstacles for women becoming general surgeons is the difficulty of balancing family life with a surgical career. The societal expectation that women should handle household chores doubles the workload for women in all fields of work. In our study, the marriage rate among female participants was 40.8%, and the childbearing rate was 26.2%, whereas the marriage rate among male participants was 79.8%, and the childbearing rate was 56.6%. According to Baptiste et al. (24), female surgeons are more likely to be responsible for household duties such as childcare, meal planning, and grocery shopping, which can impact their professional advancement and work-life balance. Female surgeons frequently have spouses who work full-time, which increases their family obligations and may impact their professional advancement. According to Bernardi et al. (13), male surgeons are more likely to request their spouses to make professional compromises in order to advance their own careers.

In this study, the average age of first childbirth for female participants was 31.72±4.00 (25-46), while the average age of first childbirth for male participants was 29.80±3.80 (20-42). In Türkiye, paternity leave is legally 10 working days, while maternity leave is 16 weeks. Additionally, the person giving birth has the right to request unpaid leave for childbirth, as long as they do not exceed the twenty-four-month period following the end date of maternity leave (25). Our study revealed an intriguing disparity regarding this issue. While a large majority of participants (73.7% of men and 89.3% of women) did not believe maternity leave for female general surgeons was unfair to colleagues, the average age of first childbirth differed significantly between sexes. Men typically have their first child during their residency, while women typically wait until after completing their residency. These findings are similar to those of another study on female otolaryngology surgeons in Türkiye. According to Eyigör et al. (26), 56.4% of female otolaryngology surgeons stated that they had their first child after their residency programs ended. In the same study, 64.9% of female surgeons had their first children after the age of 30. Baptiste et al. (24) showed that female surgeons tend to delay childbirth until completion of residency; thus, they have fewer children. The perception of pregnancy in surgical fields has a major impact on women's well-being. It was reported that female surgeons were negatively affected by male faculty members and male residents during pregnancy (27), that some female surgeons changed their fellowship preferences due to the difficulties of balancing surgery and childcare (28), and that pregnant surgical residents experienced high rates of obstetric complications and infertility (29,30).

In our study, 64% of the female participants stated that it was important for them to have a female surgeon in the institution where they worked, and 88% stated that it was important for female residents to have a female lecturer as a role model. Having a same-gender mentor creates a positive impact on female medical students and residents. These mentors have inspired them to pursue a career in surgery, encouraging them to do more research, which may even make it easier for them to rise to leadership positions later in their careers (31,32). Yorozuya et al. (33) conducted a survey among female members of the Japan Association of Women Surgeons, in which respondents stated that female mentors were easy to consult, aware of the difficulties women surgeons experience, and offered specific perspectives and role models who could provide guidance. Effective mentorship is critical for career advancement and for providing moral support to female surgeons. However, the underrepresentation of female surgeons in leadership positions restricts the availability of female role models and mentors (24,34,35). Zhuge et al. (7) suggests that the concept of the glass ceiling in surgery is a result of gender discrimination and a lack of mentorship. The glass ceiling represents barriers that prevent

women from advancing to higher positions in a hierarchy, despite the fact that more women are entering traditionally male-dominated fields.

Social media is becoming increasingly important for networking and mentorship for women who may not have access to female mentors at their workplace (36). Additionally, female surgeons are using the media to challenge traditional stereotypes. Since 2015, hundreds of thousands of people have tweeted the hashtag #ILookLikeASurgeon, highlighting the diversity among surgeons beyond the stereotype of an arrogant white male. Logghe et al. (37) noted that this movement emphasizes that surgeons come from diverse genders, backgrounds, and appearances, reflecting the diversity of humanity itself.

CONCLUSION

This study shows different views of gender prejudice among male and female surgeons in general surgery. Female respondents indicated experiencing bias and underrepresentation in academic disciplines, although male and female surgeons had differing perspectives on discrimination. Both genders agreed on the difficulty of work-life balance, with a similar percentage of individuals identifying family responsibilities as an obstacle. Even though there are now more female surgeons, the survey shows that male and female surgeons continue to view gender-related issues in the field differently.

Ethics

Ethics Committee Approval: The Mersin University Clinical Research Ethics Committee approved this study, dated February 21, 2024, and numbered 2024/193.

Informed Consent: Consent to participate in the study was implied by completing the survey.

Acknowledgments

The authors would like to thank Assistant Professor Assistant Professor Ayça Özdemir for the statistical analysis of the study. The authors would also like to thank all the participants who took part in the survey.

Footnotes

Author Contributions

Concept - S.T., H.B.; Design - S.T., T.Ç., H.B.; Supervision - H.B., S.T.; Fundings - H.B., C.Ö., E.R., S.T.; Data Collection or Processing - E.R., S.T., H.B.; Analysis or Interpretation - H.B., T.Ç., S.T.; Literature Search - H.B., S.T., C.Ö.; Critical Review - H.B., T.Ç., S.T., C.Ö., E.R.; Writing - H.B., S.T., E.R.

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

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

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ORIGINAL ARTICLE
Turk J Surg 2025;41(1):78-84

Diagnostic value of vascular endothelial growth factor (VEGF) levels in gastrointestinal cancers with ascites - A cross sectional study

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ABSTRACT

Objective: Malignant ascites is suggestive of peritoneal carcinomatosis. The distinction between malignant and non-malignant ascites in a patient with malignancy is important, as it alters the management and prognosis. Current diagnostic methods are imaging, cytology, and diagnostic laparoscopy, all of which have low sensitivities. The vascular endothelial growth factor (VEGF) is essential for tumour growth and, hence, ascitic VEGF levels can be a diagnostic method for malignant ascites.

Material and Methods: This cross-sectional study was conducted in patients with gastrointestinal malignancies and ascites. The calculated sample size was 68 patients, who were divided into those who were truly positive or negative for malignant ascites based on a composite gold standard, comprising cytology, contrast enhanced computed tomography, and laparoscopy. The ascitic VEGF levels in these patients were compared.

Results: A total of 84 patients were enrolled, of whom 60.71% were found to have malignant ascites. It was found that the greater the volume of ascites, the greater the statistical likelihood of finding truly malignant ascites. The ascitic VEGF levels had a non-normal distribution, with median values of 783.64 and 41.12 pg/mL for malignant and non-malignant ascites ($p<0.001$). Using a receiver operating characteristics curve, a cut-off of 83.68 pg/mL was obtained, with a sensitivity of 100% and a specificity of 93.94%.

Conclusion: This study demonstrates that ascitic VEGF levels are significantly elevated in patients with gastrointestinal malignancies and malignant ascites and hence can reliably be used for diagnosing malignant ascites. This study also shows that massive ascites and well-differentiated tumours have a higher rate of peritoneal carcinomatosis.

Keywords: VEGF, malignant ascites, peritoneal carcinomatosis, biomarkers, gastrointestinal malignancies

INTRODUCTION

Malignant ascites can be defined as malignant cells found in the ascitic fluid, which accounts for approximately 10% of all cases of ascites (1); it suggests peritoneal carcinomatosis. Such patients have a poor prognosis, with a mean survival time after diagnosis of 12-20 weeks (2). However, all patients with malignancies and ascites do not necessarily have malignant ascites as such patients usually have multiple comorbidities and hence have multiple causes for ascites such as hypoalbuminemia, anemia, liver and cardiac dysfunction among others. The distinction between a true malignant ascites and a non-malignant cause of ascites in a patient with malignancy is important to make as it alters the staging of the disease and hence changes the treatment.

Current methods of diagnosing malignant ascites include history and clinical examination, imaging modalities, aspiration cytology and diagnostic laparoscopy (3,4). Among the non-invasive testing methods, cytology has the best specificity, which can go up to 90-100% (5). However, due to its low sensitivity of around 50-60% (6,7), the rates of false-negative results are high, misleading the physician. Clinical symptoms may be atypical, unreliable, and subjective. Current biochemical tests such as albumin, total protein and tumour markers lack sufficient specificity (8). The specificity of computed tomographic (CT) scans for the diagnosis of peritoneal carcinomatosis ranges from 85% to 87%, but its sensitivity lies only around 42% to 68% (9). Therefore, there is a practical challenge of diagnosing malignant ascites with a reliable method.

Cite this article as: Kiruba Samuel EM, Sundaramurthi S, Hanumanthappa N, Nelamangalaramakrishnaiah VP. Diagnostic value of vascular endothelial growth factor (VEGF) levels in gastrointestinal cancers with ascites - A cross sectional study. *Turk J Surg.* 2025;41(1):78-84

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Received: 23.09.2024
Accepted: 04.02.2025
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2025.6592

Available at www.turkjsurg.com

Angiogenesis is vital for tumor growth, invasion, and metastasis. Tumor cells produce various angiogenic factors, one of which is the vascular endothelial growth factor (VEGF) (10-12). Review of the literature supports that angiogenesis promoted by VEGF is associated with fluid accumulation in human tumor effusions; malignant ascites is accompanied by high levels of VEGF in these fluids (13). While a few studies have examined VEGF as a biomarker, its diagnostic utility in differentiating malignant from non-malignant ascites in gastrointestinal malignancies remains underexplored (14-16). This study aims to evaluate VEGF levels in ascitic fluid, as a diagnostic tool and compare its utility against the existing methods. Notably, VEGF levels can be measured from the same sample that was collected for cytological assessment, eliminating the need for any additional invasive procedures.

MATERIAL and METHODS

This observational cross-sectional study was conducted in the department of surgery in a tertiary care hospital from March 2020 to December 2021, after obtaining approval from the Institute Ethics Committee (IEC). Written informed consent was obtained from all the patients before the commencement of the study. Patients were given full freedom to withdraw participation at any point. All patients more than 18 years of age, with proven gastrointestinal malignancy and associated ascites, were included. Patients with pre-testing interventions such as radiotherapy, chemotherapy, or surgery and patients with uncontrolled renal, hepatic, and cardiac dysfunction, as well as those with minimal ascites that could not be sampled for analysis, were excluded.

The aim of the study was to evaluate the role of ascitic VEGF levels in patients with gastrointestinal malignancies and concurrent ascites in diagnosing malignant ascites. The primary objective was to determine the sensitivity and specificity of detection of malignant ascites. The secondary objectives were to show the relationship between ascitic fluid VEGF levels and quantity of ascites, as well as between ascitic fluid VEGF levels and differentiation of the primary tumor, and to determine the sensitivity and specificity of malignant cytology and contrast enhanced computed tomography (CECT) in diagnosing malignant ascites.

Participants with proven gastrointestinal malignancy and associated ascites were divided into two outcome groups based on a composite gold standard comprising positive cytology for malignant cells, CT scan findings suggestive of peritoneal carcinomatosis, and diagnostic laparoscopy/laparotomy findings of peritoneal metastasis. Patients testing positive for any of these criteria were classified as having malignant ascites, while those testing negative across all criteria were categorized as non-malignant ascites. Positivity in malignant cytology was defined as the presence of malignant cells in the ascitic fluid. Positivity in a contrast CT scan was defined as the presence of findings suggestive of peritoneal metastasis, pelvic deposits, interbowel deposits, and/or omental deposits caking. Positivity in diagnostic laparoscopy/laparotomy was defined as a visible peritoneal metastasis, pelvic deposits, interbowel deposits, and/or omental deposits or caking, or through cytology of peritoneal washing or proven histopathology of intra-operative peritoneal biopsies.

Patients were selected by convenient sampling from the population that visited the surgery out-patient and emergency services who fit the inclusion criteria. The sample size was calculated to estimate the sensitivity of VEGF to differentiate malignant ascites from non-malignant causes of ascites in patients with gastrointestinal malignancies. Assuming an alpha error of 5% and an expected VEGF sensitivity 91.3%, based on a study done by Dong et al. (15), the minimum required number of diseased subjects was 34 with an absolute precision of 7%. The sample size was calculated using nMaster software version 2.0. Patients continued to be enrolled into the study until a minimum of 34 subjects were present in each outcome group. A total of 84 patients were included in this study.

Demographic and clinical data of the patients were collected. Ascitic fluid was aspirated under sterile conditions for malignant cytology and a part of this sample was taken for analyzing VEGF levels. This sample was immediately centrifuged at 3000 rpm for 15 minutes at 4 °C. Cell-free supernatant was collected, and these aliquots were stored at -40 °C before determination of VEGF levels. The diagnostic biopsies, and staging measures taken by the treating surgeon were also followed up. The kit used was from ELK technologies, an ELISA kit that measured human VEGF-A levels (ELK1129). The working principle of the test is a sandwich enzyme immunoassay. The kit was pre-coated with an antibody specific to VEGF to which standards or samples were added, after which avidin conjugated to horseradish peroxide was added. Those wells that contain VEGF will change in colour from yellow to blue, after which the concentration of VEGF will be determined by spectrophotometric methods.

Statistical Analysis

The median (interquartile range) of the ascitic VEGF levels of both groups was determined and compared using the Mann-Whitney U test to determine whether VEGF levels were elevated in malignant ascites specifically. The sensitivity and specificity of each parameter, i.e., CECT, malignant cytology and VEGF levels were also calculated and compared. All continuous variables, such as age, VEGF levels, etc., were summarized using mean [standard deviation (SD)] or median (interquartile range) depending on the normality of distribution. Categorical variables such as gender, site of tumour, grade, stage of tumour etc. were summarized using proportions (percentage). The mean VEGF

values were compared between the two study groups using Student's t-test and a receiver operating characteristic (ROC) curve was employed to determine appropriate cut-offs of VEGF to label malignant or non-malignant ascites. The sensitivity and specificity of the chosen cut-off was reported along with 95% confidence intervals. The sensitivity and specificity of malignant cytology and CECT for detecting malignant ascites were also calculated by comparing these variables to the composite gold standard and constructing a 2x2 table. All data analysis was done using STATA v.14.

RESULTS

A total of 84 patients were enrolled in the study period; 51 were found to have malignant ascites and 33 had ascites due to other causes, according to the composite gold standard.

Among the 84 participants, 48 (57.14%) were male and 36 (42.86%) were female, showing a slight male preponderance. The mean (± SD) age of the study population was found to be 53.72 (±13.13) years, with 60.71% of patients being less than 60 years. Most patients (62.65%, 52/84) were observed to not have any known medical comorbidities. Among the patients with medical comorbidities, the most common was type 2 diabetes mellitus in 17 patients (20.48%), followed by hypertension in 10 (12.05%) patients (Table 1).

In regard to the organ of origin, the common sites were colon, stomach, and pancreas in that order with 21 (25%), 16 (19.05%), and 12 (14.29%) patients, respectively (Table 2). When the tumour was characterized according to its histopathological types, it was seen that the most common type was adenocarcinoma, with 91.67% (77/84) of tumours falling in this category.

Table 1. Demographic details of the study population

	Truly positive for malignant ascites n (%), T=51	**Truly negative for malignant ascites n (%), T=33**	**Total, n (%) T=84**
Gender			
Male	28 (54.90%)	20 (60.61%)	48 (57.14%)
Female	23 (45.10%)	13 (39.39%)	36 (42.86%)
Age			
Less than 60 years	29 (56.86%)	22 (66.67%)	51 (60.71%)
60 years and above	22 (43.14%)	11 (33.33%)	33 (39.29%)
Co-morbidities			
Nil	32 (62.75%)	20 (60.61%)	52 (62.65%)
Diabetes mellitus	10 (19.61%)	7 (21.21%)	17 (20.48%)
Hypertension	7 (13.73%)	3 (9.09%)	10 (12.05%)
Hepatitis B	1 (1.96%)	1 (3.03%)	2 (2.41%)
Pulmonary tuberculosis	1 (1.96%)	0 (0.00%)	1 (1.2%)

Table 2. Organ of origin of the primary tumour in the study population

Organ of origin	**Truly positive for malignant ascites n (%), T=51**	**Truly negative for malignant ascites n (%), T=33**	**Total, n (%) T=84**
Esophagus	2	1	3 (3.57%)
Stomach	10	6	16 (19.05%)
Colon	9	12	21 (25.00%)
Rectum	3	2	5 (5.95%)
Pancreas	9	3	12 (14.29%)
Liver	2	1	3 (3.57%)
Gastro-esophageal junction carcinoma	4	1	5 (5.95%)
Ampullary carcinoma	2	2	4 (4.94%)
Hilar cholangiocarcinoma	2	1	3 (3.57%)
Distal cholangiocarcinoma	2	0	2 (2.38%)
Intra-hepatic cholangiocarcinoma	2	1	3 (3.57%)
Gall bladder	4	0	4 (4.94%)
Small bowel	0	3	3 (3.57%)

After characterization of their type, the tumours were divided on the basis of their differentiation into well, moderately, or poorly differentiated tumours, as shown in Table 3. Some tumours could not be adequately characterized as belonging to the above groups due to the limited tissue sample obtained by biopsy or fine needle aspiration. The most common group was found in the moderately differentiated tumours, with 26 (40%) patients. However, 19 patients could not be classified into these groups due to the above-mentioned reason.

In all subjects, the ascites was quantified and categorized into three groups radiologically: Minimal, moderate and massive, as shown in Table 4. All three groups had a comparable number of patients. A majority of patients who were negative for malignant ascites had minimal ascites (22/33, 66.67%). The percentage decreased as the quantity of ascites increased, with only one patient having massive ascites, yet this patient remained negative for malignant ascites. This is in contrast to the patients who tested positive for malignant ascites, where a majority of patients had massive ascites (26/51, 50.98%) and the frequency decreased in parallel with the ascites quantity. Six patients had minimal ascites, which was malignant in origin. When applying Fisher's exact test to determine the p-value, this difference in the ascites quantity between the two groups was found to be significant, with a p-value of <0.001.

Using the composite gold standard, out of a total of 84 patients, 51 (60.71%) were found to have malignant ascites while 33 (39.28%) were found to have ascites due to other causes. Each component was also analysed separately. When considering malignant cytology, 58.82% (30/51) of patients with true malignant ascites had positive cytology while a total of 54/84 (64.29%) were found to be negative for malignant cytology. On examining the CECT scans of these patients for signs of peritoneal carcinomatosis such as omental nodules and peritoneal deposits, a total of 32 patients out of the 51 had true malignant ascites (62.74%) were found to have signs suggestive of peritoneal carcinomatosis, while a total of 19 patients (37.26%) did not have such findings in their scans. If a patient tested positive in either of the categories above, they were not considered for diagnostic laparoscopy/laparotomy, with 38/84 (45.24%) patients fulfilling this criterion. Out of the remaining 46 subjects, 13 patients (28.26%) were found to have peritoneal disease intraoperatively while the remaining 33 (71.74%) did not have the same (Table 5). The sensitivity of malignant cytology and CECT was found to be 58.82% and 62.74%, respectively, while both methods were found to have 100% specificity.

The VEGF levels were found to have a non-normal distribution, and hence, the median and interquartile range were calculated for both the truly positive and negative groups, which were found to be 783.64 (655.94-875.64) pg/mL and 41.12 (35.33-46.12) pg/mL, respectively. These values were found to be significantly different between the two groups, with a p-value of <0.001, calculated using the Mann-Whitney U test. Using the values obtained, a ROC curve was plotted (Figure 1). It was seen that at a cut-off value of 83.68 pg/mL, the area under the curve was 0.9964 with a standard error of 0.0032, sensitivity of 100%, and a specificity of 93.94%.

DISCUSSION

In our study, out of 84 patients, 51 (60.71%) were positive for malignant ascites. This indicates that when patients with gastrointestinal cancers are found to have ascites, the possibility of peritoneal carcinomatosis must be seriously considered, which is consistent with the study conducted by Zhang et al. (6) where they found that 66.7% of patients with malignancy-related ascites had peritoneal carcinomatosis. When analysing

Table 3. Differentiation of the primary tumour in the study population

Differentiation of primary tumour	Truly positive for malignant ascites n (%), T=51	Truly negative for malignant ascites n (%), T=33	Total, n (%) T=84
Well-differentiated	14 (27.45%)	9 (27.27%)	23 (35.38%)
Moderately differentiated	13 (25.49%)	13 (39.39%)	26 (40%)
Poorly differentiated	4 (7.84%)	12 (36.36%)	16 (24.62%)
Not known	2 (3.92%)	17 (51.51%)	19 (22.62%)

Table 4. Quantification of ascites in the study population

Ascites quantification	Truly positive for malignant ascites n (%), T=51	Truly negative for malignant ascites n (%), T=33	Total, n (%) T=84	p-value (Fischer's exact)
Minimal	6 (21.43%)	22 (78.57%)	28 (33.33%)	<0.001
Moderate	19 (65.52%)	10 (34.48%)	29 (34.52%)	
Severe	26 (96.30%)	1 (3.70%)	27 (32.14%)	

the separate components, 35.71% of patients were found to have positive cytology, bringing the sensitivity up to 58.82% with a specificity of 100%. Regarding CECT findings for diagnosis of malignant ascites, we found a sensitivity of 62.74% and a specificity of 100%. This may be due to the subjectiveness of the reporting of CT images, which varies between radiologists, according to their level of expertise. Both of these results are in accordance with published literature (17,18). Diagnostic laparoscopy or laparotomy has a higher diagnostic accuracy (82.2% to 96.6%) (19) and a good sensitivity of up to 92% but involves a measure of operative risk and morbidity to patients who have a limited lifespan. Hence, this method is not generally used as a first-line investigation for patients with gastrointestinal malignancies and ascites but rather as a last resort in patients who have multiple causes of ascites (20). As has been demonstrated, no one method has an adequate sensitivity to use as a diagnostic gold standard, which is also non-invasive and simple to apply. Therefore, we chose to use a composite gold standard to improve the overall sensitivity of the tests as a benchmark against which we compared our test, namely ascitic VEGF levels.

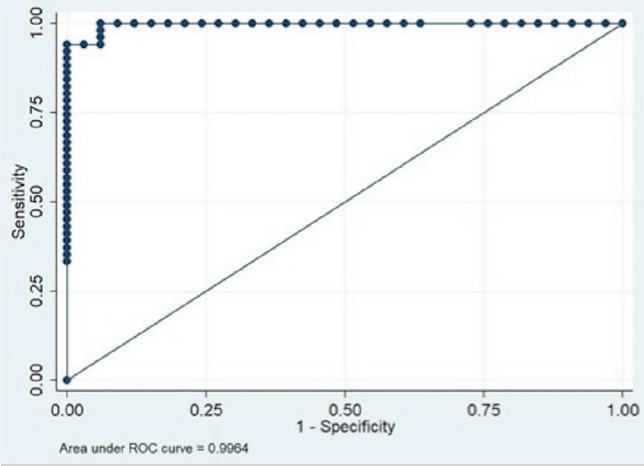

Figure 1. Receiver operating characteristic curve of ascitic VEGF levels in the study population.

VEGF: Vascular endothelial growth factor, ROC: Receiver operating characteristic

Table 5. Results of the composite gold standard in the study population

	n (%), T=84
Malignant cytology	
Positive	30 (35.71%)
Negative	54 (64.29%)
CECT report for malignant ascites	
Positive	32 (38.10%)
Negative	52 (61.90%)
Intra-operative findings suggestive of peritoneal metastasis	
Positive	13 (15.48%)
Negative	33 (39.29%)
Not applicable	38 (45.24%)
Composite gold standard results	
Truly positive	51 (60.71%)
Truly negative	33 (39.29%)

CECT: Contrast enhanced computed tomography

The VEGF is a dimeric, angiogenic glycoprotein with an average molecular mass of around 40,000 kD, which has been found to have stimulatory effects on neovascularization, capillary formation, as well as mitogenic and chemotactic effects on the endothelial cells of blood vessels. All of these actions lead to an increase in the permeability of these cells (21,22). It has been seen that an overexpression of VEGF in tumour cells allows the tumour to meet the high oxygen demands of its growth. As it increases permeability, it also forms an important part of the pathophysiology of malignant ascites, leading to speculation about its differential levels in malignant and non-malignant ascites (23). This is the issue we aimed to address in this study. When ascitic VEGF levels were compared between the patients with true malignant ascites and ascites due to other causes, the median and interquartile range values were found to be 783.64 (655.94-875.64) and 41.12 (35.33-46.12), respectively, and these differences were statistically significant. Using the values obtained, a ROC curve was plotted. It was seen that at a cut-off value of 83.68 pg/mL, the area under the curve was 0.9964 with a standard error of 0.0032, sensitivity of 100% and a specificity of 93.94%. There are just a handful of published studies that correlate ascitic fluid VEGF levels to the occurrence of malignant ascites, all of which compare ascitic VEGF levels between patients with benign and malignant pathologies, in contrast to our study, which exclusively includes patients with gastrointestinal malignancies (14,15,23-26).

We had classified tumours according to their level of differentiation. Out of 23 patients with well-differentiated tumours, 14 (60.87%) were found to be truly positive for malignant ascites, while an equal number of patients with moderately differentiated tumours were found to have both truly malignant and non-malignant ascites. Additionally, a majority of patients with poorly differentiated tumours [12/16 (75%)] were truly negative for malignant ascites. This association was found to be statistically significant. This analysis of the relationship between the differentiations of primary tumour and the presence of peritoneal carcinomatosis has not yet been conclusively proved in available literature, making this a novel finding in this study. However, three types of peritoneal spread of tumours have been elucidated based on tumour grade, namely: Random proximal distribution, seen in moderate and high-grade cancers; complete redistribution in well-differentiated tumours; and widespread cancer distribution that usually occurs in mucinous tumours. The first type is when cancer cells adhere

to the peritoneum near the local area; the second is where there is no adhesion with the peritoneum in the local area due to low metabolic activity of the tumour, leading to more widespread peritoneal dissemination rather than local disease. The last type -widespread cancer distribution- is in which the presence of adherence markers along mucus production leads to the widespread and aggressive dissemination of the tumour (19). This matches our results, with well-differentiated tumours showing a higher proportion of malignant ascites due to peritoneal carcinomatosis.

The ascites were quantified in all subject patients using radiological methods and divided into minimal, moderate, and massive. the patients were almost evenly distributed among the three groups. However, within these three groups, it was seen that a majority of patients (78.57%) with minimal ascites were found to be negative for malignant ascites while 96.3% of patients with massive ascites were found to have true malignant ascites. In other words, as the quantity of ascites increases, the higher the probability is that the patient has peritoneal carcinomatosis. This association was found to be statistically significant by Fischer's exact test. This relationship has not been studied in the literature previously and is therefore a novel finding of this study.

Peritoneal metastases from gastrointestinal cancers are often associated with malignant ascites due to VEGF-related angiogenesis and enhanced vascular permeability. The role of heated intraperitoneal chemotherapy (HIPEC), administered along with cytoreductive surgery, in patients with malignant ascites has been evaluated in many recent studies. HIPEC typically involves the circulation of heated chemotherapeutic agents at temperatures between 41-43 °C within the peritoneal cavity to enhance drug penetration, disrupt VEGF-mediated pathways, and improve local tumor control (27). The heat increases the cytotoxic effects of chemotherapy by improving drug absorption, impairing DNA repair in cancer cells, and reducing peritoneal tumor burden. Another advantage of HIPEC is that this technique reduces the systemic side effects of toxic chemotherapy as the drugs are instilled locally into the peritoneal cavity. HIPEC has shown benefits in select patients, especially with ovarian and appendiceal cancers, but its effectiveness in colorectal cancer remains debated, as seen in the PRODIGE 7 trial, and its role in pancreatic cancer is unclear (28,29).

Pressurized intraperitoneal aerosolized chemotherapy has emerged as a minimally invasive alternative to HIPEC, offering improved drug distribution and deeper tissue penetration, with potential synergy when combined with anti-VEGF therapies such as bevacizumab (30). Other therapeutic options in patients with malignant ascites include systemic chemotherapy, immunotherapy, peritoneo-venous shunting, and diuretics; but each has variable success and risks, necessitating further research to refine treatment protocols and personalize therapy based on tumor biology and patient response (31).

The strengths of our study were that we had a relatively large sample size with a total of 84 patients. They were also a heterogeneous group, with all patients having gastrointestinal malignancies, hence avoiding confounding factors and leading to more reliable results. We had a well-defined composite gold standard to compare ascitic VEGF levels, composed of three checkpoints to have dependable results.

Study Limitations

The limitations of our study were that we did not draw any correlation between the post-diagnosis survival time and VEGF levels. Another area that we did not study was the correlation between serum and ascitic VEGF levels, as well as the effect of the interventions, such as hyper-thermic intraperitoneal chemotherapy, including chemotherapy on the ascitic VEGF levels. An area in which we would like to conduct further research is the potential therapeutic value of using anti-VEGF agents in the palliation of malignant ascites.

CONCLUSION

In this study, we demonstrated that ascitic VEGF levels are significantly elevated in patients with gastrointestinal malignancies and malignant ascites. With a sensitivity of 100% and specificity of 93.94%, ascitic VEGF proved to be a highly reliable biomarker for diagnosing malignant ascites. These findings suggest that VEGF can enhance early diagnosis and potentially open avenues for targeted therapeutic interventions in managing malignant ascites.

Ethics

Ethics Committee Approval: This observational cross-sectional study was conducted in the department of surgery in a tertiary care hospital from March 2020 to December 2021, after obtaining approval from the Institute Ethics Committee (IEC).

Informed Consent: Written informed consent was obtained from all the patients before the commencement of the study.

Footnotes

Author Contributions

Concept - S.S.; Design - V.P.N.; Supervision - V.P.N.; Materials - N.H.; Data Collection or Processing - E.M.K.S.; Analysis or Interpretation - S.S.; Literature Search - E.M.K.S.; Critical Review - V.P.N.; Writing - E.M.K.S.

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

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

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ORIGINAL ARTICLE
Turk J Surg 2025;41(1):85-91

Trastuzumab significantly improves survival in resectable HER-2 positive gastric cancer: A retrospective study

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ABSTRACT

Objective: Gastric cancer (GC), with a five-year survival rate of approximately 20%, frequently displays aggressive behavior when HER-2 is overexpressed. While trastuzumab, a monoclonal antibody against human epidermal growth factor receptor-2 (HER-2), has improved outcomes in advanced GC, its effect in resectable disease is less studied.

Material and Methods: This retrospective study included patients who underwent total gastrectomy with D2 lymph node dissection between 2016 and 2021. Among 180 patients, HER-2 status was determined for 97 cases. Of these, 20 HER-2 positive patients received trastuzumab-containing therapies. A control group of 40 HER-2 negative patients was randomly selected. Overall survival (OS) was compared between groups. Univariate and multivariate analyses were used to identify prognostic factors.

Results: Sixty patients with a median follow-up of 29.5 months were analyzed. HER-2 positivity was associated with significantly improved OS (p=0.038). Univariate analyses revealed that HER-2 positivity (p=0.047), younger age (p=0.001), advanced tumor stage (p<0.001), and larger tumor size (p=0.010) were significantly related to OS. In the multivariate model, advanced tumor stage [hazard ratio (HR)=3.634, p=0.001] and younger age (HR=0.213, p<0.001) remained independent predictors of worse survival, while HER-2 positivity and tumor size lost their significance. Tumor subtype and location did not significantly influence OS.

Conclusion: The findings suggest that trastuzumab-containing treatment strategies can markedly improve survival in resectable HER-2 positive GC. Routine assessment of HER-2 status and integration of targeted therapies may enhance patient outcomes. In addition, advanced stage and younger age emerged as key prognostic factors.

Keywords: Trastuzumab, resectable gastric cancer, HER-2, survival, prognostic factors

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer-related deaths worldwide, with a 5-year survival rate of 20% (1,2). Over the years, advancements have been made in the treatment of GC; however, surgery remains the key component of curative treatment.

Overall survival (OS) in GC is influenced by factors such as age, stage of the disease, and immunohistochemical (IHC) subtypes. One of these IHC subtypes involves the c-ErbB-2 protein, also known as human epidermal growth factor receptor-2 (HER-2), which is a 185 kDa transmembrane tyrosine kinase protein (3). Activation of HER-2 promotes cell proliferation, adhesion, and migration (4). Excessive proliferation of cells results in uncontrollable tissue growth, and enhances aggressiveness of the tumor. Overexpression of HER-2 has been linked to poorer outcomes in many cancers, most notably in breast and GC (5). Trastuzumab, a recombinant humanized monoclonal antibody targeting HER-2, has been shown to significantly improve OS in HER-2 positive GC (6).

Tumor stage is the most crucial prognostic factor in GC, with a 5-year survival rate exceeding 90% for patients diagnosed at an early stage (7). Tumor stage not only affects outcomes but also influences treatment strategies. Tumor size, lymphovascular invasion and nodal status are other important ffactors, but all of

Cite this article as: Erdem O, Canbak T, Bacaksız ME, Aktaş S, Tekeşin K, Başak F. Trastuzumab significantly improves survival in resectable HER-2 positive gastric cancer: A retrospective study. *Turk J Surg.* 2025;41(1):85-91

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Received: 18.12.2024
Accepted: 10.02.2025
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2025.6687

Available at www.turkjsurg.com

these factors also contribute to overall staging (8). Tumors ≥4 cm in largest-diameter have worse outcomes (3).

According to the latest European Society for Medical Oncology (ESMO) guidelines, trastuzumab is recommended in combination with chemotherapy for HER-2 positive metastatic GC but is not yet a standard of care for non-metastatic resectable cases. However, recent studies published suggest a potential benefit of trastuzumab in the perioperative setting for HER-2 positive GC, emphasizing the need for further investigation into its role in non-metastatic disease (9,10).

Current guidelines do not endorse the use of immune checkpoint inhibitors in the perioperative treatment of locally advanced resectable GC. Our rationale for incorporating trastuzumab into our treatment strategy was based on emerging evidence and biological plausibility, as HER-2 overexpression is associated with aggressive tumor behavior.

In this study, we aimed to investigate the effect of trastuzumab on OS of the HER-2 positive resectable GC. As secondary objectives, we also investigated the prognostic significance of age, tumor size, tumor location, tumor subtype, and stage of the disease.

MATERIAL and METHODS

Ethical Approval and Study Design

• Ethical approval for this study was granted by our Institute's Local Ethics Committee of University of Health Sciences Türkiye, Ümraniye Training and Research Hospital on January 26, 2023 (approval no: B.10.1.TKH.4.34.H.GP.0.01/23).

• This is a retrospective, propensity-score matched cohort study analyzing patients who underwent total gastrectomy with D2 lymph node dissection (TG-D2) between 2016 and 2021.

• Propensity-score matching (PSM) was performed based on age, sex, tumor stage, and tumor size to balance baseline characteristics between HER-2 positive and HER-2 negative groups.

• Demographical, histopathological, follow-up, and adjuvant chemotherapy data were extracted from hospital records.

Patient Selection

● Patients included in this study:

• Patients who underwent open TG-D2 and had confirmed HER-2 status through IHC and fluorescence *in situ* hybridization (FISH).

• Those who had HER-2 testing on endoscopic biopsy and had a positive result were included in the study, regardless of whether the surgical specimen was tested for HER-2.

● Exclusion criteria:

• Patients with unknown HER-2 status.

• Patients with a negative HER-2 assessment on endoscopic biopsy and no HER-2 testing on the surgical specimen.

• Patients who underwent prior gastric resections, subtotal gastrectomy, or had inadequate lymphatic dissection.

• Patients with unresectable tumors.

Surgical Technique

• All patients underwent open total gastrectomy with D2 lymph node dissection.

• Lymph node dissection was performed according to established guidelines (11,12):

• Perigastric lymph node stations (1-6) and distant lymph node stations (7-11) were dissected.

• Although most tumors were located in the antrum, total gastrectomy was preferred due to institutional surgical strategy.

HER-2 Status Determination

Tumor cells were evaluated for their immunoreactivity patterns and scored according to the criteria recommended by Hofmann et al. (13).

• HER-2 status was determined by IHC (HercepTest, Dako, Denmark).

• Tumors with IHC scores of 2+ underwent confirmatory FISH testing (Dako, Denmark).

• HER-2 positivity was defined as IHC 3+ or IHC 2+ with FISH positivity.

• HER-2 negative patients were matched using PSM, eliminating the need for random selection.

Treatment Protocols

• Neoadjuvant chemotherapy was not routinely administered due to institutional practice during the study period.

• All HER-2 positive patients received trastuzumab in combination with adjuvant chemotherapy.

• Adjuvant chemotherapy regimens included:

• CAPOX (capecitabine + oxaliplatin)

• FOLFOX (5-fluorouracil + oxaliplatin + leucovorin)

• HER-2 positive patients received CAPOX or FOLFOX + trastuzumab.

• Docetaxel-based perioperative FLOT (fluorouracil + leucovorin + oxaliplatin + docetaxel) was not routinely used due to institutional treatment protocols during the study period.

Follow-up

• Patients were followed until death or the study cut-off date (June 1, 2023).

• Follow-up intervals:

• Every 3 months for the first 2 years.

• Every 6 months for the next 2 years.

• Annually thereafter.

• Follow-up imaging included CT or PET-CT scans.

• Disease-free survival was not analyzed.

Outcome Measures

• Primary outcome: OS, defined as time from surgery to death.

• Secondary outcomes:

• Association of HER-2 status with clinicopathologic variables.

• Prognostic factors affecting OS.

Statistical Analysis

SPSS version 26 (Windows) was used for statistical analysis. PSM was performed using a 1:1 ratio, balancing groups for age, sex, tumor stage, and tumor size. Comparisons were made using the chi-square test for categorical data, Student's t-test for parametric data, and the Mann-Whitney U test for non-parametric data. Survival analysis was performed using the Kaplan-Meier method with the log-rank test. A Cox proportional hazards regression model identified independent prognostic factors associated with OS. P-values <0.05 were considered statistically significant.

RESULTS

A total of 180 patients underwent surgery for resectable GC in our clinic. However, only 97 patients were evaluated for HER-2 status immunohistochemically, and the remaining 83 patients were excluded due to the absence of HER-2 testing. Among the 97 tested patients, 20 (20.6%) were HER-2 positive (IHC 2+ or 3+), with 12 patients (12.3%) scoring 2+ and 8 patients (8.3%) scoring 3+. To ensure comparability between groups, 40 HER-2 negative patients were selected using PSM, resulting in a final study cohort of 60 patients (Figure 1).

Of the 60 patients included in the study, 36 (60%) were male, and 24 (40%) were female, with an age range of 31 to 86 years (median: 63 years). The median follow-up duration was 29.5 months, and no patients were lost to follow-up. Demographic and histopathological characteristics were compared between HER-2 positive and HER-2 negative groups. There were no statistically significant differences in age (p=0.642), gender (p=0.721), tumor location (p=0.543), tumor subtype (p=0.911), or TNM tumor stage (p=0.367), as detailed in Table 1.

HER-2 positivity was associated with a significantly better OS (p=0.038, log-rank test). The mean OS was 55.52±6.35 months [95% confidence interval (CI): 43.07-68.98] in the HER-2 positive group and 34.98±4.48 months (95% CI: 26.19-43.77) in the HER-2 negative group. Median survival could not be computed for the HER-2 positive group since more than 50% of the patients remained alive at the end of the follow-up period, whereas it was 28.0 months in the HER-2 negative group. The mean survival for the entire cohort was 41.72±4.05 months (95% CI: 33.77-49.66). The Kaplan-Meier survival curve (Figure 2) illustrates the survival difference between the groups.

Univariate analysis identified HER-2 status (p=0.047), age (p=0.001), tumor stage (p<0.001), and tumor size (p=0.01) as factors significantly associated with OS. Tumor subtype (p=0.911) and tumor localization (p=0.321) were not significant prognostic factors. Statistically significant variables from the univariate analysis were included in the multivariate model.

In multivariate analysis, tumor stage was the most significant predictor of OS, with higher tumor stages correlating with over a threefold increased risk of death [hazard ratio (HR)=3.634, 95% CI: 1.735-7.613, p=0.001]. Kaplan-Meier analysis by stage, confirmed these findings, demonstrating that while stage 1 patients had no mortality throughout the follow-up period, stage 4 patients exhibited a rapid decline in survival (Figure 3).

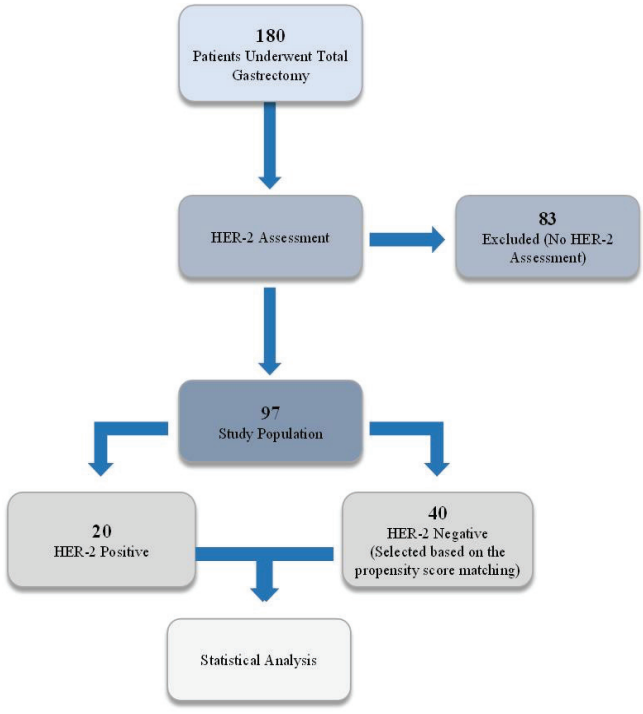

Figure 1. Study flowchart.
HER-2: Human epidermal growth factor receptor-2

Younger age emerged as a protective factor for OS (HR=0.213, 95% CI: 0.092-0.493, p=0.0001). Tumor size >4 cm was associated with a shorter OS (20.7 months vs. 39.6 months in tumors ≤4 cm), but this did not reach statistical significance in multivariate analysis (HR=2.195, 95% CI: 0.785-6.135, p=0.134). Tumor type and tumor localization were excluded from multivariate analysis due to their lack of significance in univariate testing. Detailed information on prognostic factors is provided in Table 2.

Table 1. Demographic and tumor specific data

	HER-2 positive	HER-2 negative	p (signicance)
Age			
<65 years	10 (50%)	22 (55%)	0.787
≥65 years	10 (50%)	18 (45%)	
Gender			
Female	7 (35%)	17 (42%)	0.576
Male	13 (65%)	23 (58%)	
Tumor size			
<4 cm	13 (65%)	13 (32%)	0.017*
≥4 cm	7 (35%)	27 (68%)	
Tumor location			
Cardia	4 (20%)	8 (20%)	0.889
Corpus	3 (15%)	8 (20%)	
Antrum	13 (65%)	24 (60%)	
Tumor type			
Intestinal	17 (85%)	29 (72%)	0.364
Diffuse	2 (10%)	10 (25%)	
Mixt	1 (5%)	1 (0.025)	
TNM stage			
Stage I	6 (30%)	6 (15%)	0.593
Stage II	4 (20%)	10 (25%)	
Stage III	9 (45%)	22 (55%)	
Stage IV	1 (5%)	2 (5%)	

HER-2: Human epidermal growth factor receptor-2.

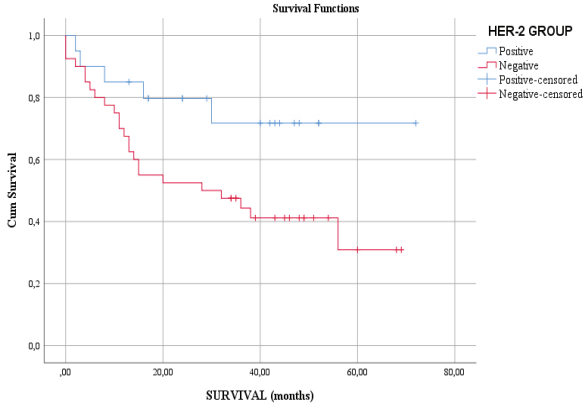

Figure 2. Kaplan-Meier survival curves showing the impact of HER-2 status on OS.

HER-2: Human epidermal growth factor receptor-2, OS: Overall survival

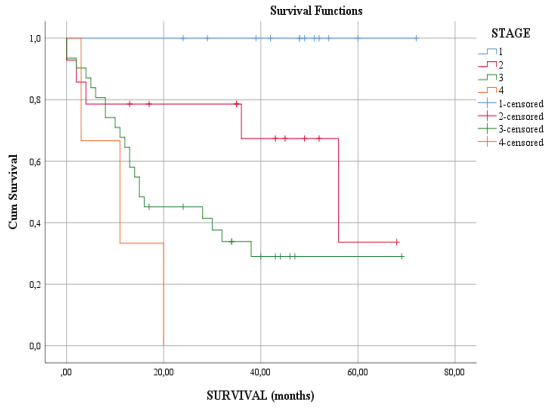

Figure 3. Kaplan-Meier survival curves showing the impact of stage on OS.

OS: Overall survival

Table 2. Associated risk for prognostic factors

	Univariate			Multivariate		
	HR	**CI 95%**	**p**	**HR**	**CI 95%**	**p**
HER-2 status (negative vs. positive)	2.656	1.012-6.973	0.047	1.837	0.681-4.958	0.230
Age (<65 vs. ≥65 years)	0.267	0.125-0.569	**0.001**	0.213	0.092-0.493	**0.000**
Stage	3.346	1.885-5.938	**0.000**	3.634	1.735-7.613	**0.001**
Tumor type	1.040	0.520-2.081	0.911			
Tumor localization	1.280	0.786-2.085	0.321			
Tumor size	5.201	1.963-13.777	**0.01**	2.195	0.785-6.135	0.134

HR: Hazard ratio, CI: Confidence interval, HER-2: Human epidermal growth factor receptor-2. Cox Regression Analysis, statistical significance at p<0.05.

DISCUSSION

HER-2 overexpression in GC can be observed in up to 30% of cases (4,14-16). In our study, 20 of 97 patients (20%) demonstrated HER-2 overexpression. Since HER-2 was first introduced in the literature, the role of HER-2 overexpression on GC prognosis has been studied widely. Previous studies have reported a fivefold increase in mortality risk among HER-2 positive GC patients (5,17,18). Before the advent of trastuzumab, HER-2 overexpression in resectable GC was a negative prognostic factor, decreasing 5-year OS from 63% to 21% (19). Following the ToGA trial and introduction of trastuzumab for HER-2 positive GC, trastuzumab became an indispensable part of standard treatment leading to improvement in patient outcomes (20).

In our cohort, all HER-2 positive patients were treated with trastuzumab containing regimens, thus we cannot compare the effect of trastuzumab directly. Although we could not directly isolate the effect of trastuzumab, the HER-2, positive group exhibited remarkably better OS than the HER-2, negative group. Considering that the OS of the HER-2 positive patients was significantly lower in former studies, the substantial improvement observed in our study (mean OS=55.5±6.4 vs. 35.0±4.5 months) strongly suggests that the addition of trastuzumab has a profound impact on survival. The 2021 Japanese Gastric Cancer Association Treatment Guidelines recommend trastuzumab-containing regimens to patients with IHC 3+ or IHC 2+/FISH-positive tumors (21). Similarly, 2024 National Comprehensive Cancer Network (NCCN) GC guidelines suggest that trastuzumab should be added to first-line chemotherapy for advanced HER-2 overexpression-positive adenocarcinoma. However, it is important to note that the current ESMO and NCCN guidelines primarily recommend trastuzumab for metastatic GC, with limited evidence supporting its routine use in non-metastatic resectable GC. While our study suggests a potential benefit of trastuzumab in this setting, further prospective studies are needed to validate these findings (22,23). Despite these recommendations for advanced disease, the role of trastuzumab in perioperative settings remains unclear, and randomized controlled trials are warranted to clarify its effectiveness in resectable GC.

This study also aimed to assess the prognostic value of TNM stage, patient age, tumor size, tumor location, and subtype. Considerable debate exists regarding the prognostic significance of patient age at diagnosis and the appropriate age cut-off for defining subgroups. Although some studies reported that age does not affect prognosis (24,25), most data contradict these findings (26,27). In a recent study, patients' age greater than 80 was found to be associated with worse disease-free survival (28). However, some reports indicate worse OS in younger patients, potentially due to more aggressive tumor biology (29,30). Lai et al. (31) found that younger patients had more undifferentiated tumors compared to older patients, yet, they showed better OS. In our study, we found that younger patients had significantly better survival. This could be attributed to factors such as the presence of comorbidities, which may impact treatment tolerance and overall health status, as well as a naturally lower life expectancy in this age group. Future studies should explore how comorbidities, treatment tolerance, and competing risks impact OS in older patients to guide personalized treatment approaches.

The prognostic value of TNM stage is well established (32,33). Consistent with literature, we observed a strong negative correlation between increasing TNM stage and OS, with TNM stage emerging as the most important prognostic factor in our cohort.

Tumor size has been included in staging systems for several tumors. Although it does not directly alter TNM stage in GC, larger tumors generally exhibit more invasive behavior, which correlates with worse OS. Debate on the cut-off point for tumor size is ongoing (34). Giuliani et al. (35) divided the patients into three groups according to the largest diameter of the tumor, <25 mm, 25 mm -5 cm, and >5 cm, and reported significantly better OS for patients with smaller tumors. Adachi et al. (36) grouped patients as <4 cm, 4 cm -10 cm, and >10 cm, and reported similar results, where patients with tumors <4 cm showed 92%

OS in ten years. Another study set the cut-off at 6 cm and also reported similar results to prior findings (34). Lastly, in a recent study, Chiu et al. (37) found that patients with early recurrence following surgery had larger tumors. We chose 4 cm as the cut-off and found tumor size to be a significant factor in univariate analysis, though it did not retain significance in the multivariate model.

A large meta-analysis by Petrelli et al. (38) reported 128,000 cases of GC and found a 25% increased risk of disease-related mortality in patients with proximal gastric tumors. Another study showed proximal cancer is not a prognostic factor (39). Yilmaz et al. (40) recently reported that tumor location serves as an independent risk factor for OS. In our study, we could not demonstrate a risk associated with tumor location.

In conclusion, our results, similar to former studies, show that trastuzumab substantially improves patient survival in HER-2 positive GC. Assessing HER-2 status and other molecular factors in tumor tissue is essential for better understanding tumor biology and tailoring patient-specific treatment. However, given the current guidelines and the limited evidence supporting trastuzumab use in resectable disease, its routine application in this setting should be approached cautiously. Prospective trials are needed to establish its role in non-metastatic GC. For the secondary results, TNM stage, younger age, and larger tumors were found to be significant negative prognostic risk factors.

Study Limitations

Our study has several limitations. First, the retrospective, single-center design may limit the generalizability of our results. The small sample size necessitated random selection of HER-2 negative patients as controls, introducing potential bias and affecting the robustness of some statistical findings. Additionally, not all patients were assessed for HER-2 positivity, further limiting the representativeness of our sample.

CONCLUSION

Finally, we did not account for patient performance status or comorbidities, factors that could influence OS and diminish the credibility of our conclusions. Furthermore, the absence of a control group treated without trastuzumab prevents a definitive conclusion regarding its benefit in resectable GC. Future prospective studies are required to confirm these findings and determine optimal patient selection criteria.

Ethics

Ethics Committee Approval: Ethical approval for this study was granted by our Institute's Local Ethics Committee of University of Health Sciences Türkiye, Ümraniye Training and Research Hospital on January 26, 2023 (approval no: B.10.1.TKH.4.34.H.GP.0.01/23).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

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

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

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

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ORIGINAL ARTICLE
Turk J Surg 2025;41(1):92-97

The identification and ligation of the parotid duct during parotidectomy

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ABSTRACT

Objective: The complication rates after parotidectomy were reported to be 13-29% and many techniques were implemented to decrease these post-parotidectomy complications.

Material and Methods: Between August 2016 and June 2022, one hundred and twenty-five patients with parotid tumors had parotidectomy and ligation of the main parotid duct in the Department of Surgical Oncology, Oncology Center, Mansoura University with the observation of its effect on the postoperative outcomes.

Results: Superficial parotidectomy was performed in 87 (69.6%) patients, total parotidectomy in 31 (24.8%) patients, and quadrantectomy in 7 (5.6%) patients. The operative time was 130.76±51.5 min, and the blood loss was 81.32±45.02 mL. A suction drain was placed in 106 patients and a non-suction drain was used in 19 patients. Postoperative complications included facial nerve morbidity in 12% of the patients, bleeding in 1 patient, seroma in 5 patients, edema in 1 patient, wound gap in 1 patient, wound infection in 1 patient, and keloid in 1 patient.

Conclusion: The identification and ligation of the main parotid duct during parotidectomy has favorable impacts on the incidence of post-parotidectomy complications such as salivary fistula, seroma, sialocele, and wound infections.

Keywords: Parotid tumors, parotidectomy, main parotid duct

INTRODUCTION

The parotid gland is the largest salivary gland in the human body, and it secretes about 50% of all saliva (1). The incidence of parotid gland tumors is 3% of all head and neck tumors, and it is benign in about 80% cases. The common location of parotid gland tumors is in the superficial lobe, and presents as retromandibular swelling in the front and below the external auditory meatus (2). The complication rates after parotidectomy for parotid tumors were reported to be 13-29% (3). Short-term post-operative complications such as pain, skin problems, numbness, mouth dryness, and scar problems are frequently studied and reported. This is because benign parotid tumors are the most common type, and patients were followed up for a short postoperative duration. Limited data are available about the late and long-term complications after parotidectomy (4). Many techniques such as superficial musculoaponeurotic system flap, sternomastoid muscle flap, temporoparietal fascia flap, nerve, and soft tissue transfer were employed to decrease the post-parotidectomy complications (5,6).

Anatomically, the parotid duct passes superficial to the masseter anteriorly and below the zygomatic arch by about 1 cm. It pierces the buccinator medially at the anterior border of the masseter to enter the oral cavity opposite the second upper molar (7). Most of the parotid tumors occur in the superficial lobe in 80% of the cases. It provides about 85-89% of the parotid salivary secretions. Hence, the ligation of the main parotid duct during superficial parotidectomy decreases the risk of postoperative salivary leak and its subsequent complications (8).

MATERIAL and METHODS

Study Design

Between August 2016 and June 2022, we included 125 patients in the Department of Surgical Oncology, Oncology Center, Mansoura University with parotid tumors

Cite this article as: Abouzid A, Shetiwy M, Hamdy M, Ezzat M, Elghaffar MA. The identification and ligation of the parotid duct during parotidectomy. *Turk J Surg.* 2025;41(1):92-97

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Received: 22.01.2024
Accepted: 29.01.2025
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2025.6339

Available at www.turkjsurg.com

who underwent parotidectomy and ligation of the main duct with the observation of the postoperative outcomes. Patients excluded from this study were those with metastatic or locally advanced parotid cancer that needs reconstruction after resection, recurrent parotid tumors, or those unfit for general anesthesia. The procedure was explained to all patients, and they signed a written informed consent before surgery. The patients had preoperative neck ultrasound (US) and computed tomography for tumor size assessment and its relation to the deep parotid lobe. Fine-needle aspiration cytology was done for pathological confirmation.

The Institutional Review Board approval of the Faculty of Medicine, Mansoura University code (R.22.03.1663) was obtained.

Surgery

All patients underwent parotidectomy under general anesthesia. A modified Blair's incision was done in the preauricular skin, and the subcutaneous tissue and superficial fascia were dissected and retracted medially to expose the whole parotid gland to the anterior border of the masseter muscle. Then it was separated from the external cartilaginous auditory canal. The small branch of the great auricular nerve that enters the parotid gland was identified and divided. The external jugular vein was ligated and divided with a 2-0 silk suture. The facial nerve trunk was identified using the tragal pointer and the tips of the mastoid processes. The dissection of the facial nerve inside the parotid gland resulted in the identification of its main branches. The superficial parotid lobe was elevated and dissected free from the facial nerve branches until the tumor was removed completely. The main parotid duct was dissected cautiously from the surrounding tissues (Figure 1) because the transverse facial artery and the buccal branch of the facial nerve can be damaged. The main duct was identified by insertion of a Nylaton catheter sized 6-8 fr (Figure 2) or a small syringe cannula (Figure 3) and then it was ligated with a 2-0 Vicryl suture. The deep lobe was resected in cases of deep lobe tumors, or superficial lobe tumors suspicious of malignancy. Hemostasis was achieved and facial nerve branches were identified and ensured to be intact. A drain was placed, and the operative bed was closed.

Data Collection and Follow-up

Patient demographics and surgical data were collected and analyzed. Early complications such as facial nerve morbidities, bleeding, wound infection, seroma, and parotid fistula were reported in addition to late complications such as tumor recurrence.

Statistical Analysis

Statistical Package for Scientific Studies (SPSS) v.26 for macOS v11.3 was used for data analysis. Qualitative data were described using numbers and percentages. Quantitative data were described, after testing normality using the Kolmogorov-Smirnov test, using medians for non-parametric data and means and standard deviation for parametric data.

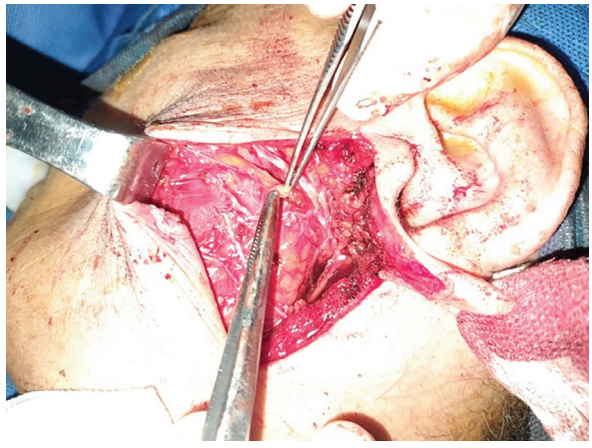

Figure 1. Dissection of the parotid duct from the surrounding tissue.

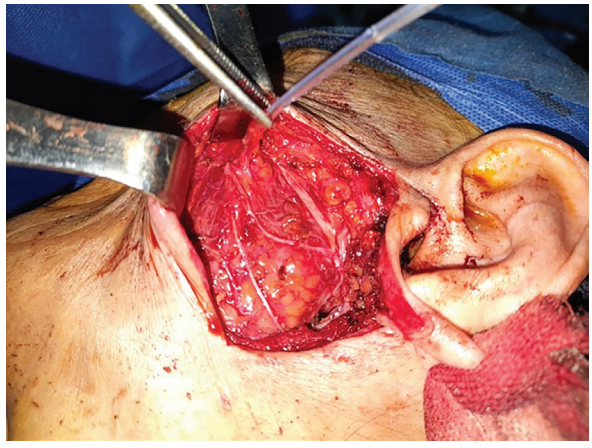

Figure 2. Insertion of a Nylaton catheter inside the parotid duct.

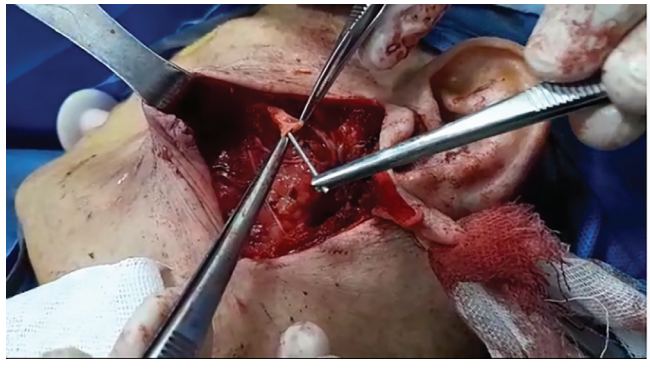

Figure 3. Insertion of a small syringe cannula inside the parotid duct.

RESULTS

Patients' Demographics

The patients had a mean age of 48.17 years. Sixty-four patients were males, and 61 patients were females. Most of the patients (74.4%) had an American Society of Anaesthesiologists score of I; 59 patients had right parotid tumors and 66 patients had left parotid tumors. Pleomorphic adenoma was the most common preoperative pathology in 74 (59.2%) patients and Warthin's tumor was the second most common in 33 (26.4%) patients. The mean preoperative tumor size was 3.16±1.12 cm (Table 1).

Table 1. Baseline characteristics of the patients

	Patients, n=125 (%)
Age, years (mean ± SD)	48.17±14.31
Gender	
-Male	64 (51.2%)
-Female	61 (48.8%)
BMI, kg/m² (mean ± SD)	32.64±5.24
Comorbidities	
-None	91 (72.8%)
-Diabetes	6 (4.8%)
-Hypertension	11 (8.8%)
-Hepatic	3 (2.4%)
-Bronchial asthma	3 (2.4%)
-Cardiac	2 (1.6%)
-Combined	9 (7.2%)
ASA score	
-I	93 (74.4%)
-II	28 (22.4%)
-III	4 (3.2%)
Side	
-Right	59 (47.2%)
-Left	66 (52.8%)
Preoperative tumor size, cm (mean ± SD)	3.16±1.12
Preoperative pathology	
-Warthin's tumor	33 (26.4%)
-Pleomorphic adenoma	74 (59.2%)
-Oncocytic neoplasm	1 (0.8%)
-Mucoepidermoid carcinoma	2 (1.6%)
-Adenoid cystic carcinoma	1 (0.8%)
-Acinar structures	1 (0.8%)
-Atypical smear	3 (2.4%)
- Inflammatory lesions	5 (4%)
-Acinic cell carcinoma	2 (1.6%)
-Epithelial and myoepithelial cells	1 (0.8%)
-Basal cell neoplasm	1 (0.8%)
-Atypical squamous differentiation	1 (0.8%)
Preoperative biopsy methods	
-Fine needle aspiration cytology	121 (96.8%)
-Core-needle biopsy	4 (3.2%)

BMI: Body mass index, ASA: American Society of Anesthesiology, SD: Standard deviation

Operative Outcomes

About 102 (81.65%) of the tumors were firm in consistency (Table 2), and 101 (80.8%) of the tumors were in the superficial parotid lobe. Superficial parotidectomy was done in 87 (69.6%) patients, total parotidectomy in 31 (24.8%) patients, and quadrantectomy in 7 (5.6%) patients. The tumors were related to both trunks of the facial nerve in 67 patients and were related to the lower nerve trunk in 52 patients. The mean operative time was 130.76±51.5 min with estimated blood loss of 81.32±45.02 mL. A suction drain was placed in 106 patients and a non-suction drain was used in 19 patients.

Postoperative Outcomes

Postoperative complications were in the form of facial nerve morbidity in (12%) of the patients, bleeding in 1 patient, seroma in 5 patients, edema in 1 patient, wound gap in 1 patient, wound

Table 2. Surgical characteristics of the patients

	Patients, n=125 (%)
Tumor consistency	
-Cystic	20 (16%)
-Firm	102 (81.65%)
-Hard	3 (2.4%)
Intraoperative tumor location	
-Superficial lobe	101 (80.8%)
-Deep lobe	11 (8.8%)
-Both superficial and deep lobes	13 (10.4%)
Type of parotidectomy	
-Superficial	87 (69.6%)
-Total	31 (24.8%)
-Quadrantectomy	7 (5.6%)
Associated block neck dissection	
-No	117 (93.6%)
-Yes	8 (6.4%)
Sternomastoid dissection	
-No	111 (88.8%)
-Yes	14 (11.2%)
Relation of the tumor to the facial nerve	
-Lower trunk	52 (41.6%)
-Upper trunk	6 (4.8%)
-Both upper and lower trunks	67 (53.6%)
Operation time (min; mean ± SD)	130.76±51.5
EBL (mL; mean ± SD)	81.32±45.02
Operative complications	
-None	117 (93.6%)
-Bleeding	2 (1.6%)
-Extensive fibrosis	3 (2.4%)
-Facial nerve injury	1 (0.8%)
-Buccal nerve injury	1 (0.8%)
-Cervical branch injury	1 (0.8%)
Methods of drainage	
-Suction drain.	106 (84.8%)
-Non-suction drain	19 (15.2%)

EBL: Estimated blood loss, SD: Standard deviation

infection in 1 patient and 1 patient had keloid. The patients stayed in the hospital for 1 day (range 1-3 days). The tumors had a pathological size of 3.54±1.27 cm and the pathological tumor types were reported in Table 3. The median duration of follow-up was 11 months (range 4-61 months); tumor recurrence was reported in 2 (1.6%) patients; and the patient's overall survival was 28.5±14.77 months.

DISCUSSION

Many complications may occur after parotidectomy, and the most common early postoperative complications are hematoma and morbidities affecting the facial nerve (9). Parotidectomy and main duct ligation were performed for adequate removal of the parotid gland without facial nerve damage and sufficient safety margin; however, postoperative complications such as Frey's syndrome and facial contour deformity can occur (10). The connection between the superficial lobe of the parotid gland and the main parotid duct has made the ligation of the duct necessary to avoid possible salivary leakage after tumor excision. If the major branch connecting the excised area after superficial parotidectomy with the main duct is not ligated, there will be a regurgitation of saliva from the remaining parotid tissue, leading to a salivary leak. In 2004, Richards et al. (7) reported in their cadaveric study on the surgical anatomy of the duct system inside the parotid gland. They found that the main parotid duct had major branches running in or beyond the deep lobe in 62.1%, while it showed no branches in 37.9%. They also found small ducts connected the superficial parotid lobe and its main duct (7).

Table 3. Postoperative outcomes and follow-up of the patients

	Patients, n=125 (%)
Postoperative complications	
-Facial nerve complications:	
Lower trunk neuropraxia	4 (3.2%)
Lower trunk palsy	4 (3.2%)
Upper trunk neuropraxia	2 (1.6%)
Upper trunk palsy	1 (0.8%)
Both trunks neuropraxia	3 (2.4%)
Both trunks palsy	1 (0.8%)
-Bleeding	1 (0.8%)
-Seroma	5 (4%)
-Edema	1 (0.8%)
-Wound gap	1 (0.8%)
-Wound infection	1 (0.8%)
-Keloid	1 (0.8%)
Hospital stay (days; median, range)	1 (1-3)
Postoperative tumor size (cm; mean ± SD)	3.54±1.27
Postoperative tumor type	
-Warthin's tumor	39 (31.2%)
-Pleomorphic adenoma	65 (52.0%)
-Mucoepidermoid carcinoma	5 (4.0%)
-Adenoid cystic carcinoma	1 (0.8%)
-Acinic cell carcinoma	5 (4.0%)
-Basal cell neoplasm	1 (0.8%)
-Salivary duct carcinoma	2 (1.6%)
-Chronic non-specific sialadenitis	2 (1.6%)
-Lymphoepithelial cyst	1 (0.8%)
-Salivary duct cyst	1 (0.8%)
-Capillary hemangioma	1 (0.8%)
-Squamous cell carcinoma	1 (0.8%)
-Myoepithelial carcinoma	1 (0.8%)
Follow-up (months; median, range)	11 (4-61)
Recurrence	
-No	123 (98.4%)
-Yes	2 (1.6%)
Treatment of recurrence	
-Surgical resection	1 (0.8%)
-Chemotherapy	1 (0.8%)
Overall survival (months; mean ± SD)	28.50±14.77

SD: Standard deviation

Superficial parotidectomy without main parotid duct ligation was the standard of care for chronic sialadenitis; and total parotidectomy was performed for deep-lobe diseases and cancers (11). The deep parotid lobe undergoes spontaneous atrophy following superficial parotidectomy and duct ligation (12). If the duct is left open or transected, there will be subsequent strictures, cheek swelling, fistulae, and obstructive sialadenitis (13). Various types of intraductal stents were used for duct identification, such as an epidural catheter, a double-J catheter, and a Vitallium wire (Stryker Corporation) (14). In this study, we used a small-caliber Nylaton catheter or small syringe cannula in all cases. The main parotid duct was ligated in all cases to decrease the postoperative complications related to salivary leaks, such as fistula, seroma, sialocele, and wound infections.

In this study, the mean operative duration was 130.76 min and we found extensive fibrosis in 3 patients, which made dissection and identification of the main duct difficult. Another study has reported a mean operative time of 210 min (15). The overall postoperative facial nerve complications were 12%, including early neuropraxia (7.2%) and permanent palsy (4.8%). The patients with neuropraxia were treated with neurotronic and eye drops if the upper trunk was involved; and patients with permanent nerve palsy had physiotherapy and rehabilitation. The literature reported that the early post-parotidectomy facial nerve morbidity rate was 42-45%, and the rate of permanent facial nerve paralysis was 0-3.9% (9). It has been reported that the histopathological characteristic of parotid tumors affects the rate of facial nerve paralysis. The rates of its permanent complications are 12-14% in patients with malignant parotid tumors (16). We had 15 patients with malignant parotid tumors in the current study; permanent facial nerve palsy was encountered in 4 cases with mucoepidermoid carcinoma, 1 case with acinic cell carcinoma, and 1 case with squamous cell carcinoma. Another study reported an incidence of 28.57% for transient facial nerve palsy after ligation of the main parotid duct with superficial parotidectomy for chronic sialadenitis (17).

Other postoperative complications reported in the current study were bleeding at 0.8%, mild seroma at 4%, edema at 0.8%, wound gap at 0.8%, wound infection at 0.8%, and keloid at 0.8%. All these complications were mild and managed conservatively. A study has reported that 17 patients with chronic sialadenitis underwent superficial parotidectomy with preservation of the main parotid duct. The postoperative complications included temporary facial palsy in 76.47%, Frey's syndrome in 17.64%, temporary paresthesia of the cheek in 17.64%, and painful neuroma of the greater auricular nerve in 11.76%. Moreover, there was an infection in the remnant of the parotid duct (11.76%) (18). Duct excision with superficial parotidectomy was performed in another study that included 17 patients with refractory chronic obstructive parotitis. The entire duct was removed in 13 cases. The posterior part of the duct was removed in the remaining 4 cases. One patient with a remnant duct developed an infection and needed its complete removal (19). The rate of sialocele after parotidectomy was usually under-reported (20), and a study has detected it using US in 15 patients (10%) during the follow-up period (21). This high incidence was consistent with previous reports (22). It was hypothesized that the remaining functioning parotid tissue after superficial or partial parotidectomy promotes sialocele formation, especially when the main parotid duct is not ligated (23). We did not encounter any case of sialocele in the current study.

During follow-up, tumor recurrence had developed in 2 patients: one patient with salivary duct carcinoma that recurred after 22 months and was treated with surgical resection, and another patient with myoepithelial carcinoma that recurred after 30 months and received chemotherapy. Regarding mouth dryness, the patients did not complain during the follow-up period, which was consistent with the study by Chaushu et al. (24) that reported no change in the patient's mouth dryness after parotidectomy compared to their pre-operative period.

Study Limitations

The limitation of this study, is that it is a case series without comparative data for those who underwent parotidectomy without duct ligation. A randomized controlled trial may be needed in the future to compare parotidectomy with or without duct ligation.

CONCLUSION

The identification and ligation of the main parotid duct during parotidectomy have favorable impacts on the incidence of post-parotidectomy complications such as salivary fistula, seroma, sialocele, and wound infections.

Ethics

Ethics Committee Approval: The Institutional Review Board approval of the Faculty of Medicine, Mansoura University code (R.22.03.1663) was obtained.

Informed Consent: All the patients had signed written consent before inclusion in this study.

Acknowledgments

The authors are grateful to all patients and colleagues at the Department of Surgical Oncology, Oncology Center, Mansoura University.

Footnotes

Author Contributions

Concept - A.A.; Design - A.A., M.A.E.; Supervision - A.A.; Materials - A.A., M.S.; Data Collection or Processing - A.A., M.H.; Analysis or Interpretation - A.A., M.S.; Literature Search - A.A., M.E.; Critical Review - A.A.; Writing - A.A.

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

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

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CASE REPORT
Turk J Surg 2025;41(1):98-101

Massive intestinal mesenteric portal vein ischemia: Percutaneous endovascular thrombolysis as minimally invasive step-up approach

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ABSTRACT

Acute mesenteric ischemia represents a group of diseases, which lead to an abrupt interruption of blood flow to the small intestine resulting in intestinal necrosis. Its first symptoms are vague and in the majority of cases nonspecific, so the diagnostic suspicion is of the utmost importance to establish the correct diagnostic and prompt treatment. It is a complex and difficult event, that needs a multidisciplinary approach involving different specialties such as gastrointestinal and vascular surgeons, interventional radiologists, and expertise from the acute care unit team. The fundamental aspect is the precocity of diagnostic based on abdominal computed angio-tomography and the immediate re-establishment of blood supply to the affected areas. In this report, we introduce a case of a patient with mesenteric venous thrombosis, who has beenundergone a percutaneous endovascular treatment (portal-mesenteric mechanical thrombectomy, besides an intravenous thrombolytic infusion), due to poor clinical response after anticoagulation approach that needed mechanical ventilation.

Keywords: Intestinal ischemia, thrombolysis, endovascular thrombectomy, emergency surgery, management

INTRODUCTION

Acute mesenteric ischemia (AMI) is the abrupt interruption of the blood flow to the small intestine, leading to cellular injury, intestinal necrosis, and considerable lethality (1-6). It is classified as occlusive or non-occlusive: The first one has three main causes: arterial embolism (50%), arterial thrombosis (15-25%) and acute mesenteric venous thrombosis (AMVT) (5-15%). The initial complaints, in the majority of cases, are vague. The presence of colic, nausea, vomiting, anorexia, and even diarrhea, lower digestive bleeding represent the most common manifestations of the disease, which has a low incidence (0.09-0.2% of all acute admissions) (2,4,6). Moreover, the acute care surgeon must be aware of the clinical history, investigating risk factors that contribute to the Virchow's triad (2). The high clinical suspicion allied to angio-computed-abdominal tomography (ACAT) can establish the prompt diagnosis, which represents the most reliable indicator of the disease's management success (4,6,7).

AMVT treatment requires a multidisciplinary approach involving gastrointestinal and vascular surgeons, interventional radiologists, and an acute care team, due to its inherent pathophysiologic complexity. The treatment of choice is based on clinical setting, hemodynamic status, and the presence of peritonitis. The goal is to reestablish, as soon as possible, the blood flow to affected areas regardless of the etiology (4,6). In AMVT, the first-line treatment is non-operative, based on anticoagulation. The approach has good outcomes in the majority of cases (1,6). In cases where there is clinical deterioration and no response to previous measures, endovascular treatment has emerged as an interesting option. It includes mechanical thrombectomy

Cite this article as: Gomes CA, Filgueiras TDS, Carvalho AM, Sartelli M, De Simone B, Catena F. Massive intestinal mesenteric portal vein ischemia: Percutaneous endovascular thrombolysis as minimally invasive step-up approacj. *Turk J Surg.* 2025;41(1):98-101

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Received: 09.04.2021
Accepted: 06.10.2021
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2021.5209

Available at www.turkjsurg.com

and/or catheter-directed thrombolysis via transhepatic or transjugular portosystemic access (1-4).

The aim of the manuscript is to report a clinical case of AMI caused by mesenteric-portal axis thrombosis, which, after a dismal response to the pharmacologic approach, underwent percutaneous endovascular thrombectomy treatment.

For this case report, informed consent was obtained from the patient (or their legal guardian) for the publication of clinical details and any accompanying images. The patient was informed about the purpose of the report, and their anonymity was ensured by omitting any identifying information.

CASE REPORT

A 22-year-old female patient, who has a family history of thrombophilia and is using oral contraceptives, was examined in the emergency room. She complained of abdominal pain that had lasted for 10 days and was refractory to common analgesia. The physical exam showed contracture and abdominal tenderness, laboratory tests showed leukocytosis, and the urgent non-contrast computed tomography (CT) revealed free liquid inside the abdominal cavity. she underwent an exploratory laparotomy in an emergency situation. The intra-operative finding was diffuse cyanosis in the small intestine, without abnormality of peristalsis or necrosis. An ACAT was performed on post-operative day one, which showed extensive thrombosis of mesenteric-portal veins, associated with intestinal edema and ascites, without imaging signs of bowel necrosis (Figure 1). The patient was then subjected to full anticoagulation with continuous infusion of unfractionated heparin-bolus of 80 UI/kg followed by 18 UI/kg/hour. Unfortunately, she showed no clinical improvements after 24 hours following the onset of treatment. However, there was progressive pain, a decline in clinical and laboratorial parameters such as leukocytosis, anemia, tachycardia, vomiting, and abdominal distension; however, there were no signs of peritonitis. After multidisciplinary discussion, the decision was to perform an endovascular percutaneous approach. The planned procedure involved percutaneous access with the NPAS kit and insertion of catheters from the portal vein to the superior mesenteric vein, followed by pharmacologic thrombolysis of the portal-mesenteric axis with recombinant tissue plasminogen activator using a multiperforated catheter (Figure 2). The next step was a mechanical thrombectomy with the rotarex device and thrombus suctioning with a guide catheter 7F (Figure 2E). The transhepatic access was embolized with histoacryl and lipiodol glue (Figure 2F). The patient remained on full anticoagulation for 21 days. She demonstrated significant improvements in clinical and laboratory parameters, despite a self-limited episode of melena. She was discharged 10 days after the procedure with an oral anticoagulant.

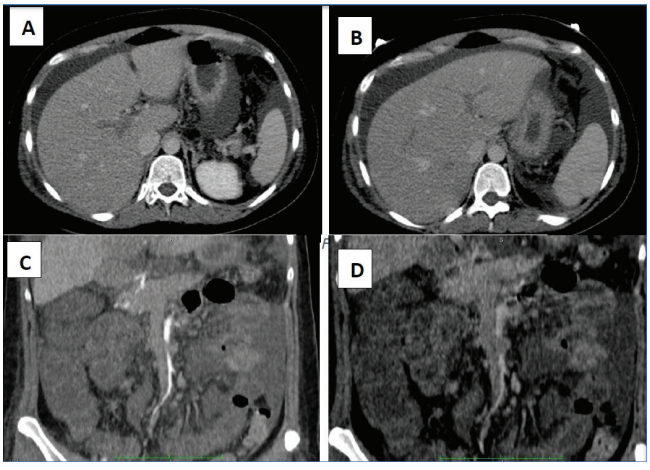

Figure 1. Extensive mesenteric-portal thrombosis.

A) and (B) - Axial CT angiography, portal phase with thrombosis of right and left port branches; portal phase CT angiography with thrombosis of the left port branch; (C) - Coronal angio-CT arterial phase with patent superior mesenteric artery; (D) - Coronal angio-CT venous phase with no superior mesenteric opacification compatible with extensive thrombosis associated with thickening of intestinal loops.

CT: Computed tomography

DISCUSSION

The AMVT corresponds to 6 to 9% of mesenteric ischemia and its mortality remains high (from 19 to 23%) (2,6), mostly due to delay in the diagnostic workup prompt treatment, which should be started in the emergency room. Another aspect that should not prevent the precocity of the diagnosis refers to delay in the ACAT requesting, due to an old paradigm: i.e., fear from the development of renal failure induced by iodine contrast in elderly patients. In this aspect, it is important to highlight that it is not an absolute truth so controversies on the subject remain (7).

The pivotal role of the contrast-enhanced CT with intravenous contrast administration is undeniable when rapid intervention is needed to improve outcomes in an emergency setting.

Moreover, a recent systematic review showed that the incidence of contrast-induced nephropathy after intravenous contrast administration is very low in the general population (8).

In the clinical history, it is relevant to search for risk factors that predispose the formation of clots, like a positive family history for thrombophilia and the use of oral contraceptives, as seen in this case (2). In stable patients without signs of peritonitis, a non-operative approach with anticoagulation is the first line of treatment, with up to three quarters of patients achieving partial resolution of the thrombus and a good clinical outcome (4). The management may be started with low molecular weight heparin (LMWH) and continued with oral administration of warfarin. If the initial symptoms are severe, suddenly worsens or ACAT shows intestinal edema and others sign of progressive venous splanchnic congestion, then, continuous infusion of unfractionated heparin should replace LMWH (1,6). Moreover,

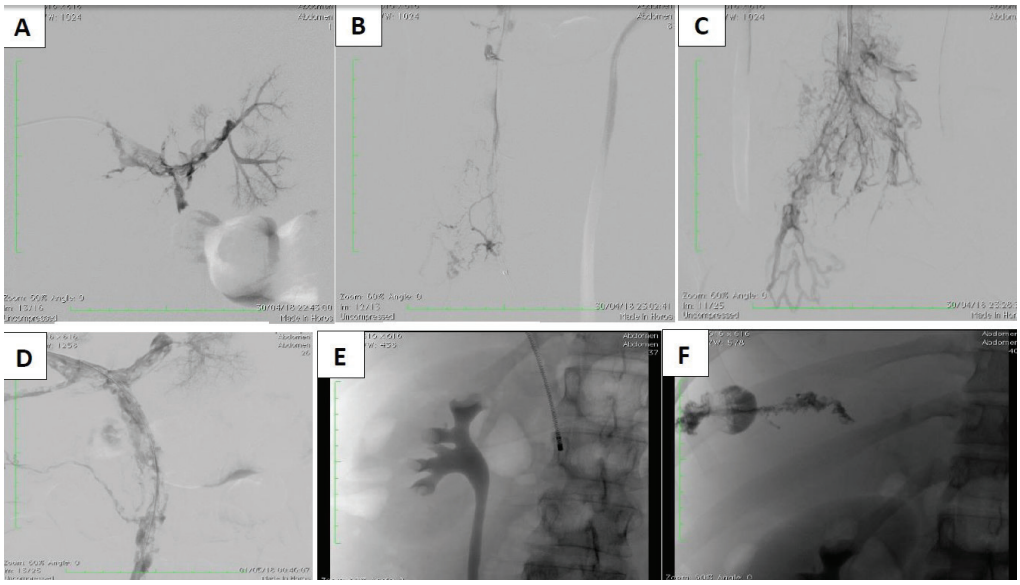

Figure 2. Extensive mesenteric-portal thrombosis.

A) - Direct portography after portal branch puncture guided by fluoroscopy; B) - Catheterization of the superior mesenteric vein and phlebography showing extension of thrombosis; (C) and (D) - Pharmacological thrombolysis with multiperforated catheter and rTPA; (E) - Rotarex device used for mechanical thrombectomy; (F) - Embolization of the puncture path with biological glue and lipiodol.

rTPA: Recombinant tissue plasminogen activator

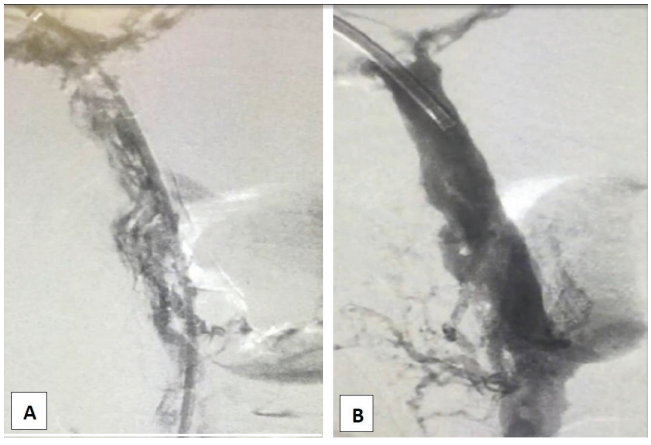

Figure 3. Extensive mesenteric-portal thrombosis. (A) Before and (B) after percutaneous mesenteric-portal vein thrombolisis.

if those severe clinical manifestation persists as observed in our patient, endovascular thrombolysis and mechanical thrombectomy has been increasingly employed (4).

The option was percutaneous trans-portal access, to reestablish immediate improvement in the venous flow and reduce the congestion in the splanchnic territory. Its use is based on minimal invasiveness and the reduction of risks of complications from the laparotomic approach and promising clinical results (2,9,10). It includes, percutaneous procedure, endovascular catheter-directed chemical thrombolysis associated with mechanical thrombectomy. In our patient, the approach was repeated twice and significant resolution of the thrombosis was immediately obtained. At the end of the procedure, the access was embolized with Histocryl glue and lipiodol to minimize bleeding (Figure 3) (4,5).

There is no specific definition yet regarding on which day of the anticoagulation treatment we should evaluate the treatment efficacy and how to evaluate it. The majority of recent series reported that anticoagulation failure was defined as no clinical improvements, and worsening of the patient's clinical features in subsequent clinical follow-up. In our case report, we have re-evaluated the anticoagulation treatment 24 hours after the first administration of heparin. On the contrary, clinical success was defined as symptom resolution as well as patency of at least 50% of the superior mesenteric vein at venography and resolution of jejunal thickening. The patients should be discharged on oral anticoagulation with an international normalised ratio 2.5-3.5. Follow-ups were performed using CT and color Doppler ultrasound (11).

In cases of AMVT, the anticoagulation should be continued for a minimum of six months after the initial treatment and, if thrombophilia was diagnosed, a life-long anticoagulation should be considered (4). However, surgery still represents the first choice approach when there is a suspicion of bowel necrosis, perforation, or abdominal compartment syndrome.

In these cases, open-abdomen damage control surgery can avoid extended intestinal resection complicated by ashort bowel syndrome (12). Nowadays, open venous thrombectomy should be expedited only rarely, except as rescue therapy in difficult cases (1-4).

CONCLUSION

The subacute presentation of pain and other symptoms observed in the report (10 days), may be due to a progressive but massive thrombosis in the mesenteric-portal territory, which delayed the clinical presentation and was also responsible for the poor response to pharmacological treatment. The option for a direct approach to the thrombus was a wise and effective choice. Thus, cases that do not obtain significant clinical improvement despite the use of heparin after 48-72 hours of close clinical monitoring may be candidates for a percutaneous endovascular approach.

Ethics

Informed Consent: For this case report, informed consent was obtained from the patient (or their legal guardian) for the publication of clinical details and any accompanying images. The patient was informed about the purpose of the report, and their anonymity was ensured by omitting any identifying information.

Footnotes

Author Contributions

Concept - C.A.G.; Design - C.A.G.; Supervision - F.C., M.S., C.A.G., B.D.S.; Data Collection or Processing - A.M.C., T.D.S.F.; Analysis or Interpretation - C.A.G., B.D.S., F.C., M.S.; Literature Search - A.M.C., T.D.S.F.; Critival Review - M.S., F.C., B.D.S.; Writing - T.D.S.F.

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

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

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CASE REPORT
Turk J Surg 2025;41(1):102-104

Spontaneous and uneventful anal expulsion of expanded polytetrafluoroethylene (e-PTFE) vascular graft after living donor liver transplantation

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ABSTRACT

Living donor liver transplantation (LDLT) is a useful therapeutic option for end-stage liver disease due to the shortage of deceased donor liver grafts, particularly in Asia and Türkiye. Right liver LDLT is frequently performed in adults and some cases require anterior section venous drainage. Synthetic grafts, particularly expanded polytetrafluoroethylene (e-PTFE), are often preferred for venoplasties. Despite its many advantages, some complications associated with these grafts have been reported, such as gastrointestinal tract migration, perforation, and bleeding. Here we present an extremely rare case about an e-PTFE graft.

Keywords: Liver transplantation, venous drainage, venoplasty, vascular graft, complication

INTRODUCTION

Living donor liver transplantation (LDLT) has been a useful therapeutic method for end-stage liver disease due to the shortage of deceased donor liver grafts (1). Right liver LDLT (RLDRLT) is frequently performed in adults (2). In RLDRLT procedures, it is preferred to keep the middle hepatic vein on the donor side to protect venous drainage of donor segment 4's venous drainage. Thus, drainage of large-diameter veins (>5 mm) of segment 5 and 8, must be reestablished. Also, in some cases, large inferior hepatic veins draining segment 6 or segment 7 require reconstruction for venous drainage due to the same reason (3,4). Various venoplasty techniques can be applied utilizing autologous or synthetic vascular grafts (5-7). When compared to autologous grafts, synthetic grafts are easy to obtain, less time-wasting, and satisfying (5-9). Consequently, synthetic grafts, particularly expanded polytetrafluoroethylene (e-PTFE) (Gore Tex®, W.L. Gore & Associates, Inc. Medical Products Division Flagstaff, Arizona, USA), have been more often preferred for venoplasties. Although e-PTFE grafts have many advantages, some rare complications such as gastrointestinal migration, penetration and bleeding have also been reported. Here we report an unusual case, in which an e-PTFE graft totally and uneventfully passed through the gastrointestinal tract and was excreted anally.

CASE REPORT

A 30-year-old female patient with end stage liver disease due to primary sclerosing cholangitis, underwent RLLDLT in 2011. The living liver donor was her husband and according to our laws it was officially allowed. Six millimeter (mm) segment 5 vein, which was draining to the donor's middle hepatic vein, was reconstructed by means of an 8 mm diameter e-PTFE graft during the back table procedure. This graft was anastomosed to the inferior vena cava (IVC). Thus, segment 5 venous drainage to the IVC was reestablished via e-PTFE vascular graft. Graft patency was confirmed

Cite this article as: Egeli T, Ünek T, Ağalar C, Sakaoğlu MB, Özbilgin M, Obuz F, et al. Spontaneous and uneventful anal expulsion of expanded polytetrafluoroethylene (e-PTFE) vascular graft after living donor liver transplantation. *Turk J Surg.* 2025;41(1):102-104

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Received: 27.10.2021
Accepted: 16.03.2022
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2022.5567

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by regular follow-up Doppler ultrsonography. The patient was discharged uneventfully, and regular follow-up was continued. Graft thrombosis was detected on abdominal computed tomography (CT) on the 3rd postoperative month (Figure 1, yellow arrows).

Eight years after surgery, the patient was admitted to the transplantation outpatient clinic because of a tubular-shaped foreign body in her stool. The examination revealed that the foreign body was an e-PTFE vascular graft, which was used in the LDLT surgery (Figure 2). The patient did not describe any gastrointestinal system complaints. The patient indicated that she applied to a local hospital due to slight abdominal pain before she came to us, where she underwent an abdominal CT. We investigated these CT scans and realized that the e-PTFE graft was transmigrated to the patient's duodenum without complication (Figure 1, red arrows). We performed a novel CT to assess any abdominal pathology resulting from vascular graft migration. No problems were detected in the gastrointestinal system or in IVC (Figure 1). The vascular graft, which was obviously seen in the previous CT, was not observed in this new study. This proved that the graft was rejected by the body. There were no further remarkable findings in the CT. Also, no traumatic changes or signs of complications were detected in endoscopic examinations. Apparently, e-PTFE graft was completely transmigrated through the gastrointestinal tract and excreted through the anus without causing any complications. Patient did not have any complaints, and she continued her routine outpatient clinic follow-up.

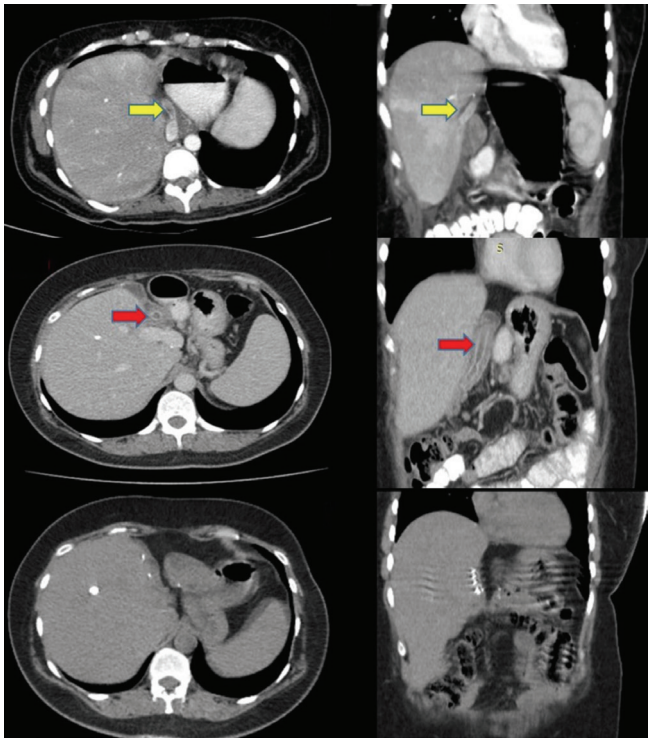

Figure 1. Thrombosis in vascular graft on the 3rd postoperative month. Computed tomography, coronal and axial views (yellow arrows). Vascular graft transmigration into duodenum (red arrows). Vascular graft was not seen in the new computed tomography.

DISCUSSION

In RLLDT LDLT, veins other than right hepatic vein which size bigger than 5 mm in graft side must be drained to recipients IVC directly or by way of grafts (9). Recently, e-PTFE synthetic vascular grafts are mostly preferred for this purpose due to its many advantages (5-9). Main complications regarding e-PTFE vascular grafts are infection and thrombosis, but they develop rarely. Also, it is clinically sufficient for the e-PTFE grafts to remain open for 2 weeks (3,5,10,11), thus late thrombosis of e-PTFE grafts have been shown no effect on survival. The use of e-PTFE grafts has proven to be reliable in LDLT (3,5).

Spontaneous migration of thrombosed synthetic grafts to the duodenum or the small bowel has been reported after abdominal vascular surgeries (12,13). However they are unusual, some complications such as penetration, perforation, obstruction, fistulization and bleeding can occur in the long-term period due to graft migration (3,12,13). The first reported case was e-PTFE vascular graft migration to the stomach following a deceased donor liver transplantation. Greft migration caused stomach perforation and required urgent surgery (14). Similarly, Hsu et al. (4) reported 3 duodenal perforation cases due to e-PTFE vascular graft migration that necessitated immediate abdominal exploration after LDLT. The first spontaneous and uneventful migration of a thrombosed e-PTFE graft to the duodenum 3 months after LDLT was reported by Sultan et al. (15). In that case, thrombosed e-PTFE graft, eroding the first

Figure 2. Expulsed expanded polytetrafluoroethylene vascular graft after defecation.

part of the duodenum, was seen during ERCP. There was no remarkable duodenal wall destruction or perforation, and patients were stable. They did not perform any intervention for this, only followed up on the condition. Follow-up CT showed disappearance of the graft from the abdomen, and endoscopic examination revealed a small ulcer at the site of the migrated graft. Probably the graft was excreted via the anal route.

In our case, the patient brought the e-PTFE vascular graft, which was used in LDLT, after observing it in her stool. This was an extremely odd, and, according to our knowledge, the first entity in the literature regarding e-PTFE vascular graft migration. Fortunately, no complication occurred regarding this complete and uneventful graft migration after the follow-up period.

CONCLUSION

Although synthetic vascular grafts such as e-PTFE are useful and reliable materials for venoplasties in LDLT, they may lead to some potential complications. Particularly in the long term, after surgery, surgeons must be careful about complications due to graft migration to the gastrointestinal tract. In case of doubt, patients should be evaluated with CT and endoscopy immediately.

Ethics

Informed Consent: Informed consent was obtained from the patient who participated in this study.

Acknowledgments

Authors thank to Dr. Aylin Bacakoğlu for her valuable contributions.

Footnotes

Author Contributions

Concept - T.E., T.Ü., C.A., M.B.S.; Design - T.E., T.Ü., C.A., M.B.S.; Supervision - T.Ü., F.O., M.A., İ.A.; Data Collection or Processing - T.E., T.Ü., C.A., M.B.S., M.Ö., C.A.; Analysis or Interpretation - T.E., T.Ü., C.A., M.B.S., M.Ö., C.A.; Literature Search - T.E., T.Ü., C.A., M.B.S., M.Ö., C.A.; Critical Review – T.E., T.Ü., C.A., F.O., M.A., İ.A.; Writing - T.E., T.Ü., C.A., M.B.S.

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

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

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CASE REPORT
Turk J Surg 2025;41(1):105-107

Everolimus induced pneumonitis in a liver transplant patient: Dilemma in the discrimination of pneumonia

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ABSTRACT

Everolimus is one of the immunosuppressive drugs used in solid organ transplantation. Many side effects have been described for these immunosuppressive drugs, similar to other drugs in this category. The purpose of this case presentation is to draw attention to drug-induced pneumonitis, which is a rare and life-threatening side effect of everolimus. A nineteen-year-old female patient who received liver transplantation for toxic hepatitis was admitted to our institute with cough and dyspnea. Everolimus had been started in conjunction with tacrolimus therapy 6 months prior to admission. Her chest imaging were consistent with pneumonitis. Markers of infection and cultures were all negative. After discontinuation of everolimus, symptoms and radiological findings resolved. The adverse effects of the drug should be kept in mind while investigating possible infectious agents in liver transplant recipients who are prone to opportunistic infections.

Keywords: Pulmonary, mTOR inhibitors, everolimus

INTRODUCTION

Everolimus is a mammalian target of rapamycin (mTOR) inhibitor that is an antineoplastic agent which is used as an immunosuppressive agent in solid organ transplantations. It has been commonly used in immunosuppressive therapy for solid organ transplantation. Everolimus is recommended alongside calcineurin inhibitor-based therapies to reduce renal side effects (1). Common side effects are hyperlipidemia, mucosal ulcerations, cytopenia, and impairment of wound healing (2,3). Non-infectious pneumonitis is an uncommon side effect of everolimus in liver transplant recipients. Here, we present a case of a liver transplant recipient with everolimus-induced pneumonitis, which is the fourth case in the literature.

CASE REPORT

A 19-year-old female liver transplant recipient was admitted to our institute with a cough and shortness of breath that had lasted for three days. Medical history revealed that she had undergone deceased donor liver transplantation for acute liver failure resulting from toxic hepatitis 18 months prior to admission. Everolimus was added as an adjunct to tacrolimus therapy due to an episode of acute cellular rejection six months prior to admission. She was hospitalized because of her respiratory symptoms and immunosuppressive state. Her temperature was 36.6 °C, blood pressure was 110/75 mmHg, heart rate was 105 beats/min, respiratory rate was 26 breaths/min, and oxygen saturation was 89% without oxygen supplementation. She was oriented and in moderate to good clinical condition. She had mild-to-moderate respiratory distress. There were crackles in the basal lobes of both lungs. Other findings of physical examination were unremarkable. Her liver enzymes and bilirubin levels were normal. White blood cell count was $1.8x10^9$/L, hemoglobin level was 9.5 g/dL, and platelet count was $266x10^9$/L. C-reactive protein and procalcitonin levels were 0.5 mg/dL and 0.05 ng/mL, respectively. While she was taking everolimus and tacrolimus at dosages of 2 mg/day and 4 mg/day, the trough levels were 6.8 ng/mL and 5.8 ng/mL, respectively. Computed tomography of the thorax showed bilateral basal patchy and nodular consolidations with

Cite this article as: Sağlam K, Köse A, Yalçınsoy M, Bayındır Y, Yılmaz S. Everolimus induced pneumonitis in a liver transplant patient: Dilemma in the discrimination of pneumonia. *Turk J Surg.* 2025;41(1):105-107

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Received: 08.11.2021
Accepted: 17.01.2022
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2022.5489

Available at www.turkjsurg.com

diffuse ground-glass opacities (Figure 1a). History, physical examination, and laboratory findings were not compatible with bacterial or fungal infection. A bronchoscopy was performed and bronchoalveolar lavage (BAL) was performed. In the BAL fluid, respiratory panel (syndromic test), polymerase chain reaction for *Aspergillus* spp., and *Mycobacterium tuberculosis*, acid-fast staining and culture for *Mycobacterium tuberculosis* were negative; BAL fluid and blood cultures did not reveal bacterial and fungal infection. Since there was no positive finding for any infectious agents, everolimus treatment was stopped as the first step of our management protocol. Fifteen days after everolimus discontinuation, her symptoms were resolved. Control computed tomography of the thorax showed marked improvement of previous consolidation areas (Figure 1b). No antibiotics or anti-viral treatments were used during this process. The patient recovered spontaneously after discontinuing everolimus treatment. The patient was discharged on day 17 with tacrolimus 4 mg/day, following an uneventful recovery.

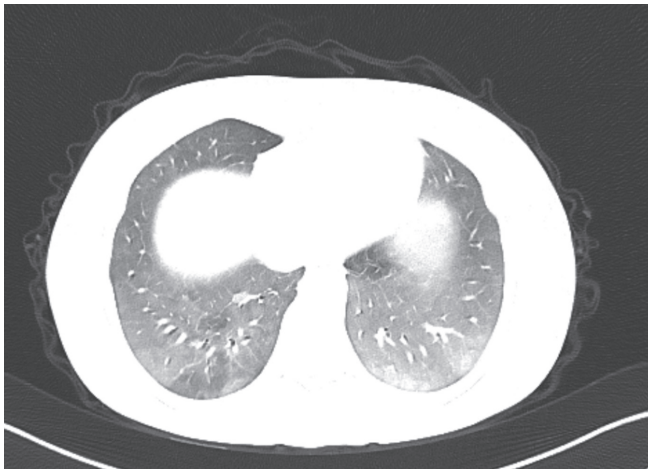

Figure 1a. Computed tomography showed bilateral basal patchy and nodular consolidations with diffuse ground-glass opacities.

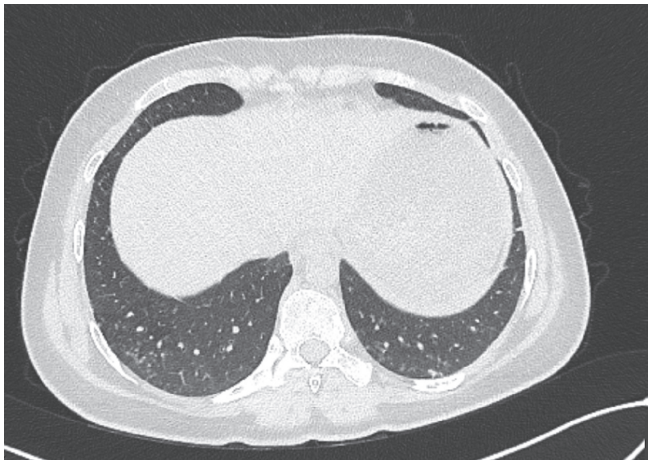

Figure 1b. Follow-up thorax computed tomography showed marked improvement of the previous signs of consolidation.

DISCUSSION

We report drug induced pneumonitis, which is a rare side effect of everolimus in liver transplantation patients.

Everolimus is an mTOR inhibitor and has antineoplastic properties. In addition to its antineoplastic properties, it is a preferred immunosuppressive agent in solid organ transplantation. Combining with calcineurin inhibitors (CNI) can decrease the side effects of CNI therapy by reducing the dose (1). Incidence of drug-induced pneumonitis in solid organ transplantation caused by sirolimus (another mTOR inhibitor) and everolimus was reported as 16.7% and 0.4%, respectively (4). Drug-induced pneumonitis was commonly reported in heart, kidney, and lung transplants but very rarely in liver transplant recipients. The mechanisms of pulmonary toxicity are unclear. Pulmonary toxicity (pneumonitis or non-infectious pneumonia) was reported in high-dose, antineoplastic therapy (2). However, some studies showed that pulmonary toxicity can occur at low drug levels. Therefore, it was suggested that pulmonary toxicity was not dose-dependent (3). Life-threatening clinical conditions such as alveolar hemorrhage and even mortalities were also reported (5).

The diagnostic criteria for sirolimus-induced pneumonia have been defined by Morelon et al. (6). The symptoms emerged after the drug was started, and the clinical symptoms regress after the drug cessation, which makes up the main components of the diagnostic criteria. The other important point was the exclusion of the infectious etiology. Pneumonia can emerge within two to six months after the first dosage, or up to 6 years after initiation of everolimus therapy (2,5,7). Common symptoms of these patients are shortness of breath and coughing (2). Laboratory findings are usually non-specific and infection markers are usually negative (5). Blood, sputum, and BAL cultures were negative, and common infectious microorganisms, including opportunistic agents, should be considered excluded. Thorax computed tomography was usually preferred in the diagnosis (4). Bilateral pulmonary infiltration on imaging modalities is common among all cases. There is no consensus on the management of these patients. Discontinuation of everolimus is the main therapeutic approach. Corticosteroids were recommended in some reports depending on the severity of the disease (5). Pulmonary symptoms resolved in one and three months after stopping everolimus in the reported two cases (3,8). In our patient, pulmonary symptoms started to regress on the 15th day, after discontinuation of everolimus treatment. It is a matter of debate whether or not we have taken risks by not starting empirical antimicrobial therapy in our patient who was immunosuppressed.

In conclusion, it is well-known that transplant recipients are prone to opportunistic infections. However, the adverse effects of the drugs should not be underestimated.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Author Contributions

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

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

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

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CASE REPORT
Turk J Surg 2025;41(1):108-111

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) for pediatric mesenchymal hamartoma: A case report

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ABSTRACT

The case involves a one-year-old male with a mesenchymal hamartoma involving the right hepatic lobe. The tumor-free segments comprised 17% of the liver volume, which placed the patient at risk for post-resection liver failure. A staged approach, the associating liver partition with portal vein ligation for staged hepatectomy, was employed. This allowed the interval growth of the liver remnant and thereafter enabled right lobectomy with adequate liver function.

Keywords: Hamartoma, liver neoplasm, hepatectomy, liver regeneration

INTRODUCTION

Resection is the primary curative option for patients with malignant liver tumors. This also applies to many benign lesions that may be complicated by massive growth or potential for malignancy, particularly among pediatric patients. However, resection is not a feasible alternative for cases wherein the remnant liver will have insufficient functional capacity. The latter has been spatially quantified as the proportion of the volumes of the remaining segments compared to the total liver, and is termed the future liver remnant (FLR). The associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) technique was first performed in 2007. It has been shown to cause a substantial increase in the FLR within a relatively short period, enabling resection while avoiding consequent liver failure (1). We report the case of a one-year-old male with a large mesenchymal hamartoma (MHL) and a small initial FLR who underwent ALPPS. To our knowledge, this is only the second patient reported for this procedure and indication worldwide, and the first reported ALPPS case in our country.

CASE REPORT

A one-year-old male had progressive abdominal distention over two months. He was otherwise asymptomatic. A computed tomography (CT) scan done at another institution showed an 11.8x12.4x13.5 cm lobulated cystic mass with septations at the right hepatic lobe. An impression of MHL was given. He was referred to our center for definitive surgical management. On admission, the patient weighed 10.7 kg (Z-score +1), with a height of 76 cm. The upper abdomen was markedly distended. The following laboratory results were obtained: Alanine transaminase (ALT): 23 U/L, aspartate transaminase (AST): 47 U/L, Gamma-glutamyl transferase: 85 U/L, albumin: 45.7 g/L, and alpha fetoprotein: 49.44 mg/L. Upon review of the CT scan, the multi-lobulated cystic tumor was determined to occupy segments IV, V, VII, and VIII (Figure 1). The FLR was estimated to be 17%. In consideration of the latter, a staged resection was recommended. The planned surgery was delayed for several days due to Coronavirus disease-2019 contingencies.

Cite this article as: Caballes A, De Lara KA. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) for pediatric mesenchymal hamartoma: A case report. *Turk J Surg.* 2025;41(1):108-111

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Received: 29.12.2024
Accepted: 30.01.2025
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2025.6696

Available at www.turkjsurg.com

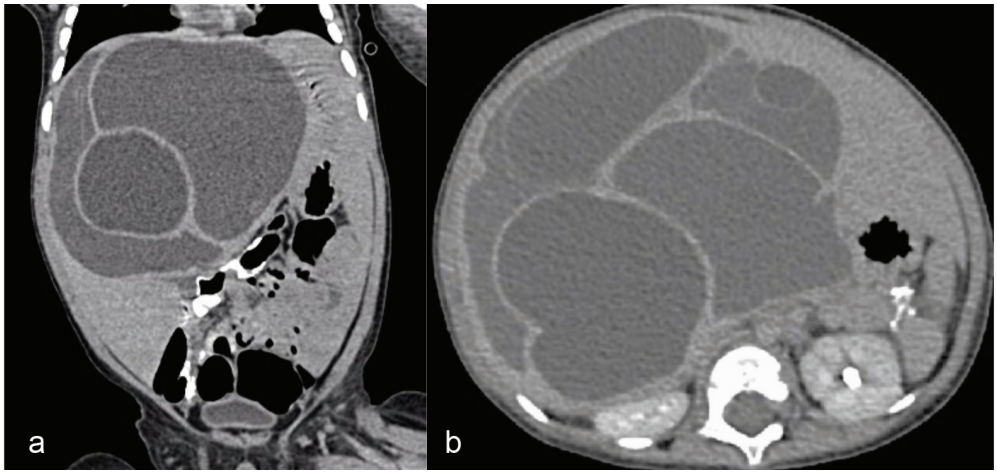

Figure 1. Selected CT scan images of the abdomen demonstrating a massive multi-lobulated cystic tumor at the right liver and the lesion-free segments II and III, a. coronal section, b. axial section.

CT: Computed tomography

The first stage was performed through a transverse upper laparotomy. The dilated right portal vein was isolated, transected, and the proximal stump was closed with a running suture (Figure 2). The left hepatic artery, hepatic duct, and portal vein, which were stretched out by the expanded right liver lobe, were dissected and traced to the left liver lobe to safeguard these during liver partition. Retrohepatic veins to the right lobe were divided and ligated. Liver separation was performed with blunt dissection, following the falciform ligament. Pringle's maneuver was not employed. Only a partial split was done, as the hepatic veins and adjacent parenchyma were spared (Figure 3). A plastic film was laid over the transection area, on which a silicone drain was placed. The operative time was 255 minutes, and the blood loss was 170 mL.

The patient's postoperative course was difficult, with hemodynamic instability and high ventilatory support requirements. The initial international normalised ratio was 1.56. Liver enzyme (ALT: 519 U/L, AST: 963 U/L) and bilirubin (DB: 4.29 umol/L, IB: 19.45 umol/L) levels were elevated. Hospital-acquired pneumonia also set in. Thus, while a CT scan showed that the FLR had increased by 47% by the 14th day after surgery, the second stage could only be done after another week.

On re-laparotomy, considerable adhesions were encountered over the right liver lobe, as well as on the previously freed-up main vascular and biliary structures going to the left liver. The left hepatic duct was injured during the dissection and duly repaired. The cystic duct and artery were transected and the gallbladder was left *in situ*. The right hepatic artery and duct were divided. Right hepatectomy was completed following the separation of the remaining parenchymal bridge and transection of the right and middle hepatic veins. The operation lasted 280 minutes, with the total blood loss being 750 mL. There was a rapid recovery and the patient required only a brief intensive care unit stay. A single episode of hematochezia occurred on the 10th postoperative day. Bile was noted at the peritoneal drain at the thirteenth postoperative day. These developments were managed conservatively. The patient was sent home 15 days after surgery.

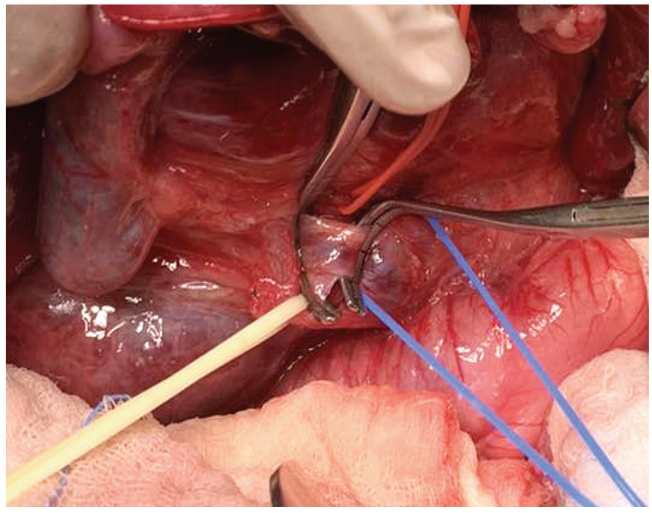

Figure 2. The right portal vein has been isolated and vascular clamps are applied proximal and distal to the point of transection. Also shown are the common bile duct (yellow tag), right hepatic artery (red tag), and portal vein (blue tag).

The lesion was confirmed to be MHL on histopathology, with margins clear of tumor. There are no indications of hepatic decompensation two years after the procedure. However, a recent CT scan performed at another institution had findings suggestive of portal vein stenosis. Additional studies to confirm this are forthcoming.

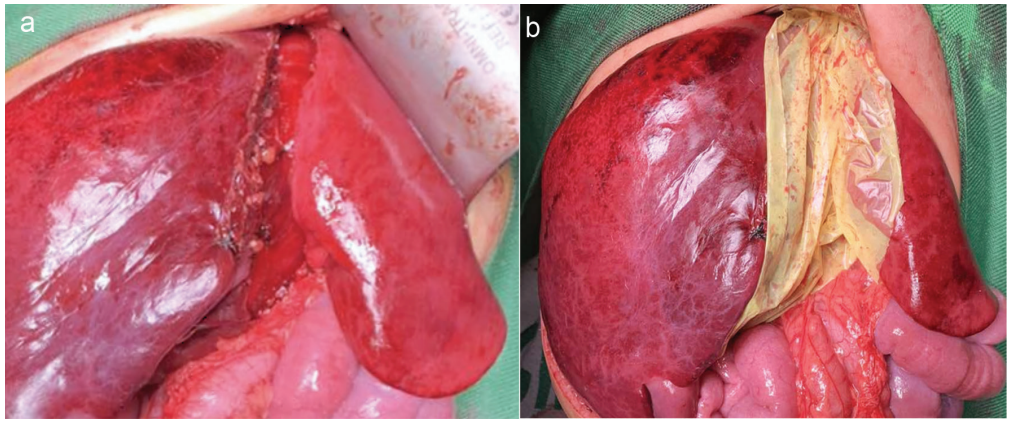

Figure 3. a. Partial hepatic separation accomplished. b. Plastic film and a drain tube are placed over the separation area.

DISCUSSION

Liver tumors comprise 1% of all pediatric solid tumors and are more commonly malignant. MHL is the second most frequent type of benign liver tumor in children, surpassed only by hemangioma (2). As with the present case, the usual presentation is a large abdominal mass in an otherwise asymptomatic preschool child. There have been a few reports of fetal and newborn MHL cases, with most having severe presentations, such as respiratory distress or bleeding. Adult MHL is rare. Imaging often demonstrates non-contrast-enhancing septated cysts in the affected liver segments. Serum AFP levels may be elevated, but not to the same extent as those of malignant tumors. Given the age group and presentation of patients, hepatoblastoma is a likely differential diagnosis. However, the AFP levels are considerably higher and cystic lesions are uncommon with hepatoblastoma.

Spontaneous regression of MHL has been reported, especially for highly vascular lesions. Only some reduction in size, rather than actual tumor resolution, has been documented within the short monitoring period of these cases (3). Progressive enlargement is the norm for MHL. Likewise, it is associated with the occurrence of undifferentiated embryonal sarcoma of the liver, a malignant tumor of mesenchymal origin. As such, resection of the involved liver segments is the recommended treatment for MHL (3,4). This, however, can be challenging for massive tumors wherein the resulting FLR may be inadequate.

The minimum FLR often recommended for a hepatectomy is 20%. Methodological and clinical concerns have nonetheless been raised regarding the estimation of liver volumes (5). While there may not be a definitive cut-off, optimizing the residual liver size is an important consideration for hepatic resections. There are several surgical options for liver tumors with insufficient FLR. Transplantation or when suitable two-stage or central hepatectomies may be utilized (5,6). Should these not be practicable, a procedure that increases the FLR prior to resection can be a reasonable option.

Following partial hepatic resections, hepatocyte regeneration is known to occur in the remaining segments. This is triggered by an increased portal venous inflow, leading to a greater influx of intestine-derived growth factors and other changes that promote regeneration. Portal vein embolization or occlusion has thus been employed to deliberately stimulate hypertrophy of the anticipated liver remnant prior to the required resection. The desired level of liver regeneration may take several weeks to be achieved, and this can be detrimental for patients with malignant lesions. As such, other approaches that more substantially redirect hepatic circulation, including transarterial embolization, liver venous deprivation, and radiation lobectomy, have been utilized to accelerate liver regeneration (6,7). With ALPPS, which incorporates ipsilateral portal venous occlusion with collateral vascular interruption through liver separation, portal venous flow is exclusively directed to the contralateral normal segments. Hypertrophy of the latter is thereby further hastened. Among 45 adult patients who had weekly CT scans after the first stage of ALPPS, 85% reached the required FLR by the seventh postoperative day (8). Contingent on the documented adequacy of FLR hypertrophy, resection could be undertaken within a week or two after the first stage of the procedure.

While ALPPS has been utilized in many adult cases, it has not yet been extensively applied in pediatric patients (9). The first reported pediatric ALPPS case was a 6-year-old child with hepatoblastoma (10). A systematic review covering pediatric patients, compared 12 who had ALPPS and nine who underwent only portal vein embolization or ligation before resection. The mean FLR was lower for the ALPPS group (11). Three pediatric patients who had centrally-located hepatoblastoma and who would have been transplant candidates based on PRETEXT stage were recently reported to have successfully undergone ALPPS (12). A partial ALPPS, with preservation of the liver parenchyma

adjacent to the hepatic veins during the first stage, was previously performed in a 54-day-old infant with hepatoblastoma (13). A 9-month-old with a massive MHL and an FLR of 22.7% also underwent ALPPS (14). As had happened with our patient, the course immediately following the first surgery was turbulent. The latter may be attributed to an acute hepatic insufficiency, which does not deteriorate into irreversible liver failure.

There were procedural aspects in the current case that could have been improved. There was undue delay in the performance of the second stage, which undermined the temporal advantage of ALPPS. The handling of the left hepatic vascular and biliary structures during the first stage should have been minimized to lessen the consequent inflammatory reaction and scarring that hampered the subsequent surgery.

CONCLUSION

The case adds to the growing number of pediatric patients with liver tumors who have been treated with ALPPS. While the procedure is utilized more for adults with malignant tumors, its applicability for benign lesions in pediatric patients, is further highlighted in the current report.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Author Contributions

Concept - A.C., K.A.D.L.; Design - A.C., K.A.D.L.; Supervision - A.C., K.A.D.L.; Data Collection or Processing - A.C., K.A.D.L.; Analysis or Interpretation - A.C., K.A.D.L.; Literature Search - A.C., K.A.D.L.; Critical Review - A.C., K.A.D.L.; Writing - A.C., K.A.D.L.

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

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

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LETTER TO THE EDITOR
Turk J Surg 2025;41(1):112-113

Letter to: The use of Bakri balloon to reduce the anastomosis tension in hepaticojejunostomy: An exchange between surgery and obstetrics/gynecology

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KEYWORDS

Balloon, balloon fix, Bakri balloon, obstetrics, surgery

Dear Editor,

Tension-free anastomoses are required for a successful operation. Cartı et al.'s (1) trial is a useful addition to relieve tension on the anastomosis in hepaticojejunostomy by using a Bakri intrauterine hemostatic balloon between the diaphragm and the liver, pushing the liver caudad and thereby decreasing anastomotic tension. We have an addition and comment.

A contrivance to "fix" the Bakri balloon at the site (between the diaphragm and the superior liver surface) may be useful. We have some concern that the balloon may move postoperatively. In the worst scenario, the balloon could be dislodged anteriorly from the liver, preventing its function to decrease anastomotic tension or injuring surrounding tissue. Lateral motion can also occur, which might injure the falciform ligament or some surface vessels on the liver and/or diaphragm, causing bleeding.

A Bakri balloon is slippery and, with intrauterine use, it often descends caudally ("balloon prolapse" into the vagina). To prevent this descent, the balloon's distal drainage hole is tied with a suture, placed at the abdominal wall, with appropriate tension (Figure 1a) (2). After hemostasis is achieved, the suture is cut and removed with the balloon. A similar procedure ("abdominal balloon-pulling") may be applied after hepaticojejunostomy to fix the balloon (Figure 1b). Even without balloon prolapse, the balloon can move at the site (between the diaphragm and liver surface). Inappropriate pushing at the site may cause erosion into the liver and/or diaphragm. With the suture made at distal portion of the balloon, the balloon is anchored distally and proximally, by the suture and balloon shaft. This may enable delicate change of the balloon position, when necessary. The suture should be cut at the time of balloon removal, similar to intrauterine balloon placement.

Cite this article as: Matsubara S, Lefor A. Letter to: The use of Bakri balloon to reduce the anastomosis tension in hepaticojejunostomy: An exchange between surgery and obstetrics/gynecology. *Turk J Surg.* 2025;41(1):112-113

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Received: 24.03.2023
Accepted: 12.06.2023
Publication Date: 27.02.2025

DOI: 10.47717/turkjsurg.2023.6093

Available at www.turkjsurg.com

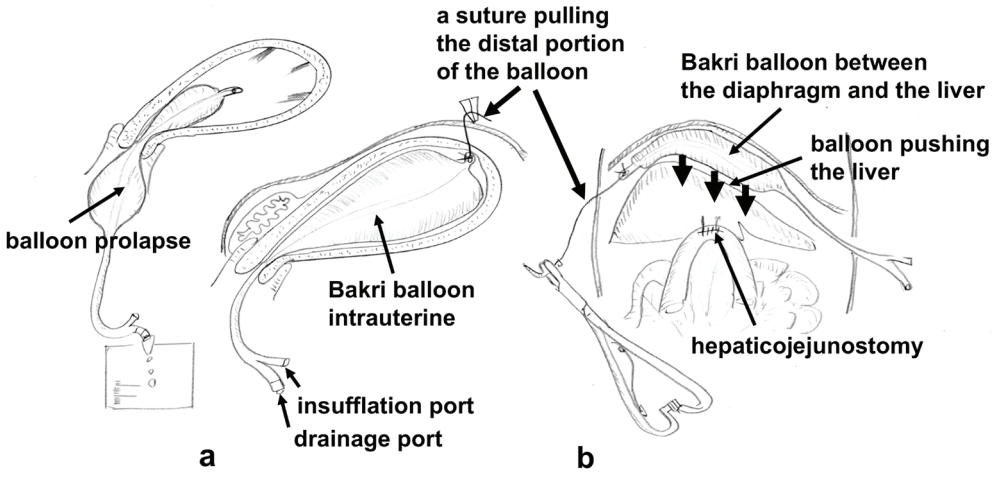

Figure 1. Schema of abdominal traction of a Bakri balloon.

a): Bakri balloon, once placed within the uterine cavity, tends to move to the caudal side (balloon prolapse; left panel). To prevent this, a thread/suture is tied to the distal end of the Bakri balloon (draining hole), its end is placed on the abdominal wall, and it is fixed/pulled on/from the abdominal wall (right panel). b): The same can be done in Bakri-balloon's liver-pushing. This may prevent balloon anterior dislodgement and lateral movement. In the latter, when some situations (for example, concern for erosion into the liver and/or diaphragm) require subtle balloon movement, pulling or loosing this suture/thread may be useful.

Obstetrics and gynecology (OBGYN) have "borrowed" various devices from surgery. The Sengstaken-Blakemore tube was used for hemostasis for obstetric uterine bleeding when a Bakri balloon was unavailable (3). For ovarian cancer surgery, an "intestinal isolation bag" is used to retract the small intestine out of the operative field, facilitating access to deep pelvic lesions. A multi-blade table-mounted wound retractor offered better visualization of the lesion (4). This time, surgery borrowed a device from OBGYN, a Bakri balloon. A Bakri balloon was also successfully used as a "pelvic spacer" for empty pelvic syndrome after pelvic exenteration for colorectal cancer (5). We believe that there may be more opportunities for further exchanges between surgery and OBGYN. This may not be confined to "devices" but can be generalized to knowledge, concepts, and/or experiences.

Lastly, we touch on our concern. During 4-decades of practice in obstetrics (SM) and general surgery (AKL), we have long been taught that surgeons should watch operations, especially in other specialties. An obstetrician should watch a general surgery operation and vice versa. This triggered us to "borrow" some devices/techniques used in other fields. However, the times have changed and the trend in life-work balance may deprive doctors of time to watch operations. Some systems facilitating information exchange and continued communication between surgery and OBGYN may be needed.

Footnotes

Author Contributions

Concept - S.M., A.L.; Design - S.M.; Data Collection or Processing - S.M.; Analysis or Interpretation - S.M.; Literature Search - S.M.; Critical Review - S.M., A.L.; Writing - S.M.

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

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

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