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

TÜRK CERRAHİ DERNEĞİ
1929
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Turkish Journal of Surgery

VOLUME 40
ISSUE 2
JUNE 2024

www.turkjsurg.com

Turkish Journal of Surgery
Volume 40 • Issue 2 • June 2024 • Page 95-182

Turkish
Journal of Surgery

VOLUME 40
ISSUE 2
JUNE 2024

Published by Turkish Surgical Society.

Owner/Editorial Manager
Ahmet Serdar KARACA
(Owner on behalf of the Turkish Surgical Society)

Print ISSN 2564-6850
Elektronic ISSN 2564-7032

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Publishing House

bilimsel tıp yayınevi
www.bilimseltipyayinevi.com

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Web : www.bilimseltipyayinevi.com

Publication Type: Periodical
Place of Printing: Step Dijital
İvedik Organize San. 1420. Cadde No: 58/1-2-3-4-5
Ostim-Yenimahalle/ANKARA
Phone: 0 (312) 395 85 71-72
Printing Date: 28 June 2024

Turkish
Journal of Surgery

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Turkish Journal of Surgery (Turk J Surg) is the official, peer reviewed, open access publication of the Turkish Surgical Society and Turkish surgical community. The journal is published quarterly on March, June, September and December and its publication language is English.

The aim of the Turkish Journal of Surgery is to publish high quality research articles, review articles on current topics and rare case reports in the field of general surgery. Additionally, expert opinions, letters to the editor, scientific letters and manuscripts on surgical techniques are accepted for publication, and various manuscripts on medicine and surgery history and ethics, surgical education and the field of forensic medicine are included in the journal.

As a surgical journal, the Turkish Journal of Surgery covers all specialties, and its target audience includes scholars, practitioners, specialists and students from all specialties of surgery.

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The journal is printed on an acid-free paper.

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06810 Çayyolu, Ankara, Türkiye
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Publisher: Bilimsel Tıp Yayınevi
Address: Bükreş Sokak No: 3/20 Kavaklıdere, Ankara, Türkiye
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INSTRUCTIONS TO AUTHORS

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- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: English abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Material and Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

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Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Material and Methods (with subheadings), Results, Discussion, Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

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Review Articles: Reviews with high citation potential prepared by authors with extensive knowledge on a particular field and whose scientific background has already been proven by a high number of publications in the related field are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

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- All videos will be peer reviewed.
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- Article length: It should not exceed 500 words.
- Reference Number: Not to exceed 5 references

Diagnosis, surgical technique and outcome should be summarized. All important steps and aspects of the surgery should be mentioned in the video. If it is a new surgical technique, appropriately labeled and cited video materials may be used. Authors can use a rare case they have encountered, a surgical technique, or videos using modern technological devices.

The following items must be provided:

- The file of the video written in Word format.
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- All videos must contain an English narration.
- All videos should also be in the highest resolution possible, more details on accepted file types and resolution are available at this link (authors' video article submission guidelines; https://turkjsurg.com/video-article-guidelines).
- The duration of the videos should not exceed five minutes and the maximum file size should be 300Mb.

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All research involving human participants must have been approved by the authors' Institutional Review Board (IRB) or by equivalent ethics committee(s) and must have been conducted according to the principles expressed in the Declaration of Helsinki. Authors should be able to submit, upon request, a statement from the IRB or ethics committee indicating approval of the research. The Journal reserves the right to reject work believed to have not been conducted in a high ethical standard, even when formal approval has been obtained.

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Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	5000	250 (Structured)	50	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1500	250	15	No tables	10 or total of 20 images
Surgical Methods	500	No abstract	5	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

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Subjects must have been properly instructed and have indicated that they consent to participate by signing the appropriate informed consent paperwork. Authors may be asked to submit a blank, sample copy of a subject consent form. If consent was verbal instead of written, or if consent could not be obtained, the authors must explain the reason in the manuscript, and the use of verbal consent or the lack of consent must have been approved by the IRB or ethics committee.

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All animal research must have approval from the authors' Institutional Animal Care and Use Committee (IACUC) or equivalent ethics committee(s), and the research must have been conducted according to applicable national and international guidelines. Approval must be received prior to beginning the research.

Manuscripts reporting animal research must state in the Methods section: The full name of the relevant ethics committee that approved the work, and the associated permit number(s). Where ethical approval is not required, the manuscript should include a clear statement of this and the reason why. The author should provide any relevant regulations under which the study is exempt from the requirement of approval.

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Tables should be included in the main document, presented after the reference list, and numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

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When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in the USA) should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

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Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004. pp. 2290-308.

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Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp. 1561-5.

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Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

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Publisher: Bilimsel Tıp Yayınevi

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FROM THE EDITOR'S DESK
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10.47717/turkjsurg.2024.20240201

Global increase in migration and its impact on surgical clinics

Dear readers of the Turkish Journal of Surgery,

We are glad to be with you again in this new issue. In our June 2024 issue, you will again have the chance to read very interesting articles.

One of them is the article by Varshney and Kapoor. In their review article on hepato-pancreato-biliary tuberculosis, the authors provide a detailed review of the literature on this topic and share their extensive experience (1).

Tuberculosis is a disease that still makes its impact in certain parts of the world and surgeons have challenges in its treatment due to its abdominal complications. The fact that tuberculosis is common only in certain parts of the world does not diminish the importance of this disease. On the contrary, recent events have shown us that a disease that is common in one part of the world can be a major problem for the whole world.

Especially in the last few decades, the number of people migrating for various reasons has increased globally. The International Organization of Migration (IOM), a United Nations institution, monitors and reports on the number of migration and its impact. According to the World Migration Report 2024 published by IOM, the number of migrants has been on a steady increase since the 70's (2). As of 2020, 3.6% of the world population are migrants. It is not difficult to predict that this number will continue to increase due to climate change, ongoing wars, pandemics and economic factors. These migration movements will certainly have medical consequences. A disease that is common in one region may have never been seen before in the new place where migrants have settled. The experience of physicians may be insufficient in the treatment of these diseases. To give an example, there may not have been a case of abdominal tuberculosis in your area for a long time. But in this new era, perhaps very soon a migrant patient will show up in the emergency room with complications. That is why I urge you to read Varshney and Kapoor's article carefully.

It is necessary to prepare all health personnel in advance for the consequences of the migration waves. This is a responsibility that all scientific journals have for public health. As TJS, we try to fulfill this responsibility as much as we can.

In closing, we ask you to se -as always- to send your best work to TJS.

Yours sincerely,

Kaya SARIBEYOĞLU

Editor-in-Chief
Turkish Journal of Surgery

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2. *IOM. World Migration Report 2024. Available from: https://publications.iom.int/books/world-migration-report-2024*

INTEGRATIVE REVIEW
Turk J Surg 2024; 40 (2): 95-103

Hepato-pancreato-biliary tuberculosis: A review

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ABSTRACT

Hepato-pancreato-biliary (HPB) tuberculosis (TB) is a rare form of extra-pulmonary TB that poses a diagnostic dilemma and is a great masquerader of malignancy. It is almost always curable but requires a high degree of suspicion and corroboratory evidence to document its existence. Medline/PubMed was searched with keywords "hepatic", "liver", "biliary" and "pancreatic" with "tuberculosis". Data were gathered and analyzed. Common symptoms of HPB TB include jaundice, weight loss, abdominal pain and other constitutional symptoms that make it indistinguishable from malignancy. Imaging modalities such as ultrasonography, computed tomography, magnetic resonance imaging may reveal dilated intrahepatic biliary radicles, mass lesion, and biliary stricture or enlarged necrotic lymph nodes. Fine-needle aspiration cytology/biopsy, brush biopsy, acid-fast bacilli (AFB) staining and molecular testing may help clinch the diagnosis. Most cases require biliary drainage and initiation of anti-tubercular therapy (ATT) whereas surgery is reserved for medically refractory cases or fibrotic strictures. However, most cases are diagnosed post-operatively on histopathology where pre-operative diagnosis is malignancy. A high index of suspicion, coupled with streamlined investigations, may help identify patients pre-operatively to be managed with ATT as TB is completely curable with medical management in most of the cases.

Keywords: Hepato-pancreato-biliary, jaundice, neoplasms, tuberculosis

INTRODUCTION

Tuberculosis (TB) continues to be prevalent in African and Asian countries like India. The most common site of involvement in TB is the lung, i.e. pulmonary TB (PTB), and extra-pulmonary TB (EPTB) accounts for 15% of all cases of TB (1). Abdominal TB is one of the common types of EPTB. Co-existent active pulmonary TB is found in only around 6-30% of patients with abdominal TB. Abdominal TB is more commonly seen in young adults as compared to PTB which has no age predilection. Abdominal TB is primarily a gastro-intestinal disease and up to two-thirds of the patients with gastro-intestinal TB have co-existent abdominal lymphadenopathy and/or peritoneal involvement. Involvement of the hepato-pancreato-biliary (HPB) system is uncommon in abdominal TB. Hepato-pancreato-biliary TB can be classified into involvement of either a primary organ such as the liver, pancreas or the biliary tree or the adjacent lymph nodes (tubercular lymphadenitis). There are very few case series (largest consisting of 38 patients, from India) of HPB TB published in the literature (2). Isolated pancreatic tuberculosis is extremely rare owing to the resistance provided by the pancreatic enzymes (lipases and deoxyribonucleases) which have anti-mycobacterial properties that interfere with mycobacterial seeding in the pancreas, and consequently, only isolated case reports of pancreatic TB have been described in the literature (3).

Routes of Spread

Hepato-pancreato-biliary tuberculosis can be part of miliary (disseminated) TB or may be a localized involvement of the HPB system. Bacteria can reach the liver and the biliary tract via the hepatic artery from the lungs or via the portal vein from the gastro-intestinal tract. Mycobacteria swallowed with the sputum cause intestinal ulcers and can then gain access to the portal vein causing primary involvement of the liver (granulomatous hepatitis). Intestinal ulcers may heal with time and the patient may thus manifest as isolated HPB TB (4). Pancreas may be involved by contiguous retroperitoneal lymph nodes. Enlarged adjacent periportal, pericholedochal or peripancreatic tuberculous nodes may compress or caseating tuberculous

Cite this article as: Varshney P, Kapoor VK. Hepato-pancreato-biliary tuberculosis: A review. Turk J Surg 2024; 40 (2): 95-103.

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Received: 23.01.2024
Accepted: 14.03.2024
Available Online Date: 28.06.2024

DOI: 10.47717/turkjsurg.2024.6338

lymph nodes may rupture into the cystic duct/common bile duct/pancreatic duct causing cholecystitis/cholangitis/pancreatitis. A stricture may form in these ducts as a result of healing by fibrosis after antitubercular therapy (ATT).

Clinical Presentation

Most common (80%) manifestation of HPB TB is pain while other symptoms like jaundice, pruritus, and gastric outlet obstruction (GOO) may be present depending upon the site of involvement. Constitutional symptoms of TB such as fever (typically low-grade with evening rise), night sweats, anorexia and weight loss may be present in one-third of the patients with HPB TB. Symptoms in most patients with HPB TB may closely resemble those of HPB malignancy further contributing to the diagnostic dilemma. Co-existent active PTB is seen in 6-38% of patients with HPB TB (5).

Liver is the most common site of involvement in HPB TB. Hepatic TB manifests most commonly as abdominal pain (40-83%), followed by fever (30-100%), hepatomegaly (10-100%) and less commonly as jaundice (0-60%), splenomegaly (0-40%) and ascites (5-25%) (6).

The order of involvement in the biliary system is as follows: Biliary tree, hilar lymph nodes followed by the gall bladder (GB).

Biliary tuberculosis may manifest as jaundice caused by the enlarged pericholedochal lymph nodes, pain and weight loss. Involvement of the intrahepatic biliary radicles (IHBR) by hepatic tubercular granulomas results in multiple and complex strictures which may resemble stone disease, cholangiocarcinoma or primary sclerosing cholangitis (PSC) (7). Isolated GB TB may present with features of acute cholecystitis or as a GB mass mimicking GB cancer (GBC). Rarely, it may even present as a cholecytoduodenal or cholecystocolic fistula (8,9).

Pancreatic TB may manifest as a mass resembling malignancy in 80% of the patients or as an abscess in around 10% (9). Concomitant peripancreatic lymph nodal involvement is seen in half of these patients. If the head of the pancreas is involved, pain (75%) and obstructive jaundice (20%) will be the predominant symptoms (10). Other presentations may include acute/chronic pancreatitis, gastro-intestinal hemorrhage secondary to splenic vein thrombosis (11-13). 50-70% of pancreatic TB is seen in patients less than 30 years of age (11).

Diagnosis

Most of the patients with HPB TB may have a history of TB or a co-existing immunocompromised state such as HIV/AIDS, long-term intake of steroids or use of biologicals. A thorough history with a high index of suspicion may help suspect HPB TB pre-operatively, especially in endemic areas. Basic investigations like Montoux test, inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may provide contributory evidence but are seldom sufficient to make the diagnosis. A positive Montoux test is very less reliable owing to the false-positive rates, especially in endemic areas and false-negative rates, especially in immunocompromised states (14). Chest X-ray evidence of healed or active pulmonary or pleural TB may support the diagnosis of HPB TB but a normal chest X-ray does not rule out the diagnosis of TB.

Imaging modalities such as contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP) may provide some clues in diagnosing HPB TB but are not specific. Hepatic TB may be either miliary or localized. Miliary hepatic TB, caused by hematogenous dissemination from an extrahepatic site via the hepatic artery, is the commoner variant and presents as diffused studding of the liver with tubercles up to 2 mm in size (6,15). Hepatic TB may manifest as multiple micro-abscesses or as micro-calcifications in the healing phase, dispersed in the liver. Localized hepatic TB, seen in one-fifth of the cases of hepatic TB, has an origin in the gastro-intestinal system and spreads via the portal vein with larger tubercles located near the portal triads. Imaging findings consistent with miliary TB include multiple dispersed low-density nodules while those with localized hepatic TB include larger nodules with enhancement at the periphery and calcifications (6). These nodules may mimic metastases or primary liver malignancy (4).

CT findings of pancreatic TB include a focal mass with mixed cystic attenuation with thin rim of peripancreatic enhancement and peripancreatic lymphadenopathy. Solitary parenchymal lesions are seen in two-thirds of the patients, whereas multifocal lesions may be seen in the remaining one-third (11,16). Calcification may be seen in 56-70% of cases and may range from punctuate to coarse (16). Even vascular invasion has been seen in up to one-third of patients with pancreatic TB, and it may appear as unresectable or borderline resectable pancreatic malignancy on imaging (17). Sometimes, the appearance may mimic that of a mucinous cystic neoplasm (MCN) (18). Pancreatic involvement may occur as part of disseminated (miliary) disease, involvement from retroperitoneal lymph nodes or as primary pancreatic TB (10). GB TB may present as a thick-walled GB on imaging (US, CT, MRI) leading to the diagnostic dilemma of GBC. Regional LNs may be enhanced in HPB TB. Ring enhancement or low-density areas within enlarged lymph nodes may indicate TB.

Sollano et al. have described the characteristic cholangiography features of biliary TB like pruning of the distal intrahepatic ducts, tight hilar strictures with dilated IHBR long smooth stricture of the distal bile duct (1-3). Biliary TB may mimic primary biliary malignancy or primary sclerosing cholangitis (PSC) on cholangiography (14).

Endoscopic ultrasound (EUS) may help to better characterize biliary involvement, especially of the lower CBD and enable a guided FNAC/biopsy from the thickened CBD or the enlarged

lymph nodes which may be crucial in clinching the diagnosis.

Magnetic resonance cholangiopancreatography (MRCP) can help delineate GB or pancreatic mass, the level and extent of biliary involvement and plan a subsequent biliary drainage procedure but is not of much diagnostic significance (8).

FDG PET has also been used but has not been found to be useful in differentiating TB from malignancies as both can be FDG-avid (19).

Laboratory parameters in HPB TB include elevated alkaline phosphatase (ALP), raised gamma-glutamyl transpeptidase (GGTP) and less commonly elevated liver enzymes [alanine transaminase (ALT) and aspartate transaminase (AST)]. Serum albumin levels may be low with reversal of the albumin: Globulin (A:G) ratio indicating a chronic debilitating illness (6). Serum amylase and lipase levels are not much useful owing to their positivity in only one-fourth of cases with pancreatic TB (9).

Image-guided fine needle aspiration cytology (FNAC) or biopsy may be done from highly suspicious areas. Endoscopic ultrasound-guided biopsy is superior to US or CT-guided biopsy (9). These biopsies should be subjected to both microbiological and histopathological examination. Microbiological methods include acid-fast bacilli (AFB) smear examination (sensitivity 0-60%) and AFB culture (sensitivity 0-10%) while histopathological examination shows caseating epithelioid granulomas with Langhan's giant cells (sensitivity 14-100%) (6,20). Caseation and multinucleated Langhan's giant cells differentiate TB from other granulomas, i.e. sarcoid. Latest molecular-based diagnostic modalities, i.e. nucleic acid amplification tests (NAAT) such as GeneXpert, interferon-gamma (IFN-γ) release assays (IGRA), polymerase chain reaction (PCR), multiplex-PCR, can also be performed on the biopsy specimens (21-23). Bile obtained during ERCP can be subjected to AFB staining as well as PCR for diagnosing TB. Brush cytology may be obtained during ERCP although the yield is low (24). Liver biopsy is sometimes required in cases of hepatic abscess not responding to conventional therapies. Tuberculosis DNA may be assessed in blood and bile samples in patients having a high index of suspicion. Even tumor markers like CA 19-9 may be elevated in HPB TB owing to biliary obstruction.

In these cases, the co-existent involvement of the pulmonary system should be actively looked for on chest X-ray, CT imaging, bronchoscopy and broncho-alveolar lavage (BAL). Even extra HPB sites in the abdomen such as peritoneum, omentum must be carefully screened for involvement in all these cases (15). Serum adenosine deaminase (ADA) levels of the ascitic fluid may be an indicator of TB as the etiology of the peritoneal disease.

The suggested sequence of investigations for the diagnosis of HPB TB is biochemical, imaging, molecular, histological, and microbiological. A definitive diagnosis of HPB TB may be very difficult in the absence of biopsy and only surgical intervention with a suspicion of malignancy may yield the final diagnosis in majority of these patients. In a series from a large center in India, none of the seven patients with HPB TB could be identified pre-operatively (5). In another series, only four (three cases of pancreatic TB, diagnosed on FNAC of presumed unresectable cancer and one case of hilar TB diagnosed on cytological evaluation of bile obtained during biliary drainage for cholangitis) out of 18 patients of HPB TB could be diagnosed pre-operatively (8). A large series of 38 patients of HPB TB included hepatic TB in 20 patients, biliary TB in 15 and mixed variant in three patients with the patients being diagnosed on the basis of microbiological and histopathological features and responding well to anti-tuberculous therapy (ATT) (2).

Therapeutic trial of ATT without a confirmed diagnosis has been given in a few cases but a fibrotic reaction following ATT has been seen in 6-25% of cases leading to worsening of the jaundice further re-iterating the diagnosis of malignancy and prompting endoscopic/surgical intervention (25,26).

Treatment

Tuberculosis is a benign infectious disease and is curable with medical management without resorting to surgical resections if the diagnosis can be made pre-operatively (5,8). Management is the prompt initiation of ATT drugs which may provide resolution of symptoms. The literature recommends the use of standard first-line anti-tuberculous drugs for 6-12 months. Multi-drug resistance (MDR) TB and drug-induced hepatoxicity mandate the use of alternative regimes. Worsening of jaundice in case of biliary strictures has been reported in 6-25% of patients due to fibrotic reaction that may develop after the initiation of ATT (25,26). Endoscopic intervention and stenting may be required in a few cases to decrease the serum bilirubin level before ATT is started. Some case series have described initiating treatment with full-course ATT despite initial abnormal LFTs unless evidence of chronic liver disease (CLD) is present (2).

Unfortunately, only a few patients can be diagnosed with investigations, and one may have to resort to surgical procedures for obtaining diagnosis and management. Surgery remains the mainstay of diagnosing HPB TB as pre-operative diagnosis is difficult. A large variety of surgical interventions varying from simple cholecystectomy to pancreatoduodenectomy and extended liver resections with a pre-operative suspicion of malignancy have been described in literature but with better outcomes in terms of morbidity and mortality when compared to malignant lesions.

Surgical options for HPB TB are varied and primarily depend on the site of involvement and the performance status of the patient (Table 1). Localized isolated hepatic TB may require surgical interventions varying from anatomical hepatectomies to just enucleation of the mass or drainage of abscesses in addition to the ATT (6). Anecdotal case reports of biliary TB symptoms

Table 1. Summary of cases of hepato-pancreato-biliary cases in literature

No	Study (Reference no.)	No of cases	Diagnosis	Pre-operative evidence for TB (FNAC/biops/brush cytology)	Management (all patients have received ATT as part of management)	Post-operative biopsy +ve for TB
1	Narayan et al. (29)	1	Cholestatic jaundice with disseminated tuberculosis	FNAC from cervical LN and liver lesions	ATT only	NA
2.	Eso et al. (30)	1	Granulomatous hepatitis with disseminated BCG injection	Liver biopsy	ATT only	NA
3.	Chong et al. (15)	1	Obstructive jaundice due to biliary TB and ampullary carcinoma	Bile aspirate and hilar stricture biopsy positive for AFB, Ampullary biopsy positive for malignancy	Whipple's surgery	Yes
4.	Jethwani et al. (31)	1	Obstructive jaundice with distal CBD stricture	PCR of bile aspirate, axillary LN biopsy +ve	ERCP stenting, ATT	NA
5.	Durairajan et al. (32)	3	1. Obstructive jaundice with mid CBD stricture	Brush cytology-non contributary	Open cholecystectomy with Roux-en-Y HJ	Yes
			2. Obstructive jaundice with mid CBD stricture	Brush cytology +ve for malignancy initially, TB after review	Radical extrahepatic bile duct excision with Roux-en-Y HJ	Yes, no malignancy
			3. Acute calculus cholecystitis	NA	Subtotal cholecystectomy	Persistent sinus
6.	Saluja et al. (8)	18	1. Hepatic TB	-ve	Segment VIII excision with CBD exploration and T-tube drainage	Yes
			2. Hepatic TB, splenic TB	-ve	Left lateral segmentectomy with splenectomy and chlecystojejunostomy	Yes
			3. GB TB	-ve	Enbloc resection of GB, segment IVB, V, with LN resection antrum and 1st part duodenum, GJ	Yes
			4. GB TB	-ve	Cholecsytectomy with omental biopsy	Yes
			5. GB TB	-ve	Cholecystectomy and lymph node biopsy	Yes
			6. Periportal LN TB, chronic cholecystitis	-ve	Cholecystectomy with CBD exploration with T tube drainage with LN biopsy	Yes
			7. Periportal LN TB, chronic cholecystitis	-ve	Cholecystectomy with CBD exploration with T tube drainage with frozen section	Yes (frozen biopsy)
			8. Periportal LN TB, chronic cholecystitis	-ve	Exploratory laparotomy + frozen section + cholecystectomy & Roux-en-Y choledochojejeunostomy	Yes (frozen biopsy)
			9. Bile duct TB	-ve	Palliative hepaticojejunostomy, LN biopsy, CBD bx	Yes
			10. Periportal LN TB, bile duct-no evidence of malignancy	-ve	Hepaticojejunostomy with frozen section	Yes

Table 1. Summary of cases of hepato-pancreato-biliary cases in literature (continue)

No	Study (Reference no.)	No of cases	Diagnosis	Pre-operative evidence for TB (FNAC/biops/brush cytology)	Management (all patients have received ATT as part of management)	Post-operative biopsy +ve for TB
			11. Pancreatic TB	-ve	Distal pancreatectomy, splenectomy with choledochojejunostomy	Yes
			12. Peripancreatic LN TB	-ve	Pancreaticoduodenectomy	Yes
			13. Pancreatic and peripancreatic LN TB	-ve	Pancreaticoduodenectomy	Yes
			14. Pancreatic and peripancreatic LN TB	-ve	Pancreaticoduodenectomy	Yes
			15. Pancreatic TB	FNAC from right supraclavicular LN and pancreatic head mass +ve for TB	ATT only	NA
			16. Pancreatic TB	FNAC from pancreatic head mass +ve for TB	ATT only	NA
			17. Pancreatic TB	FNAC from pancreatic head mass +ve for TB	ATT only	NA
			18. Bile duct TB	Brush cytology +ve for TB	ERCP stenting, ATT	NA
7.	Padhiari et al. (33)	5	1. Pseudotumor of CBD	No	Surgical (procedure NA)	Yes
			2. Pseudotumor of CBD	No	Surgical (procedure NA)	Yes
			3. CBD stricture	Brush cytology +ve for TB	ERCP stenting	NA
			4. CBD stricture	Brush cytology +ve for TB	ERCP stenting	NA
			5. CBD stricture	PCR of bile aspirate +ve for TB	ERCP stenting	NA
8.	Alsawat et al. (27)	1	Obstructive jaundice with distal CBD stricture	Mediastinal LN +ve for TB, brush cytology-inconclusive	ATT only	NA
9.	Sanabe et al. (34)	1	Pancreatic TB	-ve	Distal pancreatectomy with total gastrectomy with partial resection of transverse colon	Yes
10.	Prasad et al. (14)	1	Obstructive jaundice with hilar stricture	-ve	Cholecystectomy with T tube placement	Yes (frozen biopsy)
11.	Lee et al. (35)	1	Obstructive jaundice with hilar stricture	Bile aspirate +ve for TB, lung nodule +ve for TB	PTBD	NA
12.	Govindswamy et al. (5)	7	Duodenal perforation with pericholedochal and para aortic lymphadenopathy	-ve	Perforation closure, GJ, FJ	Yes
			Pancreatic TB	-ve	Cholecystectomy, HJ	Yes
			Obstructive jaundice with hilar stricture	-ve	Cholecystectomy, HJ	Yes
			Obstructive jaundice with hilar stricture	-ve	Cholecystectomy, HJ	Yes
			GB TB with portal vein thrombosis	-ve	Cholecystectomy, GB biopsy	Yes

Table 1. Summary of cases of hepato-pancreato-biliary cases in literature (continue)

No	Study (Reference no.)	No of cases	Diagnosis	Pre-operative evidence for TB (FNAC/biops/brush cytology)	Management (all patients have received ATT as part of management)	Post-operative biopsy +ve for TB
			GB TB with Mirrizzi's syndrome type II with cholecystoduodenal fistula	-ve	Cholecystectomy, duodenal repair, GJ	Yes
			GB TB	-ve	Cholecystectomy, HJ, GJ, JJ	Yes
13.	Ando et al. (36)	1	Obstructive jaundice with left hepatic duct stricture and enlarged hilar LN	EUS FNAC of hilar LN +ve for TB	ERCP stenting, ATT	NA
14.	Iwai et al. (37)	1	Obstructive jaundice with hilar stricture	PCR of bile +ve for TB	PTBD, ATT	NA
15.	Yeh et al. (38)	2	Obstructive jaundice with hilar stricture	-ve	HJ	Post op biopsy +ve for TB
			Obstructive jaundice with hilar stricture	PCR of bile +ve for TB, brush cytology -ve	PTBD, ATT	NA
16.	Kok et al. (39)	4	Obstructive jaundice with distal CBD stricture	FNAB +ve for TB	ERCP stenting, ATT	NA
			Obstructive jaundice with hilar stricture	Brush cytology +ve for TB	Left cholangio-jejunostomy	NA
			Obstructive jaundice with CBD stricture	-ve	Open biliary stenting	Yes (frozen biopsy)
			Obstructive jaundice with hilar stricture	-ve	HJ	Yes (frozen biopsy)
17.	Hickey et al. (6)	1	Obstructive jaundice with CBD and hilar stricture	Inguinal LN +ve for TB	ERCP stenting	NA
18.	Valeja et al. (40)	1	Obstructive jaundice with CBD stricture	-ve	HJ	Yes (frozen biopsy)
19.	Inal et al. (41)	1	Obstructive jaundice with CBD stricture	Biopsy via PTBD	PTBD stenting	NA
20.	Behera et al. (42)	1	Obstructive jaundice with CBD stricture	-ve	HJ	Yes (frozen biopsy)
21.	Bearer et al. (43)	1	Obstructive jaundice with CBD stricture	ERCP assisted bile cytology	ERCP stenting	NA
22.	Ratanarapee et al. (44)	1	Obstructive jaundice with CBD stricture	-ve	T-tube drainage	Yes (frozen biopsy)
23.	Fan et al. (13)	1	Obstructive jaundice with CBD stricture	-ve	PTBD stenting	Yes (frozen biopsy)
24.	Abascal et al. (45)	1	Obstructive jaundice with multiple CBD stricture	-ve	Laparotomy and biopsy Died of sepsis	Yes (frozen biopsy)

AFB: Acid-fast bacilli, ATT: Anti-tubercular treatment, BCG: Bacilli Calmette-Guerin, CBD: Common bile duct, ERCP: Endoscopic retrograde cholangio-pancreatography, EUS: Endoscopic ultrasound, FJ: Feeding jejunostomy, FNAB: Fine needle aspiration biopsy, FNAC: Fine needle aspiration cytology, GB: Gall bladder, GJ: Gastrojejunostomy, HJ: Hepaticojejunostomy, LN: Lymph node, NA: Not available, PCR: Polymerase chain reaction, PTBD: Percutaneous transhepatic biliary drainage, TB: Tuberculosis.

being relieved by ATT exist, but surgery remains the mainstay of treatment given the diagnostic dilemma and the presence of mechanical biliary obstruction in majority of the cases (27). Furthermore, fibrotic strictures are less prone to respond to ATT alone. Sometimes, these biliary lesions may become fibrotic in response to ATT further exacerbating the jaundice. Cholecystectomy and hepaticojejunostomy are the most commonly performed procedures for biliary TB. T-tube drainage of the CBD may be considered in these cases (5).

Isolated GB TB may mandate cholecystectomy with on-table frozen section, extended (radical) cholecystectomy, or a cholecystectomy with bile duct resection and reconstruction in the

form of a bilio-enteric anastomosis. Various surgeries ranging from pancreatoduodenectomies to distal pancreatosplenectomy have been performed for pancreatic TB, with a suspicion of malignancy in the absence of a conclusive pre-operative or intraoperative diagnosis (8). Sometimes, multi-visceral resection may be contemplated if the suspicion for malignancy is high (5).

HIV and HPB TB

Immunocompromised patients, like those with HIV/AIDS, have more severe manifestations of TB besides being more susceptible to TB reactivation and dissemination (6). EPTB is more common in these patients. Co-existent HIV infection must be actively sought in all patients with HPB TB. A higher degree of clinical suspicion coupled with a regular follow up may help detect patients with HPB TB in presence of HIV/AIDS early thereby avoiding the associated morbidity. The WHO recommends starting anti-retroviral therapy (ART) 2-8 weeks after starting ATT, especially in drug-resistant cases (28). Both ART and ATT may have complex drug interactions which must be kept in mind while treating these patients.

CONCLUSION

Hepato-pancreato-biliary TB is rare even in areas where TB is still common. It may present with varied signs and symptoms and the non-specific findings of biochemical and imaging investigations may contribute to the diagnostic conundrum, especially with HPB cancer, and it is almost impossible to make a pre-operative diagnosis of HPB TB. It is a great mimic of other benign or malignant HPB lesions. It should be considered as a differential diagnosis, especially in areas where TB is still endemic. Certain features that may hint towards the diagnosis of HPB TB are long duration of symptoms, pain out of proportion to the mass, mild (cf. deep in malignancy) jaundice, a history of TB, other systemic manifestations of TB like pulmonary or generalized lymph node involvement, associated involvement of other abdominal organs. Surgical interventions are frequently required in the absence of a definitive pre-operative diagnosis of TB and suspicion of malignancy. A high index of suspicion coupled with streamlined investigations may help identify these patients especially in endemic areas as TB is completely curable with medical management with ATT in most of the cases. The co-existence of HPB TB and HIV must be actively searched for in all cases.

Author Contributions: Concept - VKK; Design - VKK; Supervision - VKK; Fundings - VKK; Materials - VKK; Data Collection and/or Processing - PV; Analysis and/or Interpretation - PV; Literature Search - PVS; Writing Manuscript - PV, VKK; Critical Reviews - VKK.

Peer-review: Externally peer-reviewed.

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

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

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BÜTÜNLEYİCİ DERLEME-ÖZET
Turk J Surg 2024; 40 (2): 95-103

Hepato-pankreato-biliyer tüberküloz

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ÖZET

Hepato-pankreato-biliyer (HPB) tüberküloz (TB), tanısal bir ikilem oluşturan ve maligniteyi maskeleyen nadir bir ekstra pulmoner TB formudur. Neredeyse her zaman tedavi edilebilse de varlığını belgelemek için yüksek derecede şüphe ve doğrulayıcı kanıtlar gerektirir. Medline/PubMed'de "hepatic", "liver", "biliary" ve "pancreatic" anahtar kelimeleri "tuberculosis" ile birlikte aranmıştır. Veriler toplanmış ve analiz edilmiştir. Hepato-pankreato-biliyer TB'nin yaygın semptomları arasında sarılık, kilo kaybı, karın ağrısı ve maligniteden ayırt edilemeyen diğer semptomlar yer almaktadır. Ultrasonografi, bilgisayarlı tomografi, manyetik rezonans görüntüleme gibi görüntüleme yöntemleri dilate intrahepatik safra kanalları, kütleyi ve safra yolu darlığını veya genişlemiş nekrotik lenf nodlarını ortaya çıkarabilir. İnce iğne aspirasyon sitolojisi/biyopsisi, fırça biyopsisi, aside dirençli basil (AFB) boyaması ve moleküler testler tanıyı kesinleştirmeye yardımcı olabilir. Vakaların çoğunda biliyer drenaj ve anti-tüberküloz tedavinin (ATT) başlatılması gerekirken, medikal olarak dirençli vakalar veya fibrotik striktürler için cerrahi uygulanmaktadır. Bununla birlikte, çoğu vakada ameliyat öncesi tanı malignite iken ameliyat sonrası histopatoloji ile tanı konmaktadır. Yüksek bir şüphe endeksi ve kolaylaştırılmış incelemeler, vakaların çoğunda tıbbi tedavi ile TB tamamen iyileştirilebilir olduğundan ATT ile yönetilecek hastaların ameliyat öncesinde belirlenmesine yardımcı olabilir.

Anahtar Kelimeler: Hepato-pankreato-biliyer, sarılık, tümörler, tüberküloz

DOİ: 10.47717/turkjsurg.2024.6338

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (2): 104-110

Pancreatic fistula and bleeding following choledochal cyst excision: Experience of two decades

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ABSTRACT

Objective: Choledochal cyst excision (CDCE) with hepaticojejunostomy is standard of care in choledochal cysts. Complications related to inadequate healing of distal stump like post-operative pancreatic fistula (POPF) and bleeds have not been addressed in literature. We report two decade experience with these complications following CDCE.

Material and Methods: Retrospective analysis of demographics, operative details and post-operative course of patients who developed POPF (according to International Study group of Pancreas surgery classification) and bleeds following CDCE were compared with those who did not develop these complications.

Results: POPF was seen in in 34 out of 377 operated patients (incidence of 9%). In those with POPF, 24/34 (70%) had biochemical leak and 10/34 (30%) had clinically relevant POPF (B and C). All grade B POPF 6/34, required additional percutaneous drains while all grade C 4/34 required operative intervention to control sepsis. There was no mortality in the POPF group while two patients in control died from non-surgical causes. A difficult distal stump precluding closure was the only factor found associated with subsequent development of POPF (5.9% in POPF group vs. 0.5% in control group, p= 0.03). Post-operative bleeding was seen in 2 (6%) patients with POPF and in 5/343 (1.4%) in control group.

Conclusion: It is possible to anticipate development of POPF intraoperatively, during CDCE. Most of these POPFs can be managed conservatively with adequate drainage. Surgery is required only in grade C fistula and bleeds. Since these are isolated pancreatic fistulas, unlike those seen after pancreaticoduodenectomy, they are associated with more favourable outcomes.

Keywords: Choledochal cyst, choledochal cyst excision, biliary cyst, Roux-en-Y hepaticojejunostomy, post-operative pancreatic fistula, pancreatic fistula

INTRODUCTION

Choledochal cyst (CDC) is a congenital abnormal dilatation of the biliary tract in the absence of any acute obstruction constituting about 1% of benign biliary diseases (1,2). The high likelihood of complications like cholangitis, pancreatitis and a substantial lifetime risk of cholangiocarcinoma mandate a complete cyst excision once the diagnosis has been made (3). There is considerable literature regarding strategies for difficult to excise CDC and post-operative complications related to transacted proximal end, like bile leak and hepaticojejunostomy stricture (4). However, there is scant literature on the consequences of blowout of distal stump following choledochal cyst excision (CDCE), like post-operative pancreatic fistula (POPF) and secondary haemorrhage. POPF and bleeds following biliopancreatic surgery are recognised as important complications resulting in considerable morbidity prolonging hospital stay and even mortality. Although there are several management guidelines and strategies for the prevention of these complications following pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), there is little published experience on these complications following CDCE. In this study, from a tertiary care teaching hospital, it was aimed to report our experience of natural course and management of POPF and bleeds following CDCE (5).

MATERIAL and METHODS

Institutional ethics committee clearance was obtained for the study. Data pertaining to demography, clinical features, operative findings, surgical procedure details and post-operative course were extracted from hospital records of all patients who underwent CDCE in the department of surgical gastroenterology, a tertiary care teaching hospital, from January 2000 to December 2020. Clinical presentation, prior history of acute pancreatitis, episodes of cholangitis and management

Cite this article as: Katakam SK, Sharma S, Behari A, R R, Il Kumar A, Singh A, et al. Pancreatic fistula and bleeding following choledochal cyst excision: Experience of two decades. Turk J Surg 2024; 40 (2): 104-110.

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Received: 14.02.2024
Accepted: 18.04.2024
Available Online Date: 28.06.2024

DOI: 10.47717/turkjsurg.2024.6354

strategies and upper abdomen surgery were noted (6-8). The CDC were classified on basis of cholangiographic findings (MRCP or ERCP) as suggested by Alonso Lej (9).

Surgical Technique

All type I and IV CDCs underwent open complete excision of the extrahepatic biliary tree with restoration of bilio-enteric continuity via a Roux-en-Y hepaticojejunostomy (RYHJ) at hilum (10,11). While proximal mobilization of the CDC till the biliary confluence is straightforward unless the surgical dissection is made difficult by adhesion of the cyst to hepatic artery and portal vein secondary to inflammation, excision of the distal segment of CDC necessitates dissection from the pancreatic tissue in addition to the hepatic artery and portal vein (12,13). This might be particularly challenging, especially if the surrounding planes are inflamed and friable and/or the main pancreatic duct is intimately related. We maintain the plane of dissection right on the cyst wall, controlling the vessels from epicholedochal plexus with bipolar coagulation, taking care to not deviate into the pancreatic parenchyma and injure the pancreatic duct during this step. The CDC is opened in order to identify the opening of the ventral pancreatic duct from within (when possible), before transecting the CDC just below the start of waisting. We ensure vascularity at this end by flush, sharp division. The distal end is flushed with saline through a feeding tube to remove any calculi or protein plugs in the common segment. The end is then secured with continuous delayed absorbable monofilament polydioxanone suture. The suture size depends on local factors, 5-0 for thin, friable duct and 3-0 for non-inflamed duct wall holding sutures well. We do not use staplers for distal transection since we ensure it is in the narrowed distal end. RYHJ restores biliary drainage. Single wide bore (24Fr) soft latex drain is placed in the Morrison's pouch.

The drain fluid is assessed daily for volume and character (serous/haemorrhagic) and amylase values are obtained on days three and five. The drain is removed when output is clear, output less than 50 cc and amylase value less than three times if serum amylase values of the day.

Those who develop POPF are monitored for clinical signs of peritonitis or sepsis. Any unexplained tachycardia, fever, leucocytosis is evaluated with a contrast enhanced CT scan (CECT). If any undrained collection is identified, image guided percutaneous drains are placed. The patient is rigorously monitored. If sepsis persists or signs of generalised peritonitis develop, exploratory laparotomy with lavage and drainage is done. Any patient with haemorrhagic drain output is investigated with triple phase CT angiogram (TPCTA). If the potential bleeding source is identified, it is further evaluated for suitability for endovascular intervention. If no source is identified and there is increased haemorrhagic output with drop in haemoglobin or change in patient hemodynamics, the patient is taken for surgical exploration.

Inclusion criteria: All patients undergoing open CDCE in a single unit, whose drain fluid amylase (DFA) on post-operative day three was more than three times of upper limit normal amylase level.

Exclusion criteria: Patients who underwent CDCE along with any additional pancreatic surgery and patients who were referred after CDC excision done elsewhere, were excluded.

Operational definitions: POPF following choledochal cyst was defined as elevation of drain fluid amylase (DFA) to more than three times upper normal serum amylase levels (90 mg/dL) on or after post-operative day three (14). These were further subdivided into the following:

- Type A POPF or Biochemical leak included patients with documented POPF without any features of sepsis and who did not require any intervention.
- Type B POPF included patients with documented POPF, with signs of infection/without organ failure, requiring percutaneous or endoscopic drainage, angiographic procedures for bleeding.
- Type C POPF included patients with documented POPF, with organ failure and/or requiring surgical intervention.

Difficult distal stump: For the purpose of this study the term is used for denoting difficulty in dissecting and or suturing the distal part of intrapancreatic portion of choledochal cyst due to inflammation (15).

Statistical Analysis

Quantitative data was presented as mean ± standard deviation and range. Qualitative data were described as frequencies given in percentage values, based on the distribution of data. Comparisons between two groups were performed using Mann-Whitney U test (continuous variables) and Chi-square test (categorical variables). All statistical tests were two-sided, and $p< 0.05$ were considered statistically significant. Statistical analyses were performed using SPSS software, version 23, IBM Corp., Armonk, NY, United States of America).

RESULTS

During the period spanning two decades, we identified 38 cases of POPF from a total of 381 operated cases of choledochal cysts. After review, four cases were excluded as they underwent an additional procedure (pancreatoduodenectomy= 1, Duodenal preserving pancreatic head resection= 1, lateral pancreatojejunostomy= 2). For the purpose of this study, 34 patients with POPF (cases) were compared to 343 patients without POPF (controls) (Figure 1). All cases were performed by open either midline or subcostal incision.

In the entire cohort, the most common symptom at presentation was abdominal pain in 341/377 (90%) followed by jaundice in 105/377 (28%), and fever in 73/377 (19%). Lump, as a presenting

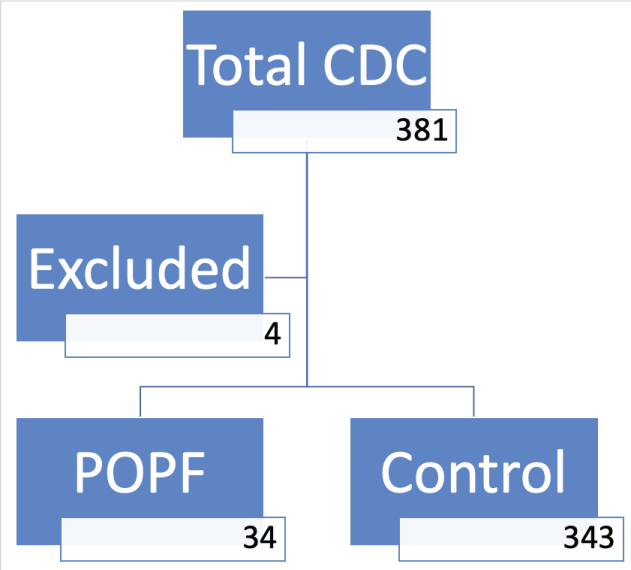

Figure 1. Consort diagram.
CDC: Choledochal cyst, POPF: Post-operative pancreatic fistula.

symptom, was seen in only 6/377 (1%) while 46/377 (12%) presented with all three features of cholangitis.

Table 1 compares the two groups with regard to demographics, clinical characteristics, type of choledochal cyst [Alonso Lej classification (9)], cystolithiasis, previous history of pancreatitis or cholangitis before surgery, need for prior biliary interventions, prior history of abdominal surgery, intra-operative findings like pericholedochal inflammation, difficult distal stump, average duration of intraoperatively placed drain retained, and hospital stay.

One hundred twenty two/377 (32%) patients had some feature to suggest cholangitis; however, most responded to antibiotics and biliary intervention was required in only 90/377 (24%) of them. Table 2 gives the details of biliary intervention. More patients were managed with internal biliary drainage, and percutaneous transhepatic biliary drainage (PTBD) was used only if the patient was deemed unfit due to organ failure or technical difficulties. The nature of biliary intervention before surgery did not impact development of POPF (p= -0.352).

Table 1. Demographics, intraoperative findings, and post-operative course following CDCE

Factors	POPF (n= 34)	Control (n= 343)	p	OR
Age	32 years (7-49 years)	32.5 years (<1-76 years)	0.9	0.3
Sex Males Females	 6 (18%) 28 (82%)	 83 (24%) 260 (76%)	0.39	0.8
Choledochal cyst type	Type 1-22 (64.7%) Type 4-12 (35.3%)	Type 1-264 (76.9%) Type 4-79 (23.1%)	0.16	0.8
History of pancreatitis	1 (2.9%)	23 (6.7%)	0.856	0.4
Prior cholangitis episodes	11 (32.3%)	111 (32%)	0.9	0.3
Cystolithiasis	11 (32.4%)	93 (27.1%)	0.389	1.3
Prior upper abdomen surgery	9 (26.5%)	69 (20.1%)	0.379	1.4
Prior biliary interventions	10 (29.4%)	80 (23.3%)	0.427	1.3
Pericholedochal inflammation	19 (55.9%)	165 (48.1%)	0.657	0.8
Difficult distal stump	2 (5.9%)	2 (0.5%)	0.032	0.7
Post-operative bleed	2 (5.9%)	5 (1.5%)	0.75	1.3
Average duration of drain	15 days (5-95 days)	5 days (1-15 days)	0.001	1.5
Average hospital stay	19 days (5-96 days)	7 days (3-38 days)	0.001	1.2

Table 2. Details of biliary intervention in unresolved cholangitis

Prior Intervention to Biliary system	POPF[a]	Control group	p
Endoscopic drainage	8 (80%)	71 (89%)	0.352
PTBD[b]	2 (20%)	9 (11%)	

[a]POPF: Post-operative pancreatic fistula.
[b]PTBD: Percutaneous transhepatic biliary drainage.

Four patients had a difficult distal stump, two each in either group. Although we did manage to place sutures in three of these patients, one patient in the control group had avulsion of inferior end of CDC and the distal stump could not be secured. Surprisingly, he did not develop POPF. Out of 34 cases of POPF, only two patients had a difficult distal stump intraoperatively. Average duration of drain stay was 15 days (5-95 days) with output of 90 mL (70-120 mL) in POPF group and in control group average drain stay was five days (1-15 days) with output of 50 mL (30-70 mL)

Incidence of POPF in our study was 34/377 (9%). Majority, 24 (70.5%), had grade a biochemical leak. Clinically relevant POPF (B and C) was present in 10 (29.5%). Those who had grade B leak were managed with additional percutaneous drains. Four (11.7%) had grade C POPF with uncontrolled sepsis and required re-exploration, lavage and drainage. There was no mortality in this group.

Seven out of 377 (1.85%) patients following CDCE had bleeding in the post-operative period. Five bleeds happened in those who did not have POPF, and two bleeds in the POPF group. All of these patients required operative intervention due to failure to identify the bleed site on CT angiography. In the POPF group, one had bleeding from hepaticojejunostomy site and was managed with reinforcement of HJ, another had bleeding from a small arterial twig which was managed by ligation. In the control group, one patient had bleeding from the gastroduodenal artery (GDA) pseudoaneurysm which was managed by suturing of GDA, and one patient had bleeding from the small unnamed arterial twig, managed by suture ligation of bleeding vessel. In three patients, no source could be identified after evacuation of clots and thorough exploration.

All cases were followed up for a mean duration of four years, with a range of 1 to 22 years. Table 3 lists all the other complications not related to distal stump in this series.

There was no mortality in the POPF group while two patients in the control group died from non-surgical causes (myocardial infarction in one and arrythmias in the other).

Table 3. List of complications other than those related to the distal stump

Complications	Incidence
Early complications	
Bile leak	18 (4.7%)
Chylous ascites	2 (0.5%)
Intra-abdominal collection	8 (2.1%)
SSI[c]	16 (4.2%)
Pulmonary complications	10 (2.6%)
Late complications	
Anastomotic stricture[d]	12 (3.1%)
Redo stricture	1 (0.2%)
Hepatolithiasis	6 (1.5%)
Cholangitis	2 (0.5%)
Liver abscess	2 (0.5%)
Acute pancreatitis	5 (1.3%)
Adhesive obstruction	5 (1.3%)

[c]SSI: Surgical site infection.
[d]Anastomotic stricture: HJ stricture.

DISCUSSION

In this review of POPF and bleeds following CDCE over two decades, we found a low incidence of POPF (9%) (34/377) and post-operative bleeds (5.9%), and all could be salvaged with timely intervention. While the study by Liu et al. have reported similar incidence of 9.2% (5/54) (15), Okada et al. have reported a higher incidence of 31.6% (6/19) (2014), probably reflecting surgical experience and nature of cases undergoing the surgery (16).

There was no difference in demography, clinical features or CDC related pre-operative complications like pancreatitis, cystolithiasis or prior abdominal surgery between the group which developed these complication and that which did not. Similarly, the incidence of cholangitis was similar in both groups. Internal biliary drainage by endoscopic retrograde cholangiopancreatography (ERCP) was the preferred modality to treat cholangitis. Previous studies suggest that multiple episodes of cholangitis would increase the risk of POPF; however, in our series, prior cholangitis episodes did not contribute to the development of POPF (p= -0.9) (17). Adequate treatment of cholangitis preoperatively by antibiotics with or without adequate drainage and excision surgery only after a cooling off period of eight weeks probably contributed to this. Previous studies suggest pre-operative PTBD to be associated with lower post operative complications than ERCP in patients undergoing PD (18,19). However, recent data suggest internal biliary drainage to be more physiological and equivalent to PTBD (20). Hence, we preferred internal drainage and it did not increase distal stump related complication rates.

Presence of peri choledochal inflammation, resulting in intraoperative difficulty in dissecting the CDC off adjacent structures in hepatoduodenal ligament did not affect the development of POPF (p= -0.65). In an attempt to predict intraoperatively itself the patients who were likely to develop POPF, we defined the entity of a difficult distal stump i.e., difficulty in dissecting and or suturing the distal part of the intrapancreatic portion of choledochal cyst due to inflammation. Intuitively, difficult distal stump should increase chances of POPF, but in our study, not all difficult distal stump resulted in POPF. In the control group, two had difficult distal stump but none developed POPF (21). In

fact, one of the patients in the control group had avulsion of the distal end and could not be secured, but he did not develop POPF. It is our routine practice to flush the distal stump to clear protein plugs and debris in the common channel prior to closure. We believe that if vascularised distal stump is sutured, it does not leak in the absence of distal obstruction.

POPF following CDCE is a kind of isolated pancreatic duct leak as opposed to POPF following PD, in which there is leak of bile mixed with pancreatic secretions. Isolated pancreatic leaks following distal pancreatectomy if drained adequately are known to be associated with fewer septic complications and morbidity and mortality as compared to POPFs following PD (14).

The incidence of POPF in our cohort was 9%. Among those with POPF, clinically significant POPF was seen in 10/34 (30%), and the rest were biochemical leaks 24/34 (70%). Grade B POPF was observed in 6/34 (18%) patients, all of whom required additional drain placement for control of leak. Grade C POPF patients was seen in 4/34 (12%) patients, and they all developed severe sepsis with peritoneal signs, necessitating laparotomy, lavage and additional drainage.

There is evidence on the use of octreotide or long acting somatostatin analogue to prevent POPF after pancreatectomy and in ameliorating the adverse consequences once POPF develops following PD and DP (22,23). All patients who developed POPF in this series had a low output pancreatic fistula. Average volume of drain output was 90 cc in POPF group and 50 cc in the control group. We did not use strategies like dietary modification or pharmacotherapy to decrease these already low output fistula.

The average duration for drains in the group which developed POPF was 15 days, ranging from as short as five days in case of biochemical leak to maximum of 95 days in those with grade C POPF. Even in high grade POPF, the fistula healed in two weeks following laparotomy, lavage and additional drainage once sepsis was controlled. The clinically significant POPF group patients, however, did have a prolonged hospital stay.

While the incidence of post-operative bleed was higher in the POPF group with 2/34 (5.9%) vs the control group with 5/343 (1.5%), it was not statistically significant (p= -0.37). There are several potential sites of bleeding in a patient following CDCE like segmental arteries arising from right hepatic artery or branches from anterior and posterior pancreatoduodenal arteries and veins (24). The bleeds can arise from suture lines as well (hepaticojejunostomy and jejunojejunostomy). One of our patients had a bleeding from HJ site which needed dismantling of anterior layer of HJ and refashioning of anastomosis. Presence of POPF is known to contribute to secondary haemorrhage following PD or DP (25). A leak from the distal stump following CDCE is a leak of pancreatic juice with all its proteolytic enzymes which can contribute to secondary haemorrhage. In our study, two patients with post-operative bleeding had associated POPF. These patients required control of the bleeding site and adequate drainage of collection to eliminate sepsis. If the source of bleeding is identified and properly managed and there is adequate drainage of pancreatic secretions and absence of sepsis, bleeds following CDCE by themselves do not result in mortality. We were able to salvage all secondary bleeds following CDCE in our series.

Despite these two complications, prolonged hospital stay and increased duration of use of drains, they do not increase mortality. CDCE, if done by surgeons, should be associated with low perioperative mortality. The two mortalities in the control group were also due to non-surgical causes. Even grade C POPF or bleeds requiring surgery can be successfully salvaged.

Other post-operative complications in this series have been detailed in Table 3. The incidence of bile leak (4.7%) and RYHJ stricture (3%) are comparable to a large series of CDC excision reported by the Dutch group (6% and 4 %) (26).

Merits, Demerits and Clinical Implications of This Study

Our study is a large, single centre experience of CDCE spanning over two decades which has looked at complications specific to blowout of distal stump (POPF and bleeds), an issue hitherto infrequently addressed in the literature. Since this is a retrospective study, dependent on documented findings, there are limitations like observer bias, documentation bias and interpretation bias. However, the results clearly illustrate that POPF and bleeds following CDCE are not as ominous as those following PD or DP, which can be very reassuring for treating surgeon. POPFs following distal stump blow out following CDCE can be well managed with adequate drainage alone. Secondary bleeds following CDCE are from small segmental arteries in vicinity of the cyst, which may not be evident on CT angiogram. Most stop spontaneously or can be controlled at surgery by suture ligation. This awareness is extremely reassuring to the treating team. Meticulous surgical technique, sticking to the pericholedochal plane, avoiding straying into pancreatic parenchyma, using bipolar diathermy forceps as opposed to hot shears for dissection helps control the pericholedochal plexus even in presence of inflammation and avoid damage to pancreas.

CONCLUSION

POPF and bleeds are rare complications following CDCE as opposed to POPFs following PD or distal pancreatectomy. POPFs following CDCE respond to conservative measures while few require additional drains either percutaneous or surgical. Most POPFs are self-limiting or heal with drainage alone if the surgeon ensures absence of obstruction in common channel. Bleeds following CDCE can arise from HJ site or segmental vessels in the hepatoduodenal ligament. Isolated bleeds do not adversely affect outcomes if appropriately controlled by endovascular or operative techniques and there is adequate

control of sepsis. These POPFs and bleeds following CDCE are a distinct group as opposed to those following PD or DP in terms of management strategies and outcomes.

Ethics Committee Approval: This study was approved by the Sanjay Gandhi Postgraduate Institute of Medical Sciences Ethics Committee (Decision no: 2023-20-MCh-EXP-5, Date: 05.04.2023).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - AB, SKK; Design - AB, SS, SKK; Supervision - AB, SS, SKK; Materials - AB, SS, RR, AKII, AS, RS, AK, RS; Data Collection and/or Processing - SKK; Analysis and/or Interpretation - SKK, SS, AB; Literature Search - SKK, SS, AB, RR, AKII, AS, RS, AK, RS; Writing Manuscript - SKK, SS; Critical Reviews - SKK, SS, AB, RR, AKII, AS, RS, AK, RS.

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

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (2): 104-110

Koledok kisti eksizyonu sonrası pankreatik fistül ve kanama: Yirmi yıllık deneyim

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ÖZET

Giriş ve Amaç: Koledok kistlerinde hepatikojejunostomi ile birlikte koledok kisti eksizyonu (KKKE) standart tedavi yöntemidir. Postoperatif pankreatik fistül (POPF) ve kanama gibi distal güdüğün yetersiz iyileşmesine bağlı komplikasyonlar literatürde ele alınmamıştır. KKKE sonrası bu komplikasyonlarla ilgili yirmi yıllık deneyimimizi sunuyoruz.

Gereç ve Yöntem: Koledok kisti eksizyonu sonrası POPF (Uluslararası Pankreas Cerrahisi Çalışma Grubu sınıflamasına göre) ve kanama gelişen hastaların demografik özellikleri, ameliyat detayları ve ameliyat sonrası seyirlerinin retrospektif analizi, bu komplikasyonların gelişmediği hastalarla karşılaştırıldı.

Bulgular: Ameliyat edilen 377 hastanın 34'ünde POPF görüldü (ensidans %9). POPF gelişenlerin 24/34 (%70)'ünde biyokimyasal kaçak ve 10/34 (%30)'ünde klinik olarak anlamlı POPF (B ve C) vardı. Tüm B sınıfı POPF 6/34, ek perkütan dren gerektirirken, tüm C sınıfı 4/34 sepsis kontrolü için operatif müdahale gerektirmiştir. POPF grubunda mortalite görülmezken, kontrol grubundaki iki hasta cerrahi dışı nedenlerle ölmüştür. Kapatmayı engelleyen zor bir distal güdük daha sonra POPF gelişimi ile ilişkili bulunan tek faktördü (POPF grubunda %5,9'a karşılık kontrol grubunda %0,5, p= 0,03). Ameliyat sonrası kanama POPF'li iki (%6) hastada ve kontrol grubunda 5/343 (%1,4) hastada görüldü.

Sonuç: Koledok kisti eksizyonu sırasında intraoperatif olarak POPF gelişimini öngörmek mümkündür. Bu POPF'lerin çoğu yeterli drenaj ile konservatif olarak yönetilebilir. Cerrahi sadece grade C fistül ve kanamalarda gereklidir. Bunlar pankreatikoduodenektomi sonrası görülenlerden farklı olarak izole pankreatik fistüller olduğundan, daha olumlu sonuçlarla ilişkilidir.

Anahtar Kelimeler: Koledok kisti, koledok kisti eksizyonu, biliyer kist, Roux-en-Y hepatikojejunostomi, postoperatif pankreatik fistül, pankreatik fistül

DOİ: 10.47717/turkjsurg.2024.6354

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (2): 111-118

Factors associated with anastomotic leak following gastrectomy for gastric adenocarcinoma and its effect on long-term outcomes

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ABSTRACT

Objective: Gastrectomy for cancer is a technically demanding surgery and anastomotic leak is an important complication of this surgery. This study aimed to identify the factors associated with anastomotic leak following gastrectomy in gastric cancer patients and its long-term effect on outcomes.

Material and Methods: This is an ambispective study of 181 patients who underwent curative gastrectomy for gastric adenocarcinoma over 13 years, at our institution. Groups with and without anastomotic leak were compared using the Mann-Whitney U test (continuous variables) and Chi-square test (categorical variables). A multivariable analysis was performed to determine the factors associated with anastomotic leak.

Results: Out of the 181 patients who underwent curative gastrectomy, 12 (6.6%) patients experienced anastomotic leak. A multivariable analysis revealed that younger age, presence of comorbidities, hypoalbuminemia, tumor location in the proximal stomach, type of reconstruction, and positive margin status were associating factors for anastomotic leak. During a median follow-up of 34 months (ranging from 12 to 130), it was observed that 25 (18.3%) patients developed anastomotic stenosis, but it was not related to anastomotic leak. The incidence of post-operative pulmonary complications, administration of adjuvant therapy, recurrence rates, and mortality due to anastomotic leak did not significantly change. Moreover, neoadjuvant therapy did not increase the incidence of anastomotic leaks.

Conclusion: Factors like younger age, presence of comorbidities, hypoalbuminemia, tumor location in the proximal stomach, type of reconstruction, and positive margin status were associated with increased risk of anastomotic leak, which needs further studies to validate the findings. Thus, preoperative optimization and resection with adequate margins may be of utmost importance in preventing anastomotic leaks.

Keywords: Gastric cancer, gastrectomy, anastomotic leak, long-term effect, gastrojejunostomy, esophagojejunostomy

INTRODUCTION

Gastric cancer is the fifth most common cancer and the fourth most common cause of cancer deaths in the world (1). Gastrectomy with D2 lymphadenectomy is the main treatment for gastric cancer (2). Gastrectomy for cancer requires expertise, with complication rates varying from 20%-46% (2). The incidence of anastomotic leak following gastrectomy is 1.5-14.4% (3-7). Mortality due to anastomotic leak is 38.5% of all surgery-related mortality after gastrectomy for gastric cancer (7). Anastomotic leaks lead to poor quality of life, lengthening hospital stay, increased financial burden, and mortality (8).

Post-operative complications can hamper recovery, delaying the initiation of adjuvant chemotherapy, which can adversely affect the overall and recurrence-free survival of patients after curative gastrectomy for gastric cancer. These complications can be disastrous to both short and long-term outcomes (9,10). There is some uncertainty about neoadjuvant therapy causing an increased risk of post-operative anastomotic leak (11).

Most of the studies have assessed risk factors for esophago-jejunal anastomotic leak, but few have addressed the complications following gastrojejunostomy leak. No randomized study is available, and the existing literature has shown conflicting results in terms of determinants of leak and its sequelae. The present study aimed to identify the factors associated with anastomotic leak following gastrectomy in gastric adenocarcinoma patients and its long-term effect on outcome.

Cite this article as: Shaganti R, Godara SK, Singh RK, R R, Misra S, Kumar S. Factors associated with anastomotic leak following gastrectomy for gastric adenocarcinoma and its effect on long-term outcomes. Turk J Surg 2024; 40 (2): 111-118.

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Received: 05.02.2024
Accepted: 03.06.2024
Available Online Date: 28.06.2024

DOI: 10.47717/turkjsurg.2024.6351

MATERIAL and METHODS

It is an ambispective observational study in which all consecutive patients who underwent potentially curative gastrectomy (total, subtotal/distal, proximal) for gastric adenocarcinoma from 2009 to 2021 at a tertiary care center were included after ethical clearance from institutional ethics committee (IEC code: 2023-93-MCh-EXP-52 PGI/BE/224/2023). Data was retrieved from a prospectively maintained hospital information system and informed consent was taken from the patient/patient's family. Patients who underwent resection or a bypass procedure for benign pathology, non-adenocarcinoma malignant pathology, or metastatic disease were excluded from the study.

Patients' demographic characteristics were recorded along with the following clinical, surgical, and pathological characteristics (e.g., pre-operative patient factors, neoadjuvant therapy, surgery-related factors, and tumor-related factors). Early post-operative complications like pulmonary, and cardiac complications were also evaluated.

All patients were divided into two groups as anastomotic leak (AL) group and no anastomotic leak (NAL) group. These groups were compared in terms of the above clinicopathological and surgical factors. All patients were followed up for at least 12 months. Follow-up data was collected from the outpatient records and/or telephonic conversations. Long-term anastomotic complications (anastomotic stenosis, fistula formation) were noted and analyzed.

The decision for neoadjuvant therapy was made after a discussion in a tumor board. Total or proximal gastrectomy or subtotal/distal gastrectomy with D2 lymph node dissection with or without adjacent organ resection was determined by the stage of the disease and location of the tumor, using standard criteria.

Anastomotic leak in the present study was defined as the leak of luminal contents from the anastomotic line that is from Roux-en-Y esophago-jejunal (RYEJ)/esophagogastric (EG) or gastro-jejunal (GJ) anastomotic site with clinical manifestations. They presented clinically as luminal contents through a wound or drain or with collection near the anastomosis associated with fever, inflammatory response, metabolic disturbance, and/or multiple-organ failure, confirmed by oral contrast CT or at re-operation.

Anastomotic stenosis in the present study was defined as anastomotic site narrowing post-gastrectomy who presented with features of gastric outlet obstruction at least after one month of surgery confirmed by endoscopy or contrast study and those requiring endoscopic intervention or revision surgery.

Anastomotic leaks containing collections were managed by percutaneous drainage, antibiotics, and enteral feeding through a feeding jejunostomy (FJ) tube (placed during primary surgery). In patients who could not tolerate enteral feeds or in whom enteral feeding access was not available, total parenteral nutrition (TPN) was initiated. Surgical re-exploration was reserved for hemodynamically unstable patients, who demonstrated signs of clinical deterioration on conservative management or in case of free contrast leak into the peritoneal cavity.

Endoscopic balloon dilation was considered a primary treatment for anastomotic stenosis following gastrectomy and surgery was reserved for the failures.

Statistical Analysis

Patients were divided into two groups as anastomotic leak (AL) and no anastomotic leak (NAL) groups. Continuous variables were expressed as median and compared using the Mann-Whitney U test. The association between categorical data was compared using the Chi-square test. Univariate analysis was done with logistic regression analysis and the variables which had $p< 0.05$ were considered for multivariable regression analysis. $P< 0.05$ was considered significant. Statistical analysis was done using the IBM SPSS 26.0 (SPSS Inc., Chicago, IL, United Stated of America) package program.

RESULTS

Of a total of 287 patients who underwent gastrectomy for gastric tumors of all types during this period, a total of 181 patients were included for analysis. Twelve (6.6%) of them had anastomotic leak (six following total gastrectomy; five following distal/subtotal gastrectomy; one following proximal gastrectomy). Nine were managed conservatively with antibiotic upgradation and the drain was kept for a longer time or percutaneous drain placement done in them. The remaining three patients underwent re-exploration due to the persistence of symptoms or deterioration with conservative management. Median time of presentation of the leak was on the 6^{th} post-operative day (range four to 48 days), and median hospital stay was 18 days (range nine to 23 days).

Median age of the patients was 54 (18-85) years with 75.7% being male. Comorbidities were more commonly seen in the AL group ($p= 0.02$). Univariate analysis suggested that the following factors were associated with anastomotic leak younger age, presence of comorbidities, pre-operative anemia, blood transfusion, hypoalbuminemia, total gastrectomy, positive margin status, and tumor location. Neoadjuvant therapy, the technique of anastomosis, the extent of lymphadenectomy, en-bloc resection of adjacent organs, and tumor-related pathological factors were not correlated with increased anastomotic leak (Table 1-3). Pulmonary complications were more common in the AL group (33.3% vs.15.4%), although the difference was not statistically significant. There was no difference in the post-operative mortality, administration of adjuvant therapy, or recurrence rates between the two groups (Table 4).

Table 1. Univariate analysis of pre-operative factors affecting anastomotic leak

Characteristic	Overall [n= 181 (100%)]	AL Group [n= 12 (6.6%)]	NAL Group [n= 156 (93.4%)]	Univariate Analysis (p)
Median Age (Years)	54 (18-85)	44 (24-65)	55 (18-85)	0.03
Sex				
Male	137 (75.7%)	9 (75%)	128 (75.7%)	0.95
Female	44 (24.3%)	3 (25%)	41 (24.3%)	
Comorbidities				
Present	62 (34.3%)	9 (75%)	53 (31.4%)	0.02
Absent	119 (65.7%)	3 (25%)	116 (68.6%)	
Addiction				
Yes	70 (38.7%)	7 (58.3%)	63 (37.3%)	0.40
No	111 (61.3%)	5 (41.7%)	106 (62.7%)	
Pre-operative Anaemia (<8.5 mg/dL)				
Present	55 (30.4%)	11 (91.6%)	44 (28.2%)	0.00
Absent	126 (69.6%)	1 (8.4%)	125 (71.8%)	
Pre-operative/Intraoperative Blood Transfusion				
Yes	74 (40.9%)	11 (91.7%)	63 (37.3%)	0.02
No	107 (59.1%)	1 (8.3%)	105 (62.1%)	
Hypoalbuminemia (<3.5 mg/dL)				
Present	53 (29.3%)	8 (66.6%)	45 (26.6%)	0.03
Absent	128 (70.7%)	4 (33.4%)	124 (73.4%)	
Pre-operative Nutrition Supplementation				
Yes	25 (13.8%)	5 (41.6%)	20 (11.8%)	0.00
No	156 (86.2%)	7 (58.4%)	149 (88.2%)	
Neoadjuvant Therapy				
Yes	37 (20.4%)	3 (25%)	34 (20.1%)	0.68
No	144 (79.6%)	9 (75%)	135 (79.9%)	

AL: Anastomotic leak, NAL: non-Anastomotic leak.

On multivariable analysis, factors that conferred significant adverse impact on anastomotic leak rate were younger age, presence of comorbidities, hypoalbuminemia, proximal tumor location, type of reconstruction, and positive margin status (Table 5).

Of the total of 181 patients, 136 were available for evaluation of long-term anastomotic complications. Out of the 136 patients, 25 (18.3%) developed anastomotic stenosis after a median follow-up of 34 months (12 to 130 months). No chronic fistula was documented. Only two out of 25 patients who developed anastomotic stricture (8%) had a history of AL, and the remaining 23 (92%) had tumor recurrence (local, distant, and both local and distant recurrence). Anastomotic leak did not influence the rate of anastomotic stenosis (8% vs. 9%, p= 0.97). Most of these patients were presented with dysphagia or gastric outlet obstruction, evaluated by upper GI endoscopy and biopsy from stricture. In the AL group, both patients with stenosis had benign stricture, underwent esophageal dilatation, and none required reoperation. In the NAL group, all stenoses were due to the recurrence of the disease. Two patients with local recurrence at the anastomotic site leading to stenosis underwent endoscopic guided SEMS placement, the remaining 21 patients were managed conservatively with best supportive care.

DISCUSSION

In the present study, anastomotic leak rate following curative gastric resection for adenocarcinoma was 6.6%. This is similar to that reported at various centers across the globe. The Japanese National Clinical Database (NCD) of digestive surgery reported an anastomotic leak rate following total gastrectomy as 4.4% (881 of 20011) in 2011. Recent studies from Japan and Korea have shown anastomotic leak incidence ranging from 1.5-4.9%, whereas studies from the Western world ranged from 5.2-14.4% (3-7).

Table 2. Univariate analysis of factors related to extent of surgery and technique affecting anastomotic leak

Characteristic	Overall [n= 181 (100%)]	AL Group [n= 12 (6.6%)]	NAL Group [n= 156 (93.4%)]	Univariate Analysis (p)
Extent of Resection				0.009
Distal/Subtotal gastrectomy	134 (74%)	5 (41.7%)	129 (76.3%)	
Proximal gastrectomy	12 (6.6%)	1 (8.3%)	11 (6.5%)	
Total gastrectomy	35 (19.3%)	6 (50%)	29 (17.2%)	
Combined Organ Resection				0.03
Performed	14 (7.7%)	3 (25%)	11 (6.5%)	
Splenectomy	9 (5%)	3 (25%)	6 (3.6%)	
Transverse colectomy	3 (1.7%)	0	3 (1.8%)	
Pancreatico-splenectomy	1 (0.6%)	0	1 (0.6)	
Liver wedge	1 (0.6%)	0	1 (0.6%)	
Not performed	167 (92.3%)	9 (75%)	158 (93.5%)	
Type of Reconstruction				0.008
Bilroth II	92 (50.8%)	2 (16.7%)	90 (53.3%)	
RYGJ	42 (22.5%)	3 (25%)	39 (23.1%)	
EGA	12 (6.6%)	1 (8.3%)	11 (6.5%)	
RYEJ	35 (19.3%)	6 (50%)	29 (17.2%)	
Technique of Anastomosis				0.75
Handsewn	161 (89%)	11 (91.7%)	150 (88.8%)	
Stapled	20 (11%)	1 (8.3%)	19 (11.2%)	
GJ Position				0.38
Antecolic	60 (33.1%)	2 (16.7%)	58 (34.3%)	
Retro colic	49 (27.1%)	5 (41.7%)	44 (26%)	
Details not available	72 (39.8%)	5 (41.7%)	67 (39.6%)	
Extent of LN Dissection				0.98
D2	170 (93.9%)	12 (100%)	158 (93.5%)	
D1	10 (5.5%)	0	10 (5.9%)	
D1+	1 (0.6%)	0	1 (0.6%)	
Margin Status				0.04
Negative margin	154 (85.1%)	8 (66.7%)	146 (86.4%)	
Positive microscopic margin	27 (14.9%)	4 (33.3%)	23 (13.6%)	

AL: Anastomotic leak group, NAL: Non-anastomotic leak group, RYGJ: Roux-en-Y gastrojejunostomy, EGA: Esophaga-gastric anastomosis, RYEJ: Roux-en-Y esophago-jejunostomy, GJ: Gastrojejunostomy, LN: Lymph node.

Of the 12 patients in the AL group, nine (75%) were successfully managed conservatively (five required percutaneous drain insertion, four had prolonged surgical drain in situ), while three (25%) patients required re-exploration. In a systematic review in 2015, surgical re-exploration was necessary in 23.7% of patients which is comparable to the present study (12). Mortality following an anastomotic leak in the present study was 8.3%, which was comparable with a large-volume retrospective study by Roh et al. (7).

In our study, younger age, presence of comorbidities, hypoalbuminemia, tumor location, type of reconstruction, and positive margin status were associated with increased risk of anastomotic leak.

We found that the leak rate was higher in younger age patients. Median age of patients in the AL group was nearly 10 years less than that in the NAL group. This is in contrast with other studies that reported more complications in the older age group (7,13). A definitive explanation is not possible, however, in the present study, we found that younger patients had a higher incidence of signet ring cell tumors involving the proximal stomach necessitating more extensive resection (total gastrectomy) and esophagojejunostomy.

The presence of co-morbidities independently increased the risk (odds ratio was 15) of anastomotic leak. Out of 12 patients presenting with leak, nine (75%) were suffering from one or more medical illnesses (diabetes, hypertension, chronic pulmonary disease, or cardiac illness). A Korean study by Roh et al. documented similar findings wherein the patients who developed AL, 61 percent were affected by one or multiple co-morbidity (7). Kim et al. in their report have suggested the presence of cardiovascular disorder as a significant factor influencing the rates of anastomotic dehiscence (odds ratio 1.8) (13). Cardiovascular diseases and diabetes may increase the need for vasopressor support in the peri-operative period, impair the microcirculation, and adversely affect the glucose

Table 3. Univariate analysis of clinicopathological characteristics of tumour affecting anastomotic leak

Characteristic	Overall [n= 181 (100%)]	AL Group [n= 12 (6.6%)]	NAL Group [n= 156 (93.4%)]	Univariate Analysis (p)
Tumour Location				0.02
Antrum and pylorus	128 (70.7%)	4 (33.3%)	124 (73.4%)	
GEJ	27 (14.9%)	4 (33.3%)	23 (13.6%)	
Whole stomach/body	26 (14.4%)	4 (33.3%)	22 (13%)	
Histopathology				0.45
Differentiated adenocarcinoma	144 (74.1%)	10 (83.3%)	124 (73.4%)	
Signet ring-cell adenocarcinoma	47 (25.9%)	2 (16.7%)	45 (26.6%)	
T Stage (AJCC 8th)				0.94
T1	11 (6.1%)	1 (8.3%)	10 (5.9%)	
T2	23 (12.7%)	1 (8.3%)	22 (13%)	
T3	65 (35.9%)	4 (33.3%)	61 (36.1%)	
T4	82 (45.3%)	6 (50%)	76 (45%)	
N Stage (AJCC 8th)				0.92
N0	34 (18.8%)	1 (8.3%)	33 (19.5%)	
N1	21 (11.6%)	1 (8.3%)	20 (11.8%)	
N2	16 (8.8%)	2 (16.7%)	14 (8.3%)	
N3	39 (21.5%)	3 (25%)	36 (21.3%)	
Nx (inadequate LNs examined or neoadj therapy given)	71 (39.2%)	5 (41.7%)	66 (39.1%)	
Number of Positive LNs	4.1	4.7	4.0	0.91
Lymphovascular Invasion				0.95
Present	44 (24.3%)	3 (25%)	41 (24.3%)	
Absent	17 (75.7%)	9 (75%)	128 (75.7%)	
Perineural Invasion				0.76
Present	52 (28.7%)	3 (25%)	49 (29%)	
Absent	129 (71.3%)	9 (75%)	120 (71%)	

AL: Anastomotic leak group, NAL: Non-anastomotic leak group, GEJ: Gastroesophageal junction, AJCC: American joint committee on cancer staging, LN: Lymph node.

Table 4. Comparison of post-operative outcomes following curative gastrectomy between the two groups

Characteristic	Overall [n= 181 (100%)]	AL Group [n= 12 (6.6%)]	NAL Group [n= 156 (93.4%)]	Univariate Analysis (p)
Immediate (<7 days) Post-operative Pulmonary complications				0.11
Present	30 (16.6%)	4 (33.3%)	26 (15.4)	
Absent	151 (83.4%)	8 (66.7%)	143 (84.6%)	
Adjuvant Chemotherapy				0.72
Taken	103 (56.9%)	6 (50%)	97 (57.4%)	
Not taken	25 (13.8%)	4 (33.3%)	21 (12.4%)	
Not known	53 (29.3%)	2 (16.7%)	51 (30.2%)	
Recurrence				0.87
Present	51 (28.2%)	4 (41.7%)	47 (43.2%)	
Absent	78 (43.1%)	5 (33.3%)	73 (43.2%)	
Not known	52 (28.7%)	3 (25%)	49 (29%)	
Hospital Mortality				0.19
Yes	7 (3.9%)	1 (8.3%)	6 (3.6%)	
No	174 (96.1%)	11 (91.7%)	163 (96.4%)	
Death				0.63
Yes	90 (49.7%)	7 (58.3%)	83 (49.1%)	
No	46 (25.4%)	0	46 (27.2%)	
Not known	45 (24.9%)	5 (41.7%)	40 (23.6%)	

AL: Anastomotic leak group, NAL: Non-anastomotic leak group.

Table 5. Multivariate analysis of factors affecting anastomotic leak rate

Characteristic	P-value on Multivariate Analysis	Odds Ratio (Confidence Interval)
Age (younger age)	0.001	0.8 (0.81, 0.94)
Presence of comorbidities	0.007	15 (2.07, 109.62)
Hypoalbuminemia	0.009	9.6 (1.76, 53.18)
Tumour location (whole stomach or body of stomach involvement)	0.04	8.1 (1.01, 66.12)
Type of reconstruction (RYEJ)	0.04	8.3 (1.01, 69.06)
Margin status (positive margin)	0.04	6 (1.03, 35.62)

RYEJ: Roex-en-Y esophagojejunostomy.

metabolism thus impeding the process of wound (anastomotic) healing.

Hypoalbuminemia (albumin <3.5 gm/dL) was also found to be an independent factor associated with anastomotic leak with an odds ratio of 10. Malnutrition renders patients more susceptible to infection, increases tissue edema, prolongs wound healing, and increases the risk of post-operative complications (10). It emphasizes the importance of pre-operative nutritional optimization. Liu et al., in their report, have documented similar results (14). On the contrary, Migita et al. and Kim et al. fhave ailed to demonstrate any association between serum albumin and anastomotic healing (8,13).

Tumors with microscopic margins positive for tumor cells (R1 resection) had a higher risk (six times) of anastomotic leak. Kim et al. have also documented a significant rise in anastomotic complications (2.3 times) with a positive resection margin (13).

Eight times increased risk of anastomotic leak was documented in patients with tumors involving the whole stomach or most of the body of the stomach necessitating total gastrectomy and esophagojejunostomy. A similar rise has been noted with proximal tumors (proximal third of the stomach) in a study by Kim et al. (13). Regardless of the anastomotic technique (stapled or sutured), RYEJ is considered technically more difficult than GJ. Moreover, the esophagus is a less compliant organ in comparison to the stomach as well as the blood supply is less robust. The proximal gross margin in the case of proximal gastrectomy (1-2 cm) is less than that in distal gastrectomy (usually >5 cm). The proximity to the tumor tissue might be responsible for poor healing capacity.

Conversely, combined organ resection, technique of anastomosis, extent of lymph node dissection, and stage of the disease did not affect the leak rate. Importantly, in our study, 37 of 181 (20.4%) patients received neoadjuvant therapy but this did not lead to an increased rate of anastomotic leak. Studies on the effect of neoadjuvant therapy in colorectal cancer have demonstrated tumor regression to the extent of complete pathologic response leading to improved local control (15). This may counteract the ill effects (tissue edema and inflammation) of neoadjuvant therapy (chemotherapy and/or radiotherapy), and thus may not translate into increased AL.

In the present study, 47/181 (25.9%) patients had signet ring cell adenocarcinoma, however, histopathological type did not significantly increase leak rates. Similarly, the need for multi-visceral resection, the extent of lymphadenectomy, the technique of anastomosis, and the stage of the disease did not have a significant effect on anastomotic dehiscence as confirmed by a Japanese study by Migita et al. (8). In the present study, 25/136 (18.3%) patients developed anastomotic stenosis during follow-up. However, post-operative leak (16.7% vs. 18.5%) was not associated with the development of stricture. Fukagawa et al. have documented the stenosis rate of 7.8% following open proximal gastrectomy, and 3.4% following open total gastrectomy (16). Multiple factors have been proposed for the development of mechanical gastric outlet obstruction: Ischemia, tension following tissue approximation, subacute obstruction, use of circular staplers, narrow diameter staplers, and the occurrence of an anastomotic leak (17). However, the present study did not show any difference in terms of anastomotic leaks.

Being an ambispective single-centre study, the limitations of this study include small sample size, the possibility of selection bias, and a low incidence of anastomotic leaks. Multicentre large prospective studies are required to validate the results.

CONCLUSION

Factors like younger age, presence of comorbidities, hypoalbuminemia, tumor location in the proximal stomach, type of reconstruction, and positive margin status were associated with increased risk of anastomotic leak, which needs further studies to validate these findings. Thus, pre-operative optimization and resection with adequate margins may be of utmost importance in preventing anastomotic leaks.

Ethics Committee Approval: This study was obtained from Sanjay Gandhi Post Graduate Institute Medical Sciences of Ethics Committee (Decision no: 2023-93-MCh-EXP-52, Date: 22.06.2023).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - RKS; Design - RKS, SR, RR; Supervision - RKS, SM, SK, RR; Data Collection and/or Processing - RKS, SKG, SR; Analysis and/or Interpretation - RKS, SKG, SR; Literature Search - SR; Writing Manuscript - SR, RKS; Critical Reviews - All of authors.

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

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (2): 111-118

Mide adenokarsinomu için gastrektomi sonrası anastomoz kaçağı ile ilişkili faktörler ve uzun vadeli sonuçlar üzerindeki etkisi

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ÖZET

Giriş ve Amaç: Kanser için yapılan gastrektomi, teknik olarak zorlu bir cerrahidir ve anastomoz kaçağı bu cerrahinin önemli bir komplikasyonudur. Bu çalışmanın amacı, mide kanseri hastalarında gastrektomi sonrası anastomoz kaçağı için öngörücü faktörleri ve bunun uzun vadeli sonuçlar üzerindeki etkisini belirlemektir.

Gereç ve Yöntem: Bu çalışma, kurumumuzda 13 yıl boyunca mide adenokarsinomu nedeniyle küratif gastrektomi yapılan 181 hastayı kapsayan amprisifik bir çalışmadır. Anastomoz kaçağı olan ve olmayan gruplar Mann-Whitney U testi (sürekli değişkenler) ve Ki-kare testi (kategorik değişkenler) kullanılarak karşılaştırıldı. Anastomoz kaçağı için öngörücü faktörleri belirlemek amacıyla çok değişkenli bir analiz yapıldı.

Bulgular: Küratif gastrektomi yapılan 181 hastadan 12 (%6,6)'sinde anastomoz kaçağı görülmüştür. Çok değişkenli analiz, genç yaş, komorbidite varlığı, hipoalbüminemi, proksimal midede tümör yerleşimi, rekonstrüksiyon tipi ve pozitif marjin durumunun anastomoz kaçağının bağımsız belirleyicileri olduğunu ortaya koymuştur. Ortanca 34 aylık (12 ile 130 arasında değişen) takip süresince, 25 (%18,3) hastada anastomoz darlığı geliştiği, ancak bunun anastomoz kaçağı ile ilişkili olmadığı görülmüştür. Ameliyat sonrası pulmoner komplikasyon insidansı, adjuvan tedavi uygulaması, nüks oranları ve anastomoz kaçağına bağlı mortalite önemli ölçüde değişmemiştir. Ayrıca, neoadjuvan tedavi anastomoz kaçağı insidansını artırmamıştır.

Sonuç: Genç yaş, komorbidite varlığı, hipoalbüminemi, proksimal midede tümör yerleşimi, rekonstrüksiyon tipi ve pozitif marjin durumu gibi faktörler anastomoz kaçağı riskini bağımsız olarak öngörmektedir. Bu nedenle, ameliyat öncesi optimizasyon ve yeterli sınırlarla rezeksiyon, anastomoz kaçaklarının önlenmesinde büyük önem taşımaktadır.

Anahtar Kelimeler: Mide kanseri, gastrektomi, anastomoz kaçağı, uzun dönem etki, gastrojejunostomi, özofagojejunostomi

DOİ: 10.47717/turkjsurg.2024.6351

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (2): 119-125

Inferior vena cava injuries: Are we doing what we really must?

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ABSTRACT

Objective: The inferior vena cava (IVC) is one of the most frequent injured intra-abdominal vessels and its treatment requires prompt action. Despite advances in reanimation in last decades, there has not been proportional improvement in IVC mortality. This report aims to discuss the mortality predictive factors including the adherence to balanced reanimation and damage control surgery (DCS) in daily trauma assistance, their repercussions on outcomes, comparing our institution outcomes to literature.

Material and Methods: A retrospective design analysis was made through database records of trauma patients at Clinic Hospital of University of Campinas, UNICAMP in order to investigate patients with IVC injuries, putting an emphasis on mortality predictive factors.

Results: Seventy-four patients were identified with IVC injury from January 1990 to August 2017. Predominant mechanism was penetrating with 87.8% (76.3% gunshot). On arrival, 37.8% of all of the victims were hypotensive, and ISS median was 24.5. Regarding location of IVC, 68.5% were infrarenal, 12.2% were suprarenal, 18.9% retrohepatic. Simple repair was performed in 60.8%. Ligation was carried out in 27% and atriocaval shunt was performed in 4.1%. There was not enough time for specific procedure in 8.1%. Associated intra-abdominal injuries were present in 97.3%, and the mean of transfusional requirements was 9.1 ± 6.9 for packed red blood cells. Overall mortality rate was 52.7%, with a mortality rate for infrarenal injuries being 39.2%. Damage control surgery was adopted in 33.8%, with 68% mortality.

Conclusion: A solid comprehension of shock reanimation has progressively been disseminated; however, trauma care professionals must assure that they are being applied with balanced reanimation and DCS.

Keywords: Abdominal vascular injury, damage control, inferior vena cava, ligation, mortality, hypovolemic shock

INTRODUCTION

Hemorrhagic shock is the most common immediate cause of death in trauma and requires immediate and coordinate action to be reversed (1,2). In the last decade, new concepts have been created in order to avoid the lethal triad of hypothermia, acidosis, and coagulopathy. Resuscitative strategies have also evolved to include principles such as permissive hypotension, minimizing the use of crystalloid before surgical control of bleeding, and blood infusion through massive transfusion protocol (3). Moreover, the constant progress on pre-hospital care, surgical technique damage control surgery (DCS) and critical care have determined a better prognosis for trauma patients (3-5).

Inferior vena cava (IVC) injuries, due to their potential for significant bleeding, play an important role, according to the literature, accounting for up to 40% of all major intra-abdominal vascular injuries (6-11).

Surgical approach for bleeding control is crucial, hence an objective and thorough evaluation of the patient's clinical condition, associated visceral injuries, complexity of vascular injury and the identification of the involved IVC segment is central to determine surgical strategy.

Historically, there has been a significant improvement in survival of patients with IVC injuries, as advances in the trauma care have been implemented, evolving from almost 100% to 34-57% mortality rate in midst 1970 (12,13). Despite the continuous and ongoing progress in trauma care, the decrease in mortality rate of such patients is no longer evident; on the contrary, recent manuscripts have reported rates of up to 66% (5). Therefore, identifying mortality predictive factors of such patients has been a priority and some elements have been pointed out including

Cite this article as: Carvalho RB, Jimenez LS, Pedro RN, Kruger VF, Mantovani MEF, Calderan TRA, et al. Inferior vena cava injuries: Are we doing what we really must? Turk J Surg 2024; 40 (2): 119-125.

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Received: 08.04.2024
Accepted: 03.06.2024
Available Online Date: 28.06.2024

DOI: 10.47717/turkjsurg.2024.6363

a) clinical status at admission,

b) amount of blood transfusion,

c) IVC segment involved, and

d) surgical repair technique (7,14,15).

Moreover, the impact of those resuscitative strategies in advanced trauma support has not yet been consistently measured as a factor influencing mortality in patients with IVC injury, specifically. The development and implementation of these conducts have been gradual and have required continuous multispecialty training before being fully implemented as a routine in trauma assistance (16).

The aim of the present study was to describe the experience of an academic level one trauma referral center on IVC injuries with emphasis on mortality predictive factors, rates and compare our institution outcomes to scientific literature. Moreover, the present manuscript seeks to discuss adherence to current principles in trauma assistance and their repercussions on outcomes.

MATERIAL and METHODS

After approval of the committee of research ethics and institutional review board of University of Campinas (School of Medical Sciences, Unicamp - number 887.154) we conducted a retrospective review of all traumatic IVC injuries between January 1990 and August 2017. Data were harvested from the database of the Division of Trauma Surgery (DTS) at Clinic Hospital of University of Campinas. This hospital is a level one trauma center with about 500 beds, and it is the referral center for 20 cities, encompassing around of 3.5 million people from the public health system.

Patients under 14 years old, who were assisted by the paediatric department and those with iatrogenic IVC injuries and/or injuries secondary to other mechanisms than trauma were excluded from the analysis.

Charts from all patients with IVC injuries were retrospectively analyzed, and information on demographic data, trauma mechanism, emergency medical system (EMS) transport and vital signs at admittance-heart rate (HR), systolic blood pressure (SBP), respiratory rate (RR) and Glasgow coma scale (GCS) were gathered. Moreover, intra-operative findings were also evaluated with emphasis on

a) IVC injury location,

b) type of IVC surgical treatment,

c) need of damage control implementation,

d) associated intra-abdominal organ injuries,

e) blood transfusion (number of packed red blood cells in the first 24 hours),

f) length of stay, and

g) outcomes (including death and complications).

Trauma scores were calculated using the revised trauma score (RTS), injury severity score (ISS) and trauma injury severity score (TRISS). All trauma victims were conducted according to systematic and institutional protocols, such as ATLS® guidelines, and all diagnosis of IVC injury were made during surgical exploration.

Statistical analysis was done with Microsoft excel (version 16.58). Data associated with mortality rate were assessed by univariate analysis. The other, above mentioned, variables were evaluated with multivariate regression analysis model to determine independent predictors of mortality. A $p< 0.05$ was considered statistically significant.

RESULTS

Epidemiological Analysis

Seventy-four patients were identified with IVC lesion; 93.2% (69) were males, with a mean age of 29.4 ± 10.2 years. The mechanism of IVC injury was gunshot wound (GSW) in 53 patients (71.6%), stab wound (SW) in 12 (16.2%), and blunt injury in 9 (12.2%). Fifty percent of the patients were transported by EMS and, on arrival, 37.8% (28) of all of the victims had SBP below 90 mmHg, with a mean overall of 86.9 ± 41.6 mmHg.

Median GCS of the patients was 15, and RTS mean was 6.5 (± 2.1), abdominal trauma index (ATI) mean was 32.8 (±14.2), and median ISS was 25.

Regarding location of the IVC injury, 68.9% (51) were infrarenal, 12.2% (9) were suprarenal, 18.9% (14) retrohepatic. There was no suprahepatic injury. Simple surgical repair was performed in 60.8% (45), ligation was done in 27% (20) and atrio-caval shunt as DCS was indicated in 4.1% (3). In 8.1% (6) of the cases, there was not enough time for specific conduct of the injury due to intraoperative patient death.

Associated intra-abdominal injuries were present in 97.3% (72) of the cases, with an average of 2.3 (± 1.4) wounded viscera per patient (Table 1).

Damage control surgery was performed with packing in 33.8% (25), and repacking was necessary in 5.4% (4).

Overall complication rate was 80% (59), and in 58.1% (42), the complications were related to severe bleeding (Table 2). Mean of transfusional requirements expressed in packed red blood cells was 9.1 (± 6.9), and only 5.4% of patients (4) did not demand any blood transfusion.

Overall mortality rate was 52.7% (39). Of these, 64.1% of the patients (25/39) died in the first 24 hours, and 23.1% (9/39) in the operating room. Mortality in the DCS group was 68% (17/25 patients).

The average length of stay of the patients was 10.9 (± 15.3) days, whereas, for patients who were eventually discharged, mean hospital stay was 16.0 (± 11.3) days.

Table 1. Presence of associated intra-abdominal injuries in the study

Organs	Cases (%)
Liver	35 (47.3%)
Abdominal vessels	31 (41.9%)
Small bowel	25 (33.8%)
Duodenum	23 (31.1%)
Large bowel	20 (27%)
Stomach	18 (24.3%)
Diaphragm	10 (13.5%)
Pancreas	10 (13.5%)
Kidney	6 (8.1%)
Ureter	5 (6.8%)
Mesentery	4 (5.4%)
Gall bladder	4 (5.4%)
Splen	3 (4.1%)
Others	6 (8,1%)

Table 2. Number of cases and percentage according to the complications identified

Type of Complication	Cases (%)
Hemorragic complication	42 (56.8%)
Infection complication	24 (32.4%)
Renal failure	4 (5.4%)
Acute respiratory distress syndrome	2 (2.7%)
Rhabdomyolysis	1 (1.4%)
Deep vein thrombosis	1 (1.4%)
Pulmonary thromboembolism	1 (1.4%)

Table 3. Factors associated with mortality using univariate analysis

Variable	p
EMS	0.0318
GCS	0.0005
SBP< 90 mmHg	0.0010
Blood transfusion	0.0034
ISS	0.0010
TRISS	<0.00010
Injury site	0.0006
Intra-operative bleeding	0.0005[2]
Type of treatment	0.0020[3]

Univariate analysis.
EMS: Emergency medical system transport, GCS: Glasgow coma scale, SBP: Systolic blood pressure, BD: Blood transfusion, ISS: Injury severity score, TRISS: Trauma injury severity score, Injury site: Anatomical location of IVC injury, Type of treatment: Management of VCI injury.

Analysis of factors associated with mortality

The application of univariate analysis identified EMS, GCS, SBP, blood transfusion (BD), ISS, TRISS, estimated blood loss, and injury treatment as predictive of mortality (Table 3); and multivariate analysis demonstrated GCS as an independent factor of mortality.

The affected IVC segment also influenced mortality (p= 0.0006) as shown by univariate analysis. Regression analysis showed retrohepatic segment as the most lethal and the infrarenal is the least (odds ratio retrohepatic vs. infrarenal 20.147/p= 0.0053).

Mortality comparison between infrarenal and suprarenal segments showed no relevant statistical differences (p= 0.1381) although suprarenal segment mortality was higher (odds ratio suprarenal vs. infrarenal= 3/p= 0.1381) (Table 4).

Table 4. Mortality by operative management and IVC level injury

IVC Segment	Cases	Treatment	Outcome		Mortality by IVC Segment
			Survivers	Non-survivers	
Retrohepatic segment	14 (19%)	Atriocaval shunt	0	3	93% (13)
		Ligation	0	1	
		Suture	1	5	
		EBT	0	4	
Suprarenal segment	9 (12%)	Ligation	0	1	67% (6)
		Suture	3	4	
		EBT	0	1	
Infrarenal segment	51 (69%)	Ligation	7	11	39% (20)
		Suture	24	8	
		EBT	0	1	
Total	74 (100%)	-	35	39	52.7%

EBT: Exsanguination before specific treatment.

DISCUSSION

Inferior vena cava injury is still associated with great mortality rate despite significant advances in trauma care. The concepts of balanced hemodynamic resuscitation, damage control surgery and fast physiological recover are the foundation of these advances.

Maciel et al. have reported a relevant series with a 13-year retrospective analysis focusing on the impact of these concepts on patients with IVC injuries. The results did not show different outcomes when compared to the literature. However, this conclusion is limited by the retrospective design of the study, and the analysis period which spanned different practices in the resuscitation of this patient population including the concepts of damage control surgery and hemostatic resuscitation which have only recently become more consolidated (17).

This fact brings attention to our series because, despite an actual well-defined resuscitation protocol, each of our IVC injured patients received assistance from different staff personnel, such as EMS responder, trauma surgeons and anesthesiologist team, possibly resulting in different strategies of reanimation. In addition, due to the long period of the present retrospective analysis, the assistance for IVC injuries provided by the surgical teams along time differed, as the emergence of new concepts in resuscitation protocols have gradually been applied in the surgical emergency routine.

That is why it is important to keep a well-trained multidisciplinary trauma staff to coordinate actions and to make sure all steps of the advanced trauma care are being followed. Training courses on definitive surgical trauma care/definitive anaesthetic trauma care course DSTC/DATC and European trauma course (ETC) have been created for this purpose, and they must be encouraged (18-20).

Several studies have reported overall mortality rate for IVC injuries of 43%, ranging from 21 to 66% (5,14). Klein et al. presented a study with the lowest mortality rate (21%) back in 1990, and they associated their results with a straightforward referral of IVC injured patients in critical state to the operating room (OR), where those patients were put on aggressive fluid resuscitation, mainly with crystalloids. Klein's findings signaled toward better outcomes resulting from the evolution in therapy (15). However, other studies that followed Klein's did not show the same trend (8,14,17,21,22).

Authors of manuscripts that have reported mortality rates above 50%, associate these findings with patients' fast arrival at the hospital, given that 30 to 50% of IVC injured patients die at the scene. The improvements in pre-hospital care and in resuscitation techniques have allowed these patients to get alive to the ER (4,11,21).

In the present study, overall mortality rate was 52.7%, and it did not differ from the literature; however, 64% of the deaths occurred within 24 hour of hospital admittance, which is higher than the 30% demonstrated in the literature (23). In patients with DCS, mortality was 68%, still high, because it was very difficult to identify the moment this approach was adopted.

In this series, the types of surgical correction for IVC injuries were direct repair (suture), ligation, and temporary vascular shunt confection as DCS.

The current literature supports infrarenal IVC ligation in clinically instable patients and in cases with complex IVC lesion as part of damage control concept (16,24). Supra-renal IVC ligation is rarely indicated due to its high mortality rates (25). Sullivan et al. have shown that IVC ligation is more often indicated in patients with clinical instabilities, hypotension, elevated ISS and blood transfusion; and therefore, it is associated with higher mortality rate (11).

Matsumoto et al. have demonstrated, based on a large retrospective analysis of 1.316 IVC injured patients, that IVC ligation was done in 34% of the cases and the mortality rate of these patients in particular was 43.7%. They have concluded that IVC ligation is related to more clinical complications, but mortality rates were not significantly different from those with other types of surgical repair (26).

Byerly et al. have also looked at the impact of IVC ligation on outcomes and concluded that IVC ligation by itself does not predict mortality although it is clearly connected with clinical complications. In their series, IVC ligation was performed in 23.4% of patients, and mortality rate in these patients were 23% (27). It is important to note that both studies did not specify the location of IVC injury neither scrutinized the IVC segment ligated. In our study, 27% of all IVC injuries were treated with IVC ligation, and the associated mortality rate was high with 65%. Two of them were ligations performed in suprarenal portion accounting for 10% of all IVC ligations, and both patients (100%) died on post-operative day one.

Considering only the outcomes of eight infrarenal IVC ligations presented in our study, comprising 90% of all IVC ligations, we reported a mortality rate of 61%, which is higher than previous studies (Table 4,5) (11,28).

It is stablished that IVC injuries at the infrarenal portion is the least lethal (14,29,30). Therefore, we were expecting a lower overall mortality rate in our study since 69% of the present manuscript IVC injuries were infrarenal, surprisingly it was not the case (Table 6). One of the possible explanations for it is the delay to implement damage control tactics during surgery.

Looking specifically at patients who underwent infrarenal IVC sutures, the present study reported mortality rate of 25% (eight cases), which is also higher than the literature (Table 5) (11,28).

Table 5. Comparison of treatment between ligation and suture in patients with IVC injury

A. Comparison without discrimination of IVC level injury

Study	Number of Patients	Ligation Rate (%)	Ligation Mortality (%)	Suture Rate (%)	Suture Mortality (%)	Overall Mortality
Navsaria (30)	48	62.5%	27.6%	37.5%	36.8%	31%
Huerta (14)	36	33%	-	-	-	56%
Sullivan (11)	100	25%	60%	57%	32.8%	51%
Singer (29)	308	23.4%	45.8%	77%	34.8%	37%
Cudworth (7)	17	37.5%	83.3%	62.50%	16.6%	38%
Van Rooyen (28)	27	14.8%	50%	59.30%	11.8%	37%
Maciel (17)	62	12.9%	75%	50%	33.3%	58%
Matsumoto (26)	1,316	34%	43.6%	66%	36.2%	36%
Byerli (27)	443	23%	23%	76.50%	16%	23%
Goes jr. (24)	114	29.80%	80.60%	70.20%	35.60%	52.60%
Hamptom (23)	35	66%	-	-	-	49%
Present study	74	27%	65%	61%	38%	52.70%

B. Comparison of the infrarenal level group

Study	Number of Patients with IR Injury n (%)	IR Ligation Rate	IR Ligation Mortality	IR Suture Rate	IR Suture Mortality	IR Mortality
Navsaria	41 (85%)	70%	-	30%	-	23%
Huerta	9 (25%)	55.5%	0	44%	100%	44%
Sullivan	51 (51%)	43%	59%	57%	21%	41%
Singer	-	-	-	-	-	-
Cudworth	4 (25%)	-	-	-	-	25%
Van Rooyen	15 (55.6%)	29%	50%	60%	11%	33%
Maciel	19 (30%)	-	-	-	-	51.70%
Matsumoto	-	-	-	-	-	-
Byerli	-	-	-	-	-	-
Goes jr.	60 (58.3%)	-	-	-		63.30%
Hamptom	19 (54%)	89%	-	11%	-	36.80%
Present study	51 (69%)	35%	61%	63%	25%	39%

IVC: Inferior vena cava, IR: Infrarenal.

Table 6. Comparison of incidence and mortality by IVC segments-Huerta et al. in 2006 (14)

	Average of 30 Years Compiled by Huerta et al.		Present Study	
IVC Level Injury	Incidence by Segment	Mortality by Segment	Incidence by Segment	Mortality by Segment
Suprahepatic	4%	78%	0%	-
Retrohepatic	19%	69%	19%	93%
Suprarenal*	35%	76%	12%	67%
Infrarenal	39%	23%	69%	39%

*Suprarenal including the pararenal segment.

Of these eight cases, five of them arrived at the hospital with hemodynamic instability and two of them had associated aortic injury; apparently these are situations that require ligation according to damage control principles (16). Multiple tries to accomplish direct repair may worsen blood loss and result in further clinical instability in an already critical patient. This did not only negatively impact the mortality rates of those patients that eventually had their IVC ligated but also of those who had their IVC repaired.

CONCLUSION

In conclusion, the present study demonstrated that the theory of advances in trauma care has progressively been disseminated, achieving solid comprehension nowadays. However, trauma care professionals must assure that they are being applied, to decrease the still high overall IVC injury mortality rate. Even when only the infrarenal IVC injuries were considered, mortality rate continued to elevate; and it can be associated with time consuming attempts to repair an injury, deferring damage control and worsening patient's blood loss.

Ethics Committee Approval: This study was approval of the committee of research ethics and institutional review board of University of Campinas School of Medical Sciences (Decision no: 887.154, Date: 24.11.2014).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - RBC, GPF; Design - RBC, MEFM, TRC; Supervision - GPF, RBC; Data Collection and/or Processing - LSJ, TRC, VFK; Analysis and/or Interpretation - RBC, GPF, RNP; Literature Search - VFK, MEFM, LSJ; Writing Manuscript - RBC, RNP; Critical Reviews - LSJ, RNP, TRC, MEFM, VFK, GPF.

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

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (2): 119-125

İnferior vena kava yaralanmaları: Gerçekten yapmamız gerekeni yapıyor muyuz?

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ÖZET

Giriş ve Amaç: İnferior vena kava (İVK) en sık yaralanan intra-abdominal damarlardan biridir ve tedavisi hızlı hareket etmeyi gerektirir. Son yıllarda reanimasyondaki ilerlemelere rağmen, İVK mortalitesinde orantılı bir iyileşme olmamıştır. Bu rapor, günlük travma yardımında dengeli reanimasyon ve hasar kontrol cerrahisine (HKC) bağlılık da dahil olmak üzere mortaliteyi öngören faktörleri ve bunların sonuçlara yansımalarını tartışmayı ve kurumumuzun sonuçlarını literatürle karşılaştırmayı amaçlamaktadır.

Gereç ve Yöntem: İnferior vena kava yaralanması olan hastaları araştırmak için Campinas Üniversitesi (UNICAMP) Klinik Hastanesi'ndeki travma hastalarının veri tabanı kayıtları üzerinden retrospektif bir tasarım analizi yapılmış ve mortaliteyi öngören faktörlere vurgu yapılmıştır.

Bulgular: Ocak 1990'dan Ağustos 2017'ye kadar 74 hastada İVK yaralanması tespit edilmiştir. Ağırlıklı neden %87,8 ile penetran yaralanmaydı (%76,3 ateşli silah). Hastaneye varışta, tüm hastaların %37,8'i hipotansifti ve İSS ortancası 24,5 idi. İnferior vena kavanın yeri açısından, %68,5'i infrarenal, %12,2'si suprarenal, %18,9'u retrohepatik idi. Hastaların %60,8'inde basit onarım yapıldı. Yüzde 27'sine ligasyon ve %4,1'ine atriyokaval şant uygulandı. Hastaların %8,1'inde spesifik ameliyat için yeterli zaman yoktu. Hastaların %97,3'ünde eşlik eden intra-abdominal yaralanma mevcuttu ve transfüzyon gereksinimi ortalama 9,1 ± 6,9 paketlenmiş kırmızı kan hücresi idi. Genel mortalite oranı %52,7 olup, infrarenal yaralanmalar için mortalite oranı %39,2'ydi. Hasar kontrol cerrahisi %68 mortalite ile %33,8'inde uygulanmıştır.

Sonuç: Şok reanimasyonuna ilişkin sağlam bir anlayış giderek yaygınlaşmaktadır ancak travma bakım uzmanları, bunların dengeli bir reanimasyon ve HKC ile uygulandığından emin olmalıdır.

Anahtar Kelimeler: Abdominal vasküler yaralanma, hasar kontrol, inferior vena kava, ligasyon, mortalite, hipovolemik şok

DOİ: 10.47717/turkjsurg.2024.6363

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (2): 126-135

Laparoscopic-assisted pancreaticoduodenectomy for periampullary carcinoma: An experience of 50 cases from a single tertiary care center

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ABSTRACT

Objective: Laparoscopic-assisted pancreaticoduodenectomy (LAPD) is being performed in several centers worldwide. The proportion of minimally invasive pancreaticoduodenectomy for periampullary carcinoma (PAC) has recently increased, owing to its potential benefits. However, the safety and feasibility of LAPD have not yet been standardized. In this study, it was aimed to report our experience with LAPD in 50 patients.

Material and Methods: Fifty patients with resectable PAC who underwent LAPD between June 2021 and August 2023 were retrospectively analyzed.

Results: Mean age of the study group was 49.9 ± 12 years, and most were females (54%). Ampullary carcinoma was the most common type (58%). Mean operative time and estimated blood loss were 460 ± 40 minutes and 426 ± 156 mL, respectively. Four patients had suspected portal vein involvement, and two patients had hemorrhage during uncinate process dissection, resulting in conversion to open surgery. Severe post-operative morbidity was noted in 13 (26%) patients. Following surgery, Grade B post-operative pancreatic fistula was present in 26% of patients, whereas Grade B and C delayed gastric emptying was present in 18% and 2% of patients, respectively. Mean hospital stay was 9.4 ± 2.8 days. Mean number of lymph nodes harvested was 13.4 ± 4. All patients underwent R0 resection, and no mortality was noted during the 30-day follow-up period.

Conclusion: LAPD is a feasible procedure for resectable PAC offering good oncological outcomes and minimal complications. It can be performed effectively by experienced surgeons in specialized centers.

Keywords: Laparoscopic-assisted, pancreas, pancreaticoduodenectomy, periampullary carcinoma

INTRODUCTION

Periampullary carcinomas (PAC) are cancers affecting the pancreatic head (within two cm of the ampulla), duodenum, ampulla of Vater, and distal common bile duct (1). Open pancreaticoduodenectomy (OPD) has been the standard surgical treatment for PAC (2). The increasing incidence of these malignancies and improvements in laparoscopic surgery techniques have led to a reassessment of surgical techniques for treatment of PAC (3). Minimally invasive pancreaticoduodenectomy includes various approaches such as total laparoscopic pancreaticoduodenectomy (TLPD), laparoscopic-assisted pancreaticoduodenectomy (LAPD), and robotic assisted pancreaticoduodenectomy. Despite advances, TLPD remains one of the most complex operations owing to its intricate surgical approach, reconstructive techniques, and associated risks of morbidity and mortality. Specific complications such as post-operative pancreatic fistula (POPF) and post-pancreatoduodenectomy hemorrhage (PPH) can have severe outcomes (4,5). POPF is a crucial concern regarding the safety and effectiveness of TLPD. The safety and efficacy of laparoscopically performed pancreaticoenteric and bilioenteric anastomoses are constrained and debatable (6,7).

LAPD revolutionizes PAC management by offering reduced blood loss and diminished post-operative pain, including faster recovery and shorter hospital stays than the traditional open approach (8). Currently, the available data does not definitively establish a safety comparison between TLPD and OPD (9-11). However, LAPD is a hybrid technique combining laparoscopic dissection with an upper midline incision for anastomosis, reducing the risk of anastomotic leaks. This innovative technique aims to harness the advantages of minimally invasive surgery while addressing the challenges associated with pancreaticoduodenectomy (PD).

Cite this article as: Singh BN, Kodali R, Anand U, Parasar K, Kant K, Anwar S, et al. Laparoscopic-assisted pancreaticoduodenectomy for periampullary carcinoma: An experience of 50 cases from a single tertiary care center. Turk J Surg 2024; 40 (2): 126-135.

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Received: 16.04.2024
Accepted: 03.06.2024
Available Online Date: 28.06.2024

DOI: 10.47717/turkjsurg.2024.6419

Existing literature on LAPD is limited, and a comprehensive understanding of patient characteristics, hospital course, and short-term outcomes is essential for evaluating the efficacy and safety of this evolving surgical approach (12-16). This article aimed to provide insights into the existing body of knowledge regarding LAPD's effectiveness and safety in PAC and advance our understanding of LAPD as a viable alternative to OPD in bridging the learning curve of TLPD.

MATERIAL and METHODS

We performed a retrospective analysis of patients who underwent LAPD at a tertiary care center in the eastern India between June 2021 and August 2023. Patients with clinical and radiological suspicion of a periampullary mass or a histological diagnosis of PAC were included. Patients with locally advanced disease, previous upper abdominal surgery, or prior neoadjuvant therapy were excluded from the study. We initially performed 80 cases of OPD during the first three years and later transitioned to LAPD. Our center performs 80-90 PD procedures per year with surgeons who have extensive laparoscopic experience and have surpassed the learning curve. The study was conducted in accordance with the principles of the Declaration of Helsinki. After obtaining approval from the Institute's Ethical Committee review board (protocol code: IEC/2022/1043), we analyzed various parameters including patient demographics, comorbidities, pre-operative blood indices, the necessity for pre-operative biliary drainage, the duration of surgery after biliary drainage, intraoperative details, early post-operative outcomes, and histopathological data. Pre-operative biliary drainage [endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic biliary drainage (PTBD)] was performed in patients presenting with cholangitis, intractable pruritus, and total bilirubin >7 mg/dL, according to our institute protocol. Most patients underwent surgery within four-six weeks of biliary drainage. Resectability criteria were assessed using a pre-operative pancreatic protocol computerized tomography scan, following the recommendations of the National Comprehensive Cancer Network 2023 (17). Data entry was performed using MS Excel 2016, and data analysis was conducted using IBM SPSS version 26.0.

Operative Details

Pre-operative

As part of the standardized pre-operative protocol, all patients underwent routine fasting with nil per oral instructions on the day before the operation. Intravenous fluids were administered to maintain hydration, along with prophylactic intravenous antibiotics administered one day before surgery, a practice especially emphasized in patients with stents at our institute. Routine antibiotic dosages were administered at the induction of general anesthesia. No somatostatin analogs were administered during the pre-operative period. Additionally, the standard pre-operative procedure includes placing indwelling urinary catheters and nasogastric tubes. Patients were placed in supine position with their legs apart to facilitate optimal access during the surgical procedure (Figure 1). The surgery involved the utilization of standard laparoscopic instruments, including the application of a LigaSure device (Medtronic), harmonic shears, and bipolar device (Ethicon). These instruments collectively contribute to efficient and precise surgery.

Intraoperative (Laparoscopic Resection)

Following the initial staging laparoscopy through a 10 mm port at the umbilicus, additional ports were strategically placed, as illustrated in Figure 2. A 10 mm supraumbilical trocar was used for pneumoperitoneum and camera insertion, with additional ports in the right midclavicular line (5 mm), left midclavicular line (12 mm), right lumbar quadrant (5 mm), and left lumbar quadrant (5 mm). The lesser sac was accessed by dividing the gastrocolic ligament, and the right gastroepiploic vessels were meticulously traced to their insertion into the gastrocolic trunk of Henle and subsequently divided between the Ligaclips. Mobilization ensued with the hepatic flexure and right colon, accompanied by extended kocherization of the duodenum, to expose the left renal vein.

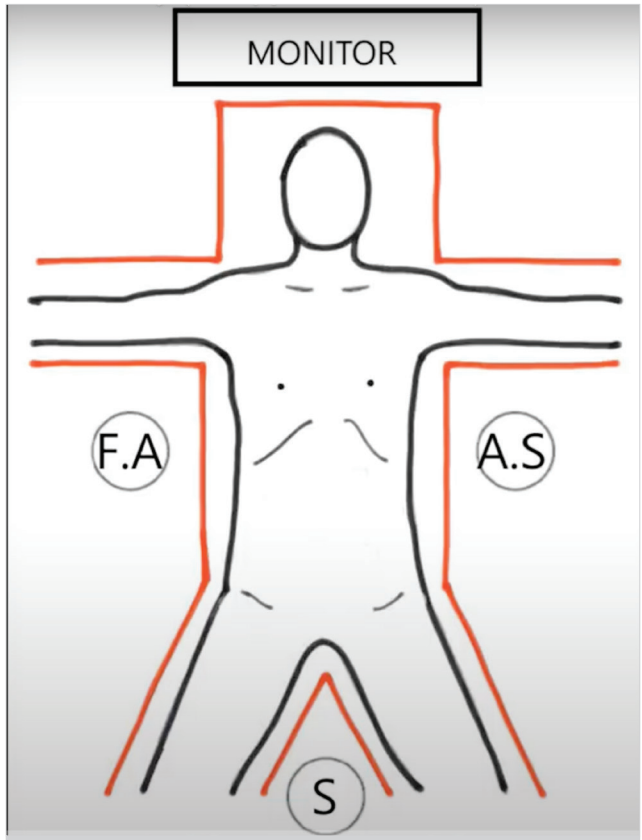

Figure 1. The patient is positioned supine with leg split (French position), surgeon stands in between the legs and assistants on either side of the patient.

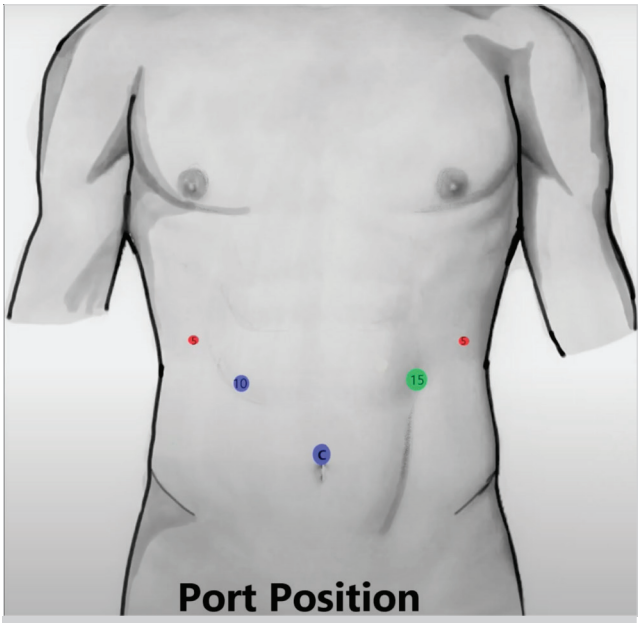

Figure 2. 10 mm supraumbilical port for pneumoperitoneum and camera access, left 15 mm and right 5 mm midclavicular as working ports, right and left lumbar 5 mm ports for retraction.

The superior mesenteric vein (SMV) course into the portal vein (PV) was identified, and the relationship between the tumor and the superior mesenteric artery (SMA) was assessed. Precise vision and blunt dissection created a tunnel between the neck of the pancreas and front of the SMV-PV (Figure 3). After PV, dissection continued cephalad toward the liver hilum, completing the porta-hepatis lymphadenectomy. The third and fourth parts of the duodenum were mobilized by dividing the ligament of Treitz. The proximal jejunum was then delivered into the supracolic compartment and divided using a linear cutting stapler, followed by division of the jejunojejunal vessels. The lymphatic tissue was cleared from the anterior surface of the aorta to trace the origin of the SMA. The stomach antrum was divided using a linear cutting stapler, followed by lymphadenectomy of the common hepatic artery, dissection, and division of the gastroduodenal artery between the ligaclips. The uncinate process of the pancreas was completely mobilized from the SMA. The pancreatic neck was then transacted using an ultrasonic harmonic device. Cholecystectomy was performed, followed by common hepatic duct transection, as the final step to fully mobilize the specimen (Figure 4). The specimen was retrieved through an upper midline laparotomy with a length of 6-7 cm, extending to the supraumbilical port.

Intraoperative (Open Reconstruction)

The stapled end of the jejunum was carefully brought through the retrocolic plane and navigated into the supracolic compartment. Depending on the condition of the pancreatic duct, a tailored approach is employed for pancreaticojejunostomy. A modified Blumgart-style end-to-side duct-to-mucosa pancreaticojejunostomy was performed in patients with a dilated pancreatic duct. Alternatively, for non-dilated ducts, an invagination/docking method was employed. To establish a secure connection between the hepatic duct and jejunum, an end-to-side duct-to-mucosa hepaticojejunostomy was performed using interrupted 4-0 polydioxanone sutures. The antecolic Hoffmeister method of side-to-side anastomosis was used for gastrojejunostomy. A single abdominal drain was placed into the right subhepatic space.

Outcomes & Definitions

Operative time was measured from the initial trocar insertion for LAPD until skin closure. Estimated blood loss was determined by calculating the total volume of fluids collected in the suction

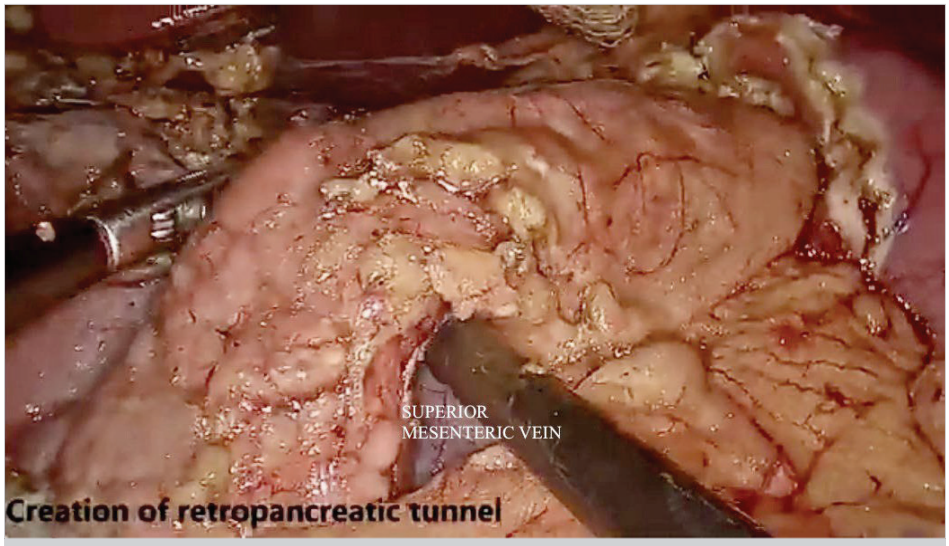

Figure 3. Blunt dissection under magnified vision used to create a tunnel behind the neck of pancreas.

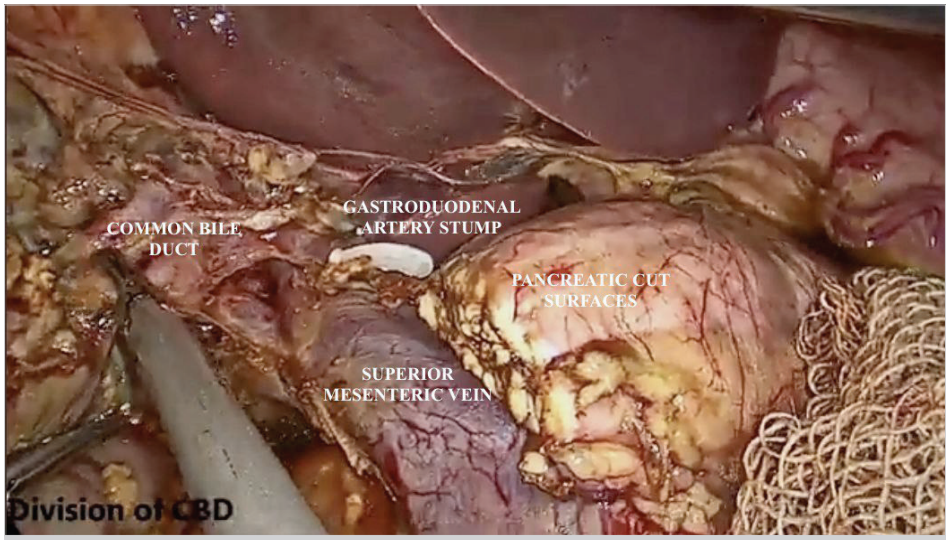

Figure 4. Common bile duct transection with exposed pancreatic cut surface, superior mesenteric vein and gastroduodenal artery stump.

device and the weight of the gauze and towels used during the procedure. Conversion from laparoscopic to open procedure was defined as the shift to laparotomy before reaching the dissection of the mid-pancreatic tissue, regardless of the specific laparotomy level. Post-operative complications (recorded for 30 days) were evaluated following the Clavien-Dindo classification and encompassed issues such as POPF, delayed gastric emptying (DGE), bile leaks, PPH, intra-abdominal collections, and surgical site infections. These complications were categorized into Grades A, B, and C, as outlined in the international study group of pancreatic surgery guidelines (18,19). Re-operation was defined as a subsequent surgical procedure necessitated within 30 days of LAPD owing to significant complications. Morbidity and mortality refer to adverse health outcomes or fatal outcomes that occur during or within 30 days after surgery. The final pathological diagnosis was established using the AJCC cancer staging manual, considering tumor size, grade, pathological type, lymphovascular invasion, perineural invasion, total number of lymph nodes inspected, and margin status. Surgical resection was categorized as R0 if cancer was undetected in any of the margins, R1 if cancer was discovered within 1 mm of the resected margins, and R2 if cancer persisted in any of the margins.

RESULTS

Mean age of the study population was 49.9 ± 12 years, and most were females (54%). The most common symptom was jaundice (86%), followed by pruritus (68%), and recurrent cholangitis (46%), with a mean BMI of 21 ± 1.7 kg/m^2. Most of the patients were ASA Grade 1 (64%). Diabetes mellitus was the most common comorbidity (26%) (Table 1).

Mean total bilirubin and direct bilirubin levels were 12.2 ± 7.6 mg/dL and 7.2 ± 4.5 mg/dL, respectively. Pre-operative Hb levels ranged between 10.1-12.5 gm/dL. Most patients (64%)

Table 1. Distribution of the study population based on demographic and clinical characteristics (n= 50)

Parameter	Frequency (n)	Percentage (%)
Age (in years)		
<60	41	82.0
≥60	9	18.0
Sex		
Female	27	54.0
Male	23	46.0
BMI		
Normal (18.5-22.9 kg/m^2)	48	96.0
Overweight (23.0-24 kg/m^2)	2	4.0
Obese (>25 kg/m^2)	0	0
ASA Grade		
I	32	64.0
II	17	34.0
III	1	2.0
Symptoms		
Jaundice	41	82.0
Weight loss	13	26.0
Vomiting	2	4.0
Recurrent cholangitis	23	46.0
Pruritus	34	68.0
Comorbidities		
Diabetes mellitus	13	26.0
Hypertension	9	18.0
COPD	3	6.0
Hypothyroidism	1	2.0
None	28	56.0

BMI: Body mass index, ASA: American society of anaesthesiologists, COPD: Chronic obstructive pulmonary disease.

Table 2. Distribution of the study population based on pre-operative parameters (n= 50)

Parameters	Mean ± SD	
Total bilirubin levels (mg/dL)	12.2 ± 7.6	
Direct bilirubin levels (mg/dL)	7.2 ± 4.5	
Prothrombin time (seconds)	14.5 ± 2.9	
Hemoglobin (g/dL)	10.8 ± 1.1	
Pancreatic duct diameter (mm)	5.05 ± 2.8	
	Frequency (n)	**Percentage (%)**
CA 19-9 (U/mL)		
<37	18	36.0
≥37	32	64.0
Albumin levels (g/dL)		
<3.4	31	62.0
3.4-5.4	19	38.0

had elevated (>37 U/mL) CA 19-9 levels (normal, <37 U/mL). Mean pancreatic duct diameter was 5.05 ± 2.8 mm (Table 2).

Endoscopic retrograde cholangiopancreatography and percutaneous transhepatic biliary drainage were performed in 33 patients presenting with cholangitis or bilirubin levels >7 mg/dL, as per our institute protocol, and mean duration of surgery following biliary drainage was four-six weeks. The average operative time was 460.7 ± 39.8 mins, and the estimated blood loss was 426 ± 156 mL. The pancreatic texture was soft in 50% of patients, whereas that of the other half had a firm texture. Conversion to open procedures was required in six patients (12%). Four cases had suspected PV involvement, and two had hemorrhage during uncinate dissection. Significant post-operative complications were noted in 13 patients (26%), of which one had a severe complication (≥Grade III of the Clavien–Dindo classification). Bleeding from a pancreatic cut surface was noted in one patient, requiring re-exploration on the second post-operative day. Grade B POPF was noted in 26% of the patients, and Grade C POPF was not reported in our study. Grade A DGE was observed in 20 cases (40%), Grade B in nine cases (18%), and Grade C in one case (2%). Ten cases of grades B and C had an intra-abdominal collection, requiring percutaneous ultrasound-guided pigtail catheter drainage. Three patients (6%) had bile leaks that resolved with conservative treatment. Surgical site wound infections were noted in 17 patients (34%). Most patients had superficial surgical site infections that required daily dressing and antibiotic coverage per culture pattern. No patient had a chyle leak. The median length of hospital stay was 9.4 ± 2.8 days. Three patients were readmitted in the first 30 days, two patients presented with DGE, managed conservatively with prokinetics, and one patient with hematemesis had a gastroduodenal stump blowout and underwent coil embolization on the 10th post-operative day. No mortality was observed during the 30-day follow-up period (Table 3).

Following oncological outcomes, the majority were ampullary lesions (58%), followed by distal cholangiocarcinoma (32%), duodenum (6%), and the pancreatic head (4%). Mean number of lymph nodes harvested was 13.4 ± 4. R0 resection was feasible in all 50 patients (100%). Perineural and lymphovascular invasions were noted in 20% and 18% of resected specimens, respectively. Other histopathological outcomes are presented in Table 4.

DISCUSSION

PD is a complex and intricate surgery that is primarily performed through an open technique in many centers. As technology and surgeons' expertise in laparoscopy have advanced, there has been a growing interest in adapting these minimally invasive pancreatic surgery methods. The first attempt at laparoscopic PD dates to 1994 by Gagner and Pomp (20). Over the years, various studies and case series have documented the progress of laparoscopic techniques in PD, demonstrating improvements in patient outcomes, reduced post-operative complications, and short hospital stays (21). TLPD is a highly complex procedure requiring advanced laparoscopic skills, expertise, and surgical proficiency, including strict adherence to oncologic principles, management of laparoscopic hemorrhage when significant vascular injuries occur, and demanding skills for pancreatic and biliary reconstruction. However, obesity, vascular involvement, and advanced disease can limit the suitability of the laparoscopic approach. This underscores the importance of careful patient selection to achieve optimal outcomes. Moreover, being a relatively novel approach, TLPD's long-term outcomes and safety profiles have not been as extensively studied as those of open procedures, and limited institutional experience may impact its widespread adoption. Continuous advancements and further research are essential to refine this technique and broaden its applicability. LAPD combines laparoscopic and open techniques, allowing surgeons to benefit from the advantages of minimally invasive surgery, while maintaining the precision and safety of pancreaticoenteric and bilioenteric anastomosis using an open technique. The present study described our experience with LAPD without imposing restrictive selection criteria.

We observed a long operative time at the beginning of the learning curve. The high-definition magnified views of the surgical field and accurate identification of anatomical structures and ligation of blood vessels reduced the need for time-consuming hemostasis, making the dissection and resection precise and efficient, and reducing surgery duration and blood loss in later cases. The feasibility of LAPD and the potential reduction in operative time may vary depending on the patient's specific condition, surgeon's expertise, and availability of advanced laparoscopic equipment. Increased operative time and rate of post-operative blood transfusions in the current study were similar to those reported in the existing

Table 3. Distribution of the study population based on intraoperative and post-operative findings (n= 50)

Parameter		Frequency (n)	Percentage (%)
		Mean ± SD	
Pre-operative biliary drainage			
ERCP		23	46.0
PTBD		10	20.0
None required		17	34.0
Operative time (minimum)		460.7 ± 39.8	
Estimated blood loss (mL)		380 ± 156	
Conversion to open surgery		6	12.0
Pancreas texture			
	Firm	25	50.0
	Soft	25	50.0
POPF grade			
	A	32	64.0
	B	13	26.0
	C	0	0
	Nil	5	10.0
DGE grade			
	A	20	40.0
	B	9	18.0
	C	1	2.0
	Nil	20	40.0
Post-operative haemorrhage		1	2.0
Bile leak		3	6.0
Respiratory complications		6	12.0
Intrabdominal collection		13	26.0
	Pelvis	1	2.0
	Peripancreatic	7	14.0
	Subdiaphragmatic	1	2.0
	Subhepatic	4	8.0
Time to passage of flatus (day) median (range)		4 (3-4)	
Time of oral intake (day) median (range)		5 (4-6)	
Post-operative ICU stay (day) median (range)		2 (1-3)	
Duration of hospital stay (day)		9.4 ± 2.8	
Wound infection		17	34.0
Superficial infections		13	26.0
Deep infections		4	8.0
Clavien-Dindo classification (grade)			
	I	36	72.0
	II	13	26.0
	≥III	1	2.0
Re-exploration		1	2.0
Re-admission (within 30 days)		3	6.0

ERCP: Endoscopic retrograde cholangiopancreatography, PTBD: Percutaneous transhepatic biliary drainage, POPF: Post-operative pancreatic fistula, DGE: Delayed gastric emptying.

Table 4. Distribution of the study population based on tumour characteristics (n= 50)

Characteristic		Frequency (n)	Percentage (%)
cTNM staging	T1N0	6	12.0
	T1N1	1	2.0
	T2N0	25	50.0
	T2N1	1	2.0
	T3N0	7	14.0
	T3N1	8	16.0
	T3N2	2	4.0
Tumour location	Distal common bile duct	16	32.0
	Duodenum	3	6.0
	Pancreatic head	2	4.0
	Ampulla	29	58.0
R0 resection		50	100.0
Perineural invasion		9	18.0
Lymphovascular invasion		10	20.0
Lymph nodes positive for malignancy		12	24.0
Number of lymph nodes harvested (mean ± SD)		13.4 ± 4.1	

literature (22). In a study by Son et al., the median operative time was 277.5 minutes (range, 258.7-330 min), with a median intraoperative estimated blood loss of 319.5 mL (range, 241.2-425 mL) (23). Tian et al. have noted that LAPD has a longer intraoperative time (372 min vs. 305 min) and lower blood loss (300 mL vs. 500 mL) than the open procedure (8). Pham et al. have reported a median total operative time of 370 min (365-442.5 min), with a median laparoscopic resection time of 253 min (240-315 min) (24).

Patients undergoing LAPD may experience reduced post-operative pain and early return of bowel function associated with LAPD contribution to faster recovery than the open approach (21). This positively impacts overall patient experience and satisfaction. Reduced wound-related issues, such as infections and hernias, contribute to smooth recovery. The assertion that post-operative complications are more common in LAPD than in the open approach is not supported by the existing literature. The outcomes of LAPD vary based on patient selection, surgeon expertise, and institutional practice. Post-operative complication rates reported in the literature vary greatly from 26% to 74% (21-24). POPF is a common concern after PD. Some studies have reported similar or slightly increased rates of POPF in LAPD, particularly during the early adoption of laparoscopic techniques (21). However, with increasing experience, surgeons often achieve comparable outcomes with increasing experience. The incidence of DGE after LAPD varies across studies, but significantly differs (14-16,21). Post-operative pneumonia is generally more related to patient factors and perioperative care than to the surgical approach itself. The choice between laparoscopic or open surgery alone may not be the primary determinant. The incidence of anastomotic, bile, and chyle leaks can vary based on the surgeon's experience and the specific technique used rather than being solely attributed to the choice of LAPD or OPD. It is important to note that LAPD is a technically challenging procedure with a steep learning curve. As surgeons gain more experience with laparoscopic techniques, complication rates often decrease (8). Patient selection, surgeon experience, and institutional practices are important in determining the outcomes. Our study described clinically relevant Grade B POPF in 13 patients (26%); Grades A, B, and C DGE in 20 (40%), nine (18%), and one (2%), respectively; PPH in one (2%); bile leak in three (6%); and respiratory complications in six (12%). The findings of other studies are consistent with those observed in the present study. Son et al. have reported 33.4% surgery-related morbidity, with bleeding and severe POPF affecting four patients, biliary fistula in one, DGE in two, and intestinal obstruction in one patient (23). In a study by Pham et al., DGE has been noted in 28% and POPF in 11% of the patients (24). In our study group of 50 patients, one patient required re-exploration on POD2 for post-operative hemorrhage from a pancreatic cut surface. Re-operation was necessary for one of 38 patients who underwent LAPD in the study by Tian et al. while it was 11% in the study by Pham et al (8,24).

The feasibility and safety of LAPD have been the subject of intense investigation and debate within the surgical community (8). As expertise grows, the feasibility of the LAPD increases, making it an option for appropriately selected cases. Successful LAPD relies heavily on meticulous selection of patients. Tumor size, vascular involvement, and overall patient

health influence the feasibility of the procedure. Patient characteristics must be carefully evaluated to identify suitable candidates for LAPD treatment. While early experiences with LAPD suggested higher complication rates than open surgery, advancements in techniques and increased surgeon expertise have reduced complication rates (23-25).

Conversion from LAPD to open surgery may be required in certain cases, such as when unexpected anatomical complexities or hemorrhage are encountered. In our study, six of the 50 cases required open conversion due to suspicious PV involvement (n= 4) and uncontrollable hemorrhage during uncinate dissection (n= 2). Conversion rate in laparoscopic PD varies from 0% to 40%, with an average of 9.1% (8,23,24,26,27). In a single-center experience of 21 cases by Al-Sadairi et al., the reported conversion rate was 19% (28). Inadequate exposure of the anatomical structures, suspicious tumor involvement to surrounding structures, vascular anomalies, hemorrhage during dissection, severe adhesions from chronic inflammation, and unexpected intraoperative complications are common reasons for open conversion. Ultimately, the surgeon's experience and judgment are important in the decision to switch from laparoscopic to open surgery. Nonetheless, the conversion should still be advocated for the patient's best interests.

Mean length of hospital stay in our study was 9.4 ± 2.8. The average length of hospital stay for LAPD in the literature ranges from seven to 23 days, with a weighted average of 13.6 days (8,23,24,28,29). These findings from previous studies are consistent with those observed in the present study although these parameters must be noted to vary among different hospitals due to variations in treatment protocols, operative techniques, post-operative complications, and cultural and organizational differences. The primary prognostic factors for PD include achieving an R0 resection margin and lymph node yield. Although numerous studies have documented 100% R0 resections, only a few have undertaken analyses specifically addressing the uncinate margin and SMV margin positivity. These aspects are crucial components of the pathological evaluation for achieving oncological radicality. The incidence of R1 resection after PD for PDAC has been reported to range from 2% to 75%, potentially attributable to variations in pathological protocols across studies (30). Notably, previous research on LAPD has indicated a low occurrence of R1 resection, often associated with a small diameter and early lesion inclusion. In our study, all cases in the LAPD group achieved R0 resection, and the median number of harvested lymph nodes in the resected specimens was 13.4 ± 4. The results of this study are consistent with those of Pham et al. wherein the median tumor size was 23 mm, with an 88% R0 resection rate and a median lymph node yield of 13 (11-15) (24). Tian F et al. have reported an R0 resection rate of 90.9 %, and ≥12 lymph nodes were resected in all patients with LAPD (8). In the largest matched-pair analysis comparing hybrid PD with open PD in 120 patients, there is a notable reduction in clinically relevant post-operative complications. Additionally, the hybrid technique demonstrates fast post-operative recovery while maintaining equivalent long-term oncologic outcomes (31). The successful implementation of LAPD in an institute depends on achieving ample procedural volume, expertise in advanced laparoscopic and pancreatic surgical techniques, and thorough training. In addition, it requires effective mentoring, supervision, and meticulous patient selection. The limitation of the current study is its single-center design, which may restrict the generalizability of the data to a wide population, and the relatively small sample size may hinder inferential statistical analysis.

CONCLUSION

We have observed several advantages of laparoscopy in our initial experience with 50 cases of LAPD, particularly during the resection phase due to enhanced visualization and magnification. This has contributed to precise dissection, resulting in decreased blood loss and the accomplishment of anastomosis through a small laparotomy incision. Further evidence, from the studies that compares different surgical techniques in terms of safety and feasibility, is warranted.

Ethics Committee Approval: This study was approved by All India Institute of Medical Science Ethics Committee (Decision no: IEC/2022/1043, Date: 01.05.2023).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - BNS, RK, UA; Design - BNS; Supervision - RK, SN, KK; Fundings - SA, KK, SW; Materials - KP, KK; Data Collection and/or Processing - SA, UA, SW; Analysis and/or Interpretation - SA, BS; Literature Search - RK, UA; Writing Manuscript - KP, BS; Critical Reviews - KP, BS, BNS.

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

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (2): 126-135

Periampuller karsinom için laparoskopi yardımlı pankreatikoduodenektomi: Tek bir üçüncü basamak bakım merkezinden 50 olgu deneyimi

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ÖZET

Giriş ve Amaç: Laparoskopi yardımlı pankreatikoduodenektomi (LAPD) dünya çapında birçok merkezde uygulanmaktadır. Periampuller karsinom (PAK) için minimal invaziv pankreatikoduodenektomi oranı, potansiyel faydaları nedeniyle son zamanlarda artmıştır. Bununla birlikte, LAPD'nin güvenliği ve uygulanabilirliği henüz standardize edilememiştir. Bu çalışmada, 50 hastada LAPD ile ilgili deneyimlerimizi sunduk.

Gereç ve Yöntem: Haziran 2021 ve Ağustos 2023 tarihleri arasında LAPD uygulanan rezektabl PAK'lı 50 hasta retrospektif olarak analiz edildi.

Bulgular: Çalışma grubunun ortalama yaşı 49,9 ± 12 yıl olup çoğunluğu kadındı (%54). Ampuller karsinom en sık görülen tipti (%58). Ortalama ameliyat süresi ve tahmini kan kaybı sırasıyla 460 ± 40 dakika ve 426 ± 156 mL idi. Dört hastada portal ven tutulumu şüphesi vardı ve iki hastada unsinat proses diseksiyonu sırasında kanama oldu ve açık cerrahiye geçildi. Ameliyat sonrası ciddi morbidite 13 (%26) hastada kaydedilmiştir. Ameliyat sonrasında hastaların %26'sında B derecesinde pankreatik fistül, %18'inde B ve C derecesinde mide boşalmasında gecikme ve %2'sinde mide boşalmasında gecikme görüldü. Ortalama hastanede kalış süresi 9,4 ± 2,8 gündü. Ortalama alınan lenf nodu sayısı 13,4 ± 4. Tüm hastalara R0 rezeksiyon uygulandı ve 30 günlük takip süresi boyunca mortalite görülmedi.

Sonuç: LAPD, rezektabl PAK için iyi onkolojik sonuçlar ve minimal komplikasyonlar sunan uygulanabilir bir prosedürdür. Uzmanlaşmış merkezlerde deneyimli cerrahlar tarafından etkili bir şekilde uygulanabilir.

Anahtar Kelimeler: Laparoskopi yardımlı, pankreas, pankreatikoduodenektomi, periampüller karsinom

DOİ: 10.47717/turkjsurg.2024.6419

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (2): 136-144

Risk factors for anastomotic complications after elective intestinal resection in Crohn's disease

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ABSTRACT

Objective: Anastomotic leaks are the most feared complications after surgery in patients with Crohn's disease. Identifying associated risk factors is crucial for prevention. We aimed to evaluate possible risk factors for anastomotic complications in our case series.

Material and Methods: This was a single-center, retrospective, observational study. Eighty-six patients who underwent intestinal resection due to Crohn's disease at the Department of General Surgery, Marmara University, Faculty of Medicine, from 2015 to 2023 were enrolled. Adult patients of either sex who are over 18 years old were included. Cases, where the anastomosis was defunctioned with a proximal diverting ileostomy or colostomy were excluded from the study.

Results: The mean (StD) age was 34.8 (14.4) years, and 50 patients (58.1%) were male. Twenty-five patients had post-operative complications (29.1%), and 10 of them (11.6%) were above grade three according to the Clavien-Dindo classification. Anastomotic leakage was observed in two, intra-abdominal collection in two, sepsis in two, enterocutaneous fistula in three, and ileus in the remaining one. While the albumin value <3 gr/dL (OR 5.15, p< 0.03) and pre-operative medical treatment (OR= 4.79; p= 0.05) were associated with higher odds of post-operative overall complications, only hypoalbuminemia 3 g/dL (OR= 14.3; p= 0.04) was associated with a higher probability of post-operative anastomotic/septic complications.

Conclusion: In patients with pre-operative hypoalbuminemia, temporary stoma creation should be considered due to the potential increased risk of high anastomotic complications. The medical treatments should be discontinued in the pre-operative period due to the increased risk of complications.

Keywords: Crohn's disease, post-operative complications, anastomotic leakage

INTRODUCTION

Crohn's patients require surgical treatment involving intestinal resection at some point in their lives. The probability of intestinal resection increases over the years from the initial diagnosis, with respective probabilities of 61% for the first year, 77% for five years, and 83% for ten years (1). Although the majority of Crohn's patients are young and do not have significant comorbidities, the rate of post-operative complications after intestinal resection is higher compared to other benign conditions (2). Mainly, intrabdominal septic events such as anastomotic leakage, enterocutaneous fistula, and intra-abdominal abscess are the most troublesome post-operative issues, with occurrence rates ranging from 5% to 20%. While the failure of anastomotic healing may manifest as leakage at the anastomotic site, leading to septic complications, chronic anastomotic healing failure may lead to the formation of enterocutaneous fistulas at incision sites or drainage canals, sometimes occurring within weeks after hospital discharge (3). In addition, the realization that these complications also contribute to another serious problem, namely disease recurrence, clearly reveals the magnitude of the problem (2,4).

Several different risk factors have been suggested for post-operative septic complications following intestinal resection in Crohn's disease, which include pre-operative albumin levels, poor nutritional status, duration of symptoms, pre-operative steroid, immunomodulatory or biological agents use, presence of abscess during laparotomy, positive histological margins, colo-colonic anastomoses, and repeated resections (2,5-10). However, other studies have reported that some of these factors are not associated with septic events, leading to ongoing debates. Better knowledge and valid evidence identifying perioperative risk factors for anastomosis safety would enable surgeons to decide in the perioperative period which patients are suitable for stoma formation or which patients provide optimal conditions for primary anastomosis.

Cite this article as: Atıcı AE, Özocak AB, Karpuz GF, Sevindi Hİ, Dağancı ŞF, Yeğen ŞC. Risk factors for anastomotic complications after elective intestinal resection in Crohn's disease. Turk J Surg 2024; 40 (2): 136-144.

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Received: 15.04.2024
Accepted: 03.06.2024
Available Online Date: 28.06.2024

DOI: 10.47717/turkjsurg.2024.6417

Therefore, this study aimed to identify independent risk factors associated with anastomotic leakage or intra-abdominal sepsis in patients undergoing bowel resection and primary anastomosis without stoma formation in Crohn's disease.

MATERIAL and METHODS

Study Design

This study was a single-center, retrospective, observational study. One hundred and two patients underwent intestinal resection due to Crohn's disease at the Department of General Surgery, Marmara University Faculty of Medicine, from 2015 to 2023, and 86 patients who met the inclusion criteria were enrolled. Patients' clinical, operative, pathologic, and short-term outcomes were recorded prospectively and analyzed retrospectively. The study protocol was approved by the Ethics Committee of Faculty of Medicine, Marmara University, and was conducted by the principles of the Declaration of Helsinki (Protocol no: 09.2023.890). The study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies (11).

Study Population and Data Collection

Adult patients of either sex who were over 18 years of age and underwent intestinal resection with primary anastomosis for active Crohn's disease were included. Patients under the age of 18, cases where the anastomosis was defunctioned with a proximal diverting ileostomy or colostomy, emergency or urgent surgical procedures, underwent stricturoplasty and instances where data were missing or invalid, preventing analysis were excluded from the study (Table 1). Patients' data, including age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, nutritional risk score (NRS), smoking, pre-operative blood tests, if any pre-operative medical treatments or interventions, characteristic of the disease, localization, anastomotic technique, operative and post-operative parameters, early post-operative complications, length of hospital stay, reoperations, readmissions, and mortality rates were recorded and analyzed as possible risk factors for anastomotic leak.

Table 1. Study population

n= 102	
Intestinal resection plus anastomosis	
	Two loop ileostomy
	Two loop colostomy
	Two end colostomy
	Ten end ileostomy
n= 86	
Intestinal resection plus anastomosis	
Without stoma	

Outcomes

This retrospective study aimed to examine patient- and surgery-related risk factors that could impact the safety of anastomosis in patients with Crohn's disease undergoing intestinal resection. Secondary outcomes included the overall complication rate, length of hospital stay (LOS), reoperations, and mortality rate within 30 days.

Surgical Approach

The decision for surgical resection was made during multidisciplinary meetings of the inflammatory bowel disease (IBD), which included gastroenterologists, general and gastrointestinal surgeons, and radiologists. All surgeries were performed with a conservative approach (open technique). By adhering to the basic principles of bowel resection for Crohn's disease, all visible disease was eliminated with limited and clear surgical margins-all patients who had intestinal anastomosis, conducted with either stapled or hand-sewn methods. Hand-sewn anastomoses were performed by either end-to-side or side-to-side anastomoses. Stapled anastomoses were performed by two methods: Functional side-to-side anastomosis with the use of a linear stapler and side-to-end anastomosis with the use of a circular stapler. The choice between hand-sewn anastomosis and stapled anastomosis was left to the surgeon's discretion.

Outcome Measures

Anastomotic leak was defined based on the 1991 UK Surgical Infection Study Group, and it was confirmed if there was fecal discharge from the drain, peritonitis, post-operative cutaneous fistulas from the anastomotic site, or by imaging methods such as computed tomography (12). The Clavien-Dindo (C-D) classifications defined post-operative complications, categorizing surgical complications from grade I to grade V (13). Surgical site infection within 30 days is defined according to the Centers for Disease Control criteria (14).

Statistical Analysis

All statistical analysis was performed using the SPPS software program version 26.0 (SPSS, Inc., Chicago, IL, United States of America). Descriptive statistics were presented as either mean standard deviation (StD) or median for continuous variables according to their normality of distribution. Categorical data were expressed as numbers and proportions. Univariate analysis was used to identify the factors significantly associated with overall and anastomotic/septic complications. Then, variables with $p< 0.25$ in the univariate analysis were entered into a multivariate binary logistic regression analysis to determine the independent predictors of these overall and anastomotic complications. The area under the model's curve was calculated to evaluate the discriminatory ability of the model utilized. $P< 0.05$ indicated significant results.

RESULTS

Demographic Characteristics

Clinical characteristics and pre-operative parameters of all patients (n= 86, 100%) who met the inclusion criteria and those who underwent intestinal resection due to Crohn's disease from 2015 to 2023 were analyzed. Mean (StD) age was 34.8 (14.4) years, and 50 patients (58.1%) were males. Mean (StD) BMI of the patients was 21.4 (3.8) kg/m^2. According to the ASA score, the study population had no severe comorbidities (ASA I/II, 93%). A small number of patients were active smokers (25.6%). In most patients, albumin value was over 3 gr/dL (69.8%). However, hemoglobulin value was below 12 gr/dL in 61.6% of patients. Demographic data are shown in Table 2.

Most (68.6%) patients used medical treatment before surgery, including corticosteroid, immunomodulator, biological, or combination. Median disease duration before intestinal resection was 61.7 months (range, 0-204), and 44.2% of the patients required surgery within the first five years after initial diagnosis. Forty patients (46.5%) had a previous abdominal surgery. Ten patients (11.6%) had an intra-abdominal abscess before surgery and were drained preoperatively. Indication for surgery was non-stenotic, non-perforating disease in 45 patients (52.3%), 18 (20.9%) stenotic and 22 (25.6%) perforating. Most patients had no perianal involvement (82.6%). The disease was located in the small bowel only in 32 patients (37.2%), small and large bowel in 41 patients (47.7%), and large bowel only in 13 patients (15.1%). Baseline patient characteristics are shown in Table 3.

Operative and Post-operative Results

While 69 patients (80.2%) underwent ileocecal resection, 13 patients (15.1%) underwent colon, and only four (4.6%) underwent ileum resection. Gastrointestinal continuity was achieved with a stapler in 55 patients (64%), and the hand-sewn anastomosis was performed in 30 patients (34.9%). Anastomosis configuration was end-to-side in 43%, side-to-side in 45.3%, and end-to-end in 9.3%. In the post-operative pathological examination, 75% of the patients were perforating type, and 55% had positive surgical margins. Within the study population, 25 patients had post-operative complications (29.1%), and 10 (11.6%) were above grade three according to the Clavien-Dindo classification. Of these ten patients with serious complications, anastomotic leakage was observed in two, intra-abdominal collection in two, sepsis in two, enterocutaneous fistula in three, and ileus in the remaining one. Incisional surgical site infection was observed in eleven patients, and wound dehiscence occurred in four. Three patients were re-operated, two due to anastomotic leakage and one patient due to ileus and wound dehiscence. No patient died during the 30-day post-operative period. Median length of hospital stay was six days (range 3-28). Operative and post-operative data are shown in Table 4.

Table 2. Demographic data

	All Cases
	n= 86 (%)
Age, mean ± StD	34.8 ± 14.4
Age, montreal, years	
<16	3 (3.5)
17-40	55 (64)
40<	27 (31.4)
Sex	
Female	36 (41.9)
Male	50 (58.1)
BMI, mean ± StD, kg/m^2	21.4 ± 3.8
BMI, kg/m^2	
19<	26 (30.2)
<19	9 (10.5)
ASA	
1	35 (40.7)
2	45 (52.3)
3	5 (5.8)
Nutritional risk score	
Normal	29 (33.7)
Low	30 (34.9)
Smoking	
No	63 (73.3)
Yes	22 (25.6)
Hb, g/dL	
12<	28 (32.6)
<12	53 (61.6)
Albumin, g/dL	
3<	60 (69.8)
<3	14 (16.3)
Leukocyte, mm^3	
<10000	55 (56.7)
10000<	42 (43.3)
CRP, mg/L	
<5	9 (10.5)
5<	41 (47.7)

BMI: Body mass index, ASA: American society of anesthesiologists, Hb: Hemoglobin, CRP: C-reactive protein.

Table 3. Patient characteristics

	All Cases
	n= 86(%)
Medical treatment	
No	23 (26.7)
Yes (corticosteroid or anti-TNF)	59 (68.6)
Time from first diagnosis to surgery, months (min-max)	61.7 (0-204)
Time from first diagnosis to surgery, years	
<5	38 (44.2)
5<	35 (40.7)
Previous abdominal surgery	
No	37 (43)
Yes	40 (46.5)
Pre-operative abdominal drainage	
No	75 (87.2)
Yes	10 (11.6)
Pre-operative clinic behaviour	
Non stenotic non penetrating	45 (52.3)
Stenotic	18 (20.9)
Penetrating (fistulizing)	22 (25.6)
Perianal disease	
No	71 (82.6)
Yes	14 (16.3)
Location	
Small intestine	32 (37.2)
Ileocecal	41 (47.7)
Colonic	13 (15.1)
Pre-operative medical treatment	
Not interrupted	27 (31.4)
Interrupted	20 (23.3)

Table 4. Operative and post-operative data

	All Cases
	n= 86 (%)
Surgery	
Small intestine resection	4 (4.6)
Ileocecal resection	69 (80.2)
Colectomy	13 (15.1)
Anastomosis	
End to side	37 (43)
Side to side	39 (45.3)
End to end	8 (9.3)
Surgical technique	
Hand-sewn	30 (34.9)
Stapler	55 (64)
Surgical margin	
Positive	14 (16.3)
Negative	70 (81.4)
Histopathology	
Perforan	27 (31.4)
Non-perforan	57 (66.3)
Post-operative complications	
No	61 (70.9)
Yes	25 (29.1)
Anastomotic leak	2/25 (8)
Intra-abdominal collection	2/25 (8)
Sepsis	2/25 (8)
Enterocutaneous fistula	3/25 (12)
Ileus	1/25 (4)
Surgical site infection (incisional)	11/25 (48)
Wound dehiscence	4/25 (16)
Dindo-Clavien classification	
Dindo-Clavien grade 1-2	76 (88.3)
Dindo-Clavien grade 3a ≤	10 (11.6)
Hospital stay, days, median (min-max)	6 (3-28)
Re-operation*	3 (3)
Mortality (first 30 days)	0

Std: Standart deviation.
*2 anastomotic leak, 1 ileus-wound dehiscence.

Factors Associated with Post-operative Overall Complications

In the univariate analysis, post-operative overall complications were associated with the low albumin level, below 3 g/dL (OR= 2.7; p= 0.089), perianal disease (OR= 2.0; p= 0.22), pre-operative medical treatment (OR= 3.6; p= 0.04), surgical technique (OR= 1.9; p= 0.21), and histopathology (OR= 2.3; p= 0.089). According to multivariate regression analysis, albumin value <3 gr/dL (OR= 5.15, p< 0.03) and pre-operative medical treatment (OR= 4.79; p= 0.05) were associated with higher odds of post-operative overall complications. Factors associated with overall complications in both univariate and multivariate analyses are presented in Table 5.

Factors Associated with Post-operative Anastomotic/ Septic Complications

In the univariate analysis, post-operative anastomotic/septic complications were associated with the low albumin level,

Table 5. Risk factors associated with overall complications in patients with anastomosis after intestinal resection in Crohn's disease

	No Complications	Complications	Univariate	p	Multivariate	p
	n= 61	n= 25	OR (95% CI)		OR (95% CI)	
Albumin, g/dL			2.7 (0.8-9.0)	0.089	5.15 (1.16-22.85)	**0.03**
3<	44	16				
<3	7	7				
Perianal disease			2.0 (0.6-6.6)	0.22		
No	52	19				
Yes	8	6				
Medical treatment			3.6 (0.9-13.8)	0.04	4.79 (0.99-23.11)	**0.05**
No	20	3				
Yes (corticosteroid or anti-TNF)	38	21				
Surgical technique			1.9 (0.6-5.6)	0.21		
Hand-sewn	24	6				
Stapler	37	18				
Histopathology			2.3 (0.86-6.2)	0.089		
Perforan	44	13				
Non-perforan	16	11				

OR: Odds ratio, anti-TNF: Anti-tumor necrosis factor.

below 3 g/dL (OR= 5.6; p= 0.017), low nutritional risk score (OR= 7.0; p= 0.049), and smoking (OR= 4.4; p= 0.049). According to multivariate regression analysis, only albumin value below 3 g/dL (OR= 14.3; p= 0.04) was associated with a higher probability of post-operative anastomotic/septic complications. Factors associated with anastomotic leak in univariate and multivariate analyses are presented in Table 6.

Table 6. Risk factors associated with anastomotic/septic complications in patients with anastomosis after intestinal resection in Crohn's disease

	All Cases	Anastomotic Leakage	Univariate	p	Multivariate	p
	n= 86	n= 9	OR (95% CI)		OR (95% CI)	
Sex			1.2 (0.27-5.47)	0.79		
Female	33	3				
Male	45	5				
Smoking			4.4 (0.9-21.7)	0.049		
No	60	3				
Yes	18	4				
Nutritional risk score			7 (0.78-62.3)	0.049		
Normal	28	1				
Low	24	6				
Albumin, g/dL			5.6 (1.2-26.1)	0.017	14.3 (1.0-195.2)	**0.04**
3<	56	4				
<3	10	4				
Surgical technique			1.4 (0.25-7.69)	0.69		
Hand-sewn	28	2				
Stapler	50	5				

OR: Odds ratio, anti-TNF: Anti-tumor necrosis factor.

DISCUSSION

Anastomotic leaks and intrabdominal sepsis are the most feared complications after intestinal resection in patients with Crohn's disease. Identifying associated risk factors is crucial for deciding whether intestinal anastomosis can be performed during surgery. Therefore, numerous and heterogeneous risk factors have been identified that adversely affect early post-operative morbidity and mortality. These factors range from pre-operative laboratory values, medications used preoperatively, duration and clinical characteristics of the disease to perioperative features and even pathological characteristics. However, the results of subsequent studies have led to the questioning of these risk factors. Additionally, most previous studies were retrospective, the study populations were heterogeneous, and limitations ensured that the subject always remained current and active.

These are the initial results of an observational study designed by our clinic, as a tertiary referral center for inflammatory bowel disease, to evaluate risk factors for anastomotic/septic complications in patients with Crohn's disease. In this retrospective analysis, anastomotic/septic and overall complication rates were 10.4% and 29.1%, respectively. The analysis of factors related to anastomotic/septic complications revealed that only serum albumin levels independently influence the anastomotic leakage. Interestingly, previously identified risk factors for anastomotic complications, including steroids, biologicals, the presence of percutaneous drainage of intra-abdominal abscess before surgery, and a hand-sewn anastomosis were not related to the development of anastomotic leaks in this study, which might be attributed to the exclusion of all diverted patients, unlike in previous studies. Excluding diverted patients would eliminate those considered high-risk. In terms of general complications, low albumin levels and pre-operative medical treatment were found to be associated. As we cannot fully characterize pre-operative medical treatment, it is impossible to say which agent is effective in this. Considering that the most common problem among the overall post-operative complications of our case series is wound dehiscence and superficial surgical site infection, we can predict that the most likely agent is steroids, which negatively affect wound healing. Therefore, stopping steroid treatment in the pre-operative period is essential in terms of superficial surgical site complications.

On the other hand, there are controversial results in the literature regarding pre-operative medical treatments with immunosuppressive and biological agents. It is known that immunosuppressive and biological agents have opposing dual effects, including reducing inflammatory activity and worsening immunomodulatory activity (10). In a meta-analysis, pre-operative biologic therapy has been found to be associated with a modest increase in the risk of infectious complications, with a trend toward mostly non-infectious complication rates. In contrast, a recent study has found a significant association between pre-operative infliximab therapy and infectious and non-infectious post-operative complications, respectively (15,16). In contrast, two meta-analyses and one retrospective international multicenter study have reported no significant association between pre-operative biological therapy and the incidence of post-operative complications (10,17,18). Most of the studies included in these meta-analyses are retrospective or case-control studies and, therefore, do not allow control for critical confounding factors such as concomitant steroid therapy, as in our study.

Albumin, a negative acute phase reactant, can reflect the severity of systemic inflammation, malnutrition, or concomitant liver dysfunction, as well as serve as an essential element for collagen synthesis and fibroblast proliferation during the proliferative and remodeling phases of the wound healing process (19,20). In the current study, pre-operative hypoalbuminemia (<3 gr/dL) was an independent risk factor for anastomotic leakage, which is consistent with previous reports (7,20-22). Although hypoalbuminemia is not a direct indicator of pre-operative nutritional status, pre-operative feeding by enteral or parenteral may be considered if malnutrition exists and has been shown to improve outcomes (23).

Patients who necessitate pre-operative percutaneous drainage of intra-abdominal abscesses face heightened risks of anastomotic leakage and post-operative morbidity subsequent to intestinal resection and primary anastomosis (24). A recent multicenter study, involving 335 Crohn's disease patients undergoing percutaneous drainage followed by surgery, has reported a complication rate of 32.2% (25). It is known that this high rate is generally due to the fact that patients have the perforating type, which has a more aggressive course with excessive inflammation and high recurrence rates (24). In our current study, we did not observe a relationship indicating that pre-operative percutaneous abscess drainage increases the rate of anastomotic leakage or overall complication rates. We attribute this to the small number of total patients, the limited number of patients who underwent percutaneous abscess drainage, and the low number of patients with perforating type. Therefore, our study cannot provide guidance for patients who underwent pre-operative abdominal abscess drainage.

Current smoking habits also showed a significant correlation with anastomotic complications in the univariate but not multivariate analysis. Tobacco use is a risk factor for both anastomotic leak and disease recurrence due to various nicotine-related mechanisms, as shown in previous studies (26). Microthrombosis caused by increased platelet adhesion, decreased perfusion, reduced tissue oxygenation, and

vasoconstriction are among the mechanisms implicated, which suggests that patients with active or recent smoking habits should be informed about the increased risk of anastomotic leakage and disease recurrence (27).

Similar to many studies on this topic, the design of the current study is limited, notably by its retrospective observational analysis without a pre-operative protocol that can cause the presence of selection bias. Second, we were unable to fully characterize the severity of a patient's illness before surgery due to some data not being available, including weight loss, body mass index, and pre-operative medical treatment regimes. However, we believe that the level of albumin could provide an idea approximately in this regard. Third, we did not include emergency cases. Although this may seem like a limitation, it perhaps increases the value of our results. Because patients operated on in acute settings are likely those with septic conditions or intestinal obstruction, potentially increasing their risk of post-operative complications, it would lead to heterogeneity in our results. Although this study reported the results of the tertiary reference center for inflammatory bowel disease, large-scale prospective randomized controlled studies are needed to determine definitively the risk factors for anastomotic/septic complications in Crohn's disease.

Finally, well-timed, well-optimized elective surgery can only be achieved in a setting of close cooperation and multidisciplinary approach between inflammatory bowel disease surgeons and gastroenterologists (24,28). This collaboration will also help us better understand the course and characteristics of the disease and reduce post-operative complications and disease recurrences.

CONCLUSION

Understanding these risk factors could assist in the pre-operative management of patients with Crohn's disease. First, it could signify the need for pre-operative nutritional support in instances of inadequate nutritional status. Second, the medical treatments should be discontinued in the pre-operative period due to the increased risk of overall complications. Finally, in patients with pre-operative hypoalbuminemia, temporary stoma creation should be considered due to the potential increased risk of high anastomotic complications.

Ethics Committee Approval: This study was obtained from Marmara University Faculty of Medicine Clinical Research Ethics Committee (Decision no: 09.2023.890, Date: 14.07.2023).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – AEA, ŞCY; Design – AEA, ŞFD; Supervision – ŞCY, HİS; Data Collection and/or Processing – ABÖ, GFK, HİS, ŞFD; Analysis and/or Interpretation – AEA, ŞCY; Literature Search – ABÖ, GFK; Writing Manuscript - AEA; Critical Reviews – ABÖ, GFK, ŞFD, HİS.

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

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (2): 136-144

Crohn hastalığında elektif intestinal rezeksiyon sonrası anastomoz komplikasyonları için risk faktörleri

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ÖZET

Giriş ve Amaç: Cerrahi tedavi gerektiren Crohn hastalarında, anastomoz kaçakları morbiditenin en önemli sebeplerinden biridir. Bu komplikasyonu önlemek açısından ilişkili risk faktörlerinin belirlenmesi çok önemlidir. Olgu serimizde, anastomoz komplikasyonları açısından olası risk faktörlerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: 2015-2023 yılları arasında Marmara Üniversitesi Tıp Fakültesi Genel Cerrahi Kliniğinde Crohn hastalığı nedeniyle bağırsak rezeksiyonu ve anastomoz yapılan, 18 yaş üzeri 86 hasta retrospektif, gözlemsel ve tek merkezli olarak planlanan bu çalışmaya dahil edildi. Proksimal saptırıcı ileostomi veya kolostomi ile anastomoz yapılmayan olgular çalışma dışı bırakıldı.

Bulgular: Hastaların ortalama yaşı 34,8 (±14,4) yıl olup, 50 (%58,1)'si erkektir. Yirmi beş hastada ameliyat sonrası komplikasyon (%29,1) görüldü ve bunların 10 (%11,6)'u Clavien-Dindo sınıflamasına göre derece üç ve üzerindeydi. İki hastada anastomoz kaçağı, iki hastada intra-abdominal koleksiyon, iki hastada sepsis, üç hastada enterokütanöz fistül ve bir hastada ileus görüldü. Albümin değeri <3 g/dL (OR= 5,15, p< 0,03) ve ameliyat öncesi medikal tedavi (OR= 4,79; p= 0,05) postoperatif genel komplikasyonlarla ilişkili bulunurken, yalnızca hipoalbüminemi <3 g/dL (OR= 14,3; p= 0,04) postoperatif anastomoz/septik komplikasyonlarla ilişkili bulundu.

Sonuç: Crohn hastalarında postoperatif anastomoz kaçağı ile ilişkili tek risk faktörü olarak albümin düşüklüğü saptanmıştır. Hipoalbüminemili hastalarda koruyucu stoma düşünülmelidir. Pre-operatif dönemde kullanılan Crohn'a özgü medikal tedavilerin genel komplikasyonları arttırabilmesi nedeniyle, bu tedavilerin pre-operatif dönemde kesilmesi önerilir.

Anahtar Kelimeler: Crohn hastalığı, postoperatif komplikasyonlar, anastomoz kaçağı

DOİ: 10.47717/turkjsurg.2024.6417

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (2): 145-153

Predictors of citations and altmetric scores in general surgery literature

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ABSTRACT

Objective: This study aimed to determine various article characteristics influencing the citations and altmetric scores using papers published in a year in four high-ranking surgery journals.

Material and Methods: We included all papers (n= 819 articles) published between January 2015 to December 2015 in the Annals of Surgery, British Journal of Surgery, JAMA Surgery and Journal of American College of Surgeons. Article characteristics were manually extracted. We determined citation count using the Web of Science database and used univariate analysis and negative binomial regression to determine which article characteristics affect citations and altmetric scores.

Results: Mean number of citations and altmetric score received by the article were 44.6 (0-475) and 19.2 (0-665) respectively. Majority of the articles contained at least one citation (98.3%) and altmetric score (98.2%). In regression analysis, citation count was significantly associated with the journal [Annals of Surgery (IRR= 1.93), JAMA surgery (IRR= 1.76)] and non-funded research (IRR= 0.83). The altmetric score was significantly associated with the country of the corresponding author (US) (IRR= 1.3), study subtopic, journal [JAMA surgery (IRR= 2.33)], non-funded (IRR= 0.74) and non-open-access publication (IRR= 0.44).

Conclusion: Article metrics were found to be associated with specific study subtopics, country of the corresponding author, funding, open-access publication and the journal. These results might help editors, reviewers and authors to produce, review and publish more impactful studies. A similar study in the future may help to better understand the changing dynamics of academic publishing.

Keywords: Citation count, altmetric attention score, bibliometrics, general surgery, negative binomial regression

INTRODUCTION

Medical research is the cornerstone of furthering medical knowledge, discovering new treatments, and improving the lives of patients, and requires a significant effort and expenditure of resources on the part of academic institutions, as well as their faculty and staff. While all research contributes to increasing the span of knowledge in medical science, quantifying the impact of an individual study is often a challenging task, which is traditionally done using citation count. The number of citations received by an article is often a surrogate of that article's scientific impact and importance (1). With the advent of open-access publishing and all the literature being made publicly available, a new metric called "Altmetrics" became popular to measure the "social" impact of the study. This could be seen as a surrogate for social media attention, dissemination and influence (2). Altmetric score is complementary to the citation count and both correlate well with each other (3).

Previous studies have tried to evaluate article characteristics associated with higher citation count in surgical subspecialties such as neurosurgery, urology, orthopaedics and plastic surgery (4-7). However, little is known about the factors predicting higher citation counts in general surgery. A study conducted by Mullins et al. has shown that manuscripts with higher citation counts in the general surgery literature are more likely to be clinical, collaborative, multi-institutional, and larger and more sample size (8). However, the sample size is smaller and prone to selection bias. In addition, to the best of our knowledge, article characteristics on which the altmetric score depend have not been evaluated in the general surgical literature.

This study aimed to determine various article characteristics which can influence citation count and altmetric attention score using papers published in a year in the four high-ranking general surgery journals. The results might help editors,

Cite this article as: Chaudhary D, Acharya S, Aggarwal V, Huzaifa M, Kain P, Garg R, et al. Predictors of citations and altmetric scores in general surgery literature. Turk J Surg 2024; 40 (2): 145-153.

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Received: 06.08.2023
Accepted: 18.06.2024
Available Online Date: 28.06.2024

DOI: 10.47717/turkjsurg.2024.6201

reviewers and authors to produce, review and publish more impactful studies which may be important to the field.

MATERIAL and METHODS

Study Design and Data Collection

As the study did not involve human participants, research ethics committee approval was not applicable. We selected four top-ranked journals in "General Surgery" with high impact factors (IF) - The Annals of Surgery (AS) (IF 13.79), British Journal of Surgery (BJS) (IF 6.939), JAMA Surgery (IF 16.68) and Journal of American College of Surgeons (JACS) (6.532). These journals were chosen based on their importance in surgery according to the SCImago Journal Rank Indicator. We identified all research articles published in these journals during the one year between January 2015 to December 2015. Article types such as editorials and letters to editors were excluded, which yielded a total of 819 eligible studies.

In February 2022, after six hours of training in the use of the Web of Science (WoS) at the institute's library, the authors extracted the following article characteristics from each of the above-selected articles and entered manually in a spreadsheet software. Data on citation count and altmetric attention score were entered between February 6th to February 14th, 2022. We randomly selected 40 articles to confirm the accuracy of data collection.

The following data were extracted from each study:

1. Journal of publication (AS, BJS, JAMA Surgery, JACS)
2. Title of the study
3. Study design (experimental study, interventional, prospective cohort, retrospective cohort/case-control, cross-sectional study, case report/case series, systematic review/meta-analyses and guidelines)
4. Study subtopic
5. Number of characters in the title (excluding trailing or double spaces)
6. The month of publication (from January 2015 to December 2015)
7. Page count
8. Country of the corresponding author
9. Number of authors
10. Number of references
11. Whether any funding was received (Yes/No)
12. Whether the paper was Open Access (Yes/No).

Dependent variables:

13. Number of citations in WoS core collection
14. Altmetric attention score.

Statistical Analysis

We inserted data into a statistical database (SPSS, v.26.0, ©IBM Inc.) for analysis. Descriptive analysis was performed to quantitatively describe the features of the sample. Continuous variables were compared by independent t-test and analysis of variance (for normal distribution) for two or more than two groups respectively. Wilcoxon-rank sum test and Kruskal Wallis test were used for non-normal data - if the Shapiro-Wilk test was significant.

Regression: The mean of the number of citations, citations/year and the altmetric attention score was lower than their variance (overdispersion). Thus, the negative binomial regression model was used to determine the article characteristics which can affect the dependent variables. To transform the percentage of author self-citations into count data, we rounded off the percentage to the nearest whole number.

The analysis was performed on the entire study cohort. There were no missing values in the data set. All statistical tests were two-sided, and p values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Article Characteristics

A total of 819 articles were analyzed. Characteristics of the included articles are shown in Table 1. Most of the studies belonged to the category of gastrointestinal surgery (54.0%). "Prospective cohort" was the most common study design (29.2%) closely followed by the 'retrospective cohort/case control' study (28.7%). Approximately a third of the studies were published in the AS (34.7%), and around half of the lead authors of the studies belonged to the United States (US) (48.4%). Most of the studies were not funded (57.1%) and were not open access (65.9%). Mean number of authors was 10 (5.7), mean character count in the title was 108.1 (35.5), mean page count was 8.1 (2.2), and mean reference count was 32.7 (17.7).

Mean number of citations received by the article in the WoS core collection were 44.6 (range 0-475). Mean altmetric attention score was 19.2 (0-665). The overwhelming majority of articles contained at least one citation (98.3%) and altmetric attention score (98.2%) respectively.

Univariate Analysis

In univariate analysis, study design, study subtopic, journal of publication, funded research, character count, reference count and the number of authors were statistically significantly associated with the number of citations. The altmetric attention score was statistically significantly associated with the study subtopic, the journal of publication, the country of the corresponding author, funded research and if the paper was open access (Table 2).

Table 1. Article characteristics

Variable	n (%)
Study Design	
• Experimental Study	18 (2.2)
• Interventional	91 (11.1)
• Prospective Cohort	239 (29.2)
• Retrospective Cohort/Case Control	235 (28.7)
• Cross Sectional	35 (4.3)
• Case Report/Case Series	39 (4.8)
• Systematic Review/Meta-Analyses	158 (19.3)
• Guidelines	4 (0.5)
Clinical Category	
• Basic Science and Statistics	49 (6.0)
• Cardiothoracic and Vascular Surgery	21 (2.6)
• Endocrine Surgery	24 (2.9)
• Gastrointestinal Surgery	442 (54.0)
• Gynaecological Surgery	3 (0.4)
• Obesity	5 (0.6)
• Burns and Plastic Surgery	11 (1.3)
• Urologic Surgery	17 (2.1)
• Surgical Infections	7 (0.9)
• Trauma and Critical Care	54 (6.6)
• Vascular Surgery	46 (5.6)
• Miscellaneous	89 (10.9)
• Breast	47 (5.7)
• Orthopaedics	4 (0.5)
Journal	
• Annals of Surgery	284 (34.7)
• JAMA Surgery	198 (24.2)
• British Journal of Surgery	130 (15.9)
• Journal of American College of Surgeons	207 (25.3)
Country of Lead Author	
• Australia	10 (1.2)
• Canada	28 (3.4)
• USA	396 (48.4)
• UK	103 (12.6)
• France/Germany/Netherlands/Italy	120 (14.7)
. [#]Others	162 (19.8)
Country of Corresponding Author	
• Australia	10 (1.2)
• Canada	28 (3.4)
• USA	406 (49.6)
• UK	99 (12.1)
• France/Germany/Netherlands/Italy	119 (14.5)
. [#]Others	157 (19.2)

Table 1. Article characteristics (continue)

Variable	n (%)
Month of Publication	
• January	74 (9.0)
• February	61 (7.4)
• March	64 (7.8)
• April	83 (10.1)
• May	71 (8.7)
• June	79 (9.6)
• July	66 (8.1)
• August	88 (10.7)
• September	55 (6.7)
• October	50 (6.1)
• November	61 (7.4)
• December	67 (8.2)
Funding	
• Yes	351 (42.9)
• No	468 (57.1)
Open Access	
• Yes	279 (34.1)
• No	540 (65.9)
Character Count	108.12 ± 35.54
Page Count	8.13 ± 2.23
Reference Count	32.69 ± 17.66
Number of Authors	10.02 ± 5.78

*Plus-minus values mean ± SD. The number in parenthesis denotes percentages.
[#]Denote these countries: Brazil, Belgium, Sweden, Spain, South Korea, Denmark, China, Japan, Switzerland, India, Egypt, Greece, Ireland, Türkiye, New Zealand, Norway, Portugal, Singapore, Taiwan.

Regression Analysis

The variance inflation factor for each variable included in the regression model was <5. Thus, there was no multicollinearity and all the statistically significant variables in univariate analysis were put in the regression model. The results are shown in Table 3. Adjusted analysis showed that the study design was not statistically significantly associated with the citation count. Under the study subtopic, endocrine surgery, cardiothoracic surgery and plastic surgery were negatively associated with the altmetric score [incidence rate ratio (IRR= 0.21, 0.29, 0.19 respectively)]. "AS" was statistically significantly associated with the number of citations (IRR= 1.93) and the "JAMA surgery" was statistically significantly associated with both the number of citations and the altmetric attention score (IRR= 1.76, 2.33 respectively).

Table 2. Univariate analysis: Median citations and altmetric attention score by article characteristics

Characteristic	Median Citations (IQR)	p	Median Altmetric (IQR)	p
Study Design				
Experimental Study	24.00 (8.50-35.00)	0.003	7.00 (1.00-9.50)	0.48
Interventional	25.00 (12.00-42.00)		6.00 (3.00-17.00)	
Prospective Cohort	32.00 (16.00-54.00)		5.00 (2.00-13.00)	
Retrospective Cohort/Case Control	30.00 (16.00-59.00)		8.00 (3.00-21.00)	
Cross Sectional	21.00 (12.00-48.00)		5.00 (2.00-16.00)	
Case Report/Case Series	14.00 (1.00-59.00)		5.00 (2.00-7.00)	
Systematic Review/Meta-Analyses	35.00 (19.00-59.00)		6.00 (3.00-14.00)	
Guidelines	34.50 (13.50-80.25)		6.00 (2.00-8.50)	
Study sub-Topic				
Basic Science and Statistics	34.00 (20.00-83.00)	0.001	17.00 (7.00-32.00)	<0.001
Cardiothoracic and Vascular Surgery	21.00 (12.00-49.00)		5.00 (2.00-18.00)	
Endocrine Surgery	25.00 (12.25-45.00)		2.00 (1.00-7.75)	
Gastrointestinal Surgery	34.00 (16.75-62.00)		6.00 (3.00-12.00)	
Gynaecological Surgery	35.00 (N/A)		30.00 (N/A)	
Obesity	85.00 (44.00-97.00)		34.00 (30.00-97.00)	
Burns and Plastic Surgery	30.00 (23.00-46.00)		5.00 (1.00-8.00)	
Urologic Surgery	22.00 (6.00-59.00)		7.00 (2.50-31.50)	
Surgical Infections	26.00 (16.00-47.00)		10.00 (2.00-26.00)	
Trauma and Critical Care	21.50 (10.75-31.50)		6.50 (3.00-28.25)	
Vascular Surgery	34.00 (16.00-55.25)		4.50 (2.00-11.50)	
Miscellaneous	23.00 (13.50-40.50)		9.00 (3.00-25.50)	
Breast	20.00 (12.00-49.00)		4.00 (2.00-17.00)	
Orthopaedics	34.00 (25.50-52.25)		49.00 (14.00-97.50)	
Journal				
Annals of Surgery	37.00 (20.00-73.00)	<0.001	6.00 (3.00-13.00)	<0.001
JAMA Surgery	31.00 (16.00-59.00)		24.50 (10.00-54.00)	
British Journal of Surgery	29.00 (13.00-49.00)		5.00 (2.00-10.00)	
Journal of American College of Surgeons	23.00 (12.00-41.00)		3.00 (2.00-8.00)	
Country of Lead Author				
Australia	34.50 (24.25-58.75)	0.195	7.00 (4.75-12.75)	<0.001
Canada	33.00 (17.00-57.00)		9.50 (5.25-21.75)	
USA	28.00 (13.00-54.00)		7.00 (3.00-25.00)	
UK	29.00 (19.00-52.00)		8.00 (3.00-17.00)	
France/Germany/Netherlands/Italy	37.50 (20.00-63.25)		5.00 (2.00-8.00)	
[#]Others	31.50 (15.00-59.00)		5.00 (2.00-10.25)	

Table 2. Univariate analysis: Median citations and altmetric attention score by article characteristics (continue)

Characteristic	Median Citations (IQR)	p	Median Altmetric (IQR)	p
Month of Publication				
January	32.50 (16.00-74.00)	0.148	5.00 (2.00-27.25)	0.177
February	39.00 (18.00-78.00)		6.00 (2.00-15.00)	
March	36.00 (16.00-62.75)		6.00 (2.00-16.75)	
April	27.00 (14.00-51.00)		5.00 (2.00-15.00)	
May	42.00 (19.00-71.00)		8.00 (5.00-21.00)	
June	29.00 (13.00-48.00)		6.00 (3.00-13.00)	
July	28.50 (14.75-53.00)		6.50 (3.00-11.25)	
August	27.00 (12.25-49.00)		5.00 (2.25-18.75)	
September	25.00 (12.00-49.00)		6.00 (3.00-24.00)	
October	30.00 (15.50-60.25)		5.50 (2.00-16.25)	
November	26.00 (14.50-49.50)		5.00 (2.50-10.00)	
December	31.00 (16.00-54.00)		6.00 (3.00-15.00)	
Funding				
Yes	33.00 (19.00-59.00)	0.004	7.00 (3.00-18.00)	0.003
No	28.00 (13.00-54.00)		5.00 (3.00-13.00)	
Open Access				
Yes	32.00 (15.00-59.00)	0.305	10.00 (4.00-33.00)	<0.001
No	30.00 (15.00-53.00)		5.00 (2.00-10.00)	
Character Count	(0.090)	0.010	-0.072	0.039
Page Count	0.168	<0.001	-0.050	0.151
Reference Count	0.216	<0.001	0.032	0.367
Number of Authors	0.192	<0.001	0.066	0.058

#Denote these countries: Brazil, Belgium, Sweden, Spain, South Korea, Denmark, China, Japan, Switzerland, India, Egypt, Greece, Ireland, Türkiye, New Zealand, Norway, Portugal, Singapore, Taiwan.

Table 3. Negative binomial regression IRR for the outcomes

Variable	Citations	Altmetric Score
Study Design		
Experimental Study	0.65 (0.21-1.97)	
Interventional	0.91 (0.33-2.54)	
Prospective Cohort	1.17 (0.42-3.22)	
Retrospective Cohort/Case Control	1.17 (0.43-3.23)	
Cross Sectional	0.92 (0.32-2.67)	
Case Report/Case Series	0.74 (0.26-2.13)	
Systematic Review/Meta-Analyses	1.09 (0.39-3.02)	
Guidelines	1	
Clinical Category		
Basic Science and Statistics	1.63 (0.56-4.72)	1.20 (0.40-3.58)
Cardiothoracic and Vascular Surgery	0.78 (0.26-2.37)	0.29 (0.09-0.88)
Endocrine Surgery	1.33 (0.44-4.03)	0.21 (0.07-0.67)
Gastrointestinal Surgery	1.44 (0.52-4.02)	0.46 (0.16-1.29)

Table 3. Negative binomial regression IRR for the outcomes (continue)

Variable	Citations	Altmetric Score
Gynaecological Surgery	0.98 (0.21-4.61)	0.63 (0.13-3.04)
Obesity	1.56 (0.40-6.00)	2.10 (0.53-8.28)
Burns and Plastic Surgery	0.93 (0.28-3.09)	0.19 (0.05-0.64)
Urologic Surgery	1.06 (0.34-3.28)	0.30 (0.10-0.94)
Surgical Infections	1.16 (0.33-4.08)	0.41 (0.11-1.52)
Trauma and Critical Care	0.76 (0.26-2.20)	0.85 (0.28-2.51)
Vascular Surgery	1.19 (0.41-3.44)	0.35 (0.12-1.06)
Miscellaneous	0.92 (0.33-2.62)	0.49 (0.17-1.42)
Breast	1.26 (0.44-3.64)	0.57 (0.19-1.69)
Orthopaedics	1	1
Journal		
Annals of Surgery	1.93 (1.56-2.38)	1.16 (0.94-1.44)
JAMA Surgery	1.76 (1.36-2.27)	2.33 (1.80-3.01)
British Journal of Surgery	1.09 (0.87-1.36)	1.03 (0.78-1.36)
Journal of American College of Surgeons	1	1
Country of Lead Author		
Australia		0.83 (0.41-1.67)
Canada		1.41 (0.90-2.23)
USA		1.28 (1.02-1.62)
UK		1.21 (0.90-1.62)
France/Germany/Netherlands/Italy		0.70 (0.54-0.91)
#Others		1
Funding		
No	0.83 (0.72-0.96)	0.74 (0.63-0.87)
Yes	1	1
Open Access		
No		0.44 (0.37-0.53)
Yes		1
Variable	**Citations**	**Altmetric Score**
Character Count	1.00 (0.99-1.00)	0.99 (0.994-0.999)
Page Count	1.11 (1.06-1.17)	
Reference Count	1.01 (0.999-1.00)	
Number of Authors	0.99 (0.985-1.01)	

*IRR stands for incidence rate ratios. Values in the table are expressed as IRR (95% confidence interval).

#Denote these countries: Brazil, Belgium, Sweden, Spain, South Korea, Denmark, China, Japan, Switzerland, India, Egypt, Greece, Ireland, Türkiye, New Zealand, Norway, Portugal, Singapore, Taiwan.

The altmetric score was statistically significantly higher when the corresponding author belonged to the US (IRR= 1.3). Non-funded research was negatively associated with both citation counts and altmetric attention scores (IRR= 0.83, 0.74 respectively). Non-open access publication was negatively associated with the altmetric attention score (IRR= 0.44). Page count and the number of references were both borderlines positively associated with the number of citations.

DISCUSSION

In this study, we evaluated what article characteristics could affect citation rates and altmetric attention score in high-ranked general surgery literature. We found that the study design was not associated with higher citation counts or altmetric attention scores. Earlier studies evaluating the effect of study design on citation rates have been mixed. While some studies based on orthopaedics or urology indicate that

randomized trials and systematic reviews are associated with higher citation counts, other studies based on plastic surgery and emergency medicine fail to do so (5,7,9,10). However, the literature on the effect of study design on altmetric scores is sparse. Puzas et al. have evaluated 840 articles in dermatology and found that journal type, presence of conflicts of interest and open-access articles are associated with higher altmetric attention scores (11).

Surgical sub-fields such as endocrine surgery, cardiothoracic, vascular surgery and burns, plastic surgery were found to be significantly negatively associated with altmetric scores when compared to orthopaedic surgery. This could be due to a higher prevalence of certain diseases and/or more familiarity with particular fields to the people. Publication in AS was significantly associated with higher citation rates, and publication in JAMA Surgery was strongly associated with both higher citation rates and altmetric scores. This is expected given the fact that JAMA surgery has the highest impact factor among all surgical journals in the world (12). IF is a measure of the average number of citations received by the article in time. It is intuitive, therefore, that IF correlates well with citation counts. Moreover, there is enough evidence that across medical and surgical specialities, altmetric scores correlate well with citation counts (3).

US authors emerged as a significant predictor of higher altmetric scores in adjusted analysis. The reasons for this observation could be many. The US currently leads the world's medical research output (13,14). This is largely in part due to high research funding and a diverse scientific community. In addition, most of the top-ranked journals have emerged from the US. American authors and reviewers are biased towards the articles published locally which can falsely amplify article metrics (15,16). Moreover, studies indicate that even among top journals, papers published by high-income countries gather more metrics than low and middle-income countries (17).

Funded research also emerged as a significant predictor of higher citation counts and altmetric scores. Non-funded articles roughly received 20% fewer citations and had 25% lower altmetric scores than the funded articles independent of the study subtopic and study design in adjusted analysis. A study conducted by Mosleh et al. shows that funded projects receive more citations than non-funded ones across life sciences (18). This indicates that funded projects have more visibility on social media and in the research community and are seen as a marker of quality. Thus, funding agencies should judiciously use resources to allocate funds to impactful studies. We also found that open-access publications have significantly higher altmetric scores than non-open access publications by nearly 2.2 folds. However, similar results were not obtained with citation counts. This has been seen in studies conducted in orthopaedic and otolaryngology literature as well (19,20). With the advent and popularity of "Scihub" and "Libgen" however, which provides free access to nearly 85% of the paywalled literature, the results could be significantly distorted as the majority of the medical literature may be 'open access' (21).

We used a robust methodology in this study. We used a large sample size and included both the traditional measure of scientific impact i.e. citation counts and more contemporary social media indicators of scientific impact i.e. altmetric attention scores to determine which article characteristics can affect these measures. The results could be helpful to journal editors, reviewers and authors to predict and invest time and resources to the papers which may have high impact in the field. We chose four journals with the highest impact factors. Since these journals are widely read by both the "experts" and the public, the results are more generalizable to the general surgery literature. We used a window of seven years post-publication to adequately capture the number of citations and altmetric scores.

This study has limitations. We used a retrospective observational design which can potentially generate confounding. In addition, there is a recent trend towards more collaborative research and the increased publication of systematic reviews and randomized trials and a relatively lower preference towards qualitative studies (22,23). Thus, the results might differ if the study is done in the future. It will be useful, therefore, to perform a similar study at a future time point to better understand the changing dynamics of the academic publishing. Similarly, the inclusion of smaller or more specialized journals may alter the results. However, we believe that the chosen journals have a broad readership and widely cover the subspeciality subtopics. We used WoS core collection for the citations. The results may vary if other databases are used including Google Scholar or Scopus which have been shown to have higher citation counts than WoS (24).

CONCLUSION

Article metrics were improved with specific study subtopics, when the author belonged to the US, when the research was funded, open access or published in a journal with higher impact factor. The results might help editors, reviewers and authors to produce, review and publish more impactful studies. Similar studies at a future time point will help to better understand the changing dynamics of the academic publishing.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - VA, DC, SA; Design - VA, DC, SA; Supervision - VA; Data Collection and/or Processing - All of authors; Analysis and/or Interpretation - DC, SA, VA; Literature Search - DC, SA, VA, PK, KM, SK, AV; Writing Manuscript - DC, SA, VA; Critical Reviews - VA, RG, MH.

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

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (2): 145-153

Genel cerrahi literatüründe atıfların ve altmetrik puanlarının belirleyicileri

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ÖZET

Giriş ve Amaç: Bu çalışmanın amacı, dört üst düzey cerrahi dergisinde bir yılda yayımlanan makaleleri kullanarak, alıntıları ve altmetrik puanları etkileyen çeşitli makale özelliklerini belirlemektir.

Gereç ve Yöntem: Ocak 2015-Aralık 2015 tarihleri arasında Annals of Surgery, British Journal of Surgery, JAMA Surgery ve Journal of American College of Surgeons dergilerinde yayımlanan tüm makaleler (n= 819 makale) dahil edildi. Makale özellikleri manuel olarak çıkarıldı. Alıntı sayısını belirlemek için Web of Science veri tabanı kullanıldı ve hangi makale özelliklerinin alıntıları ve altmetrik puanları etkilediğini belirlemek için tek değişkenli analiz ve negatif binom regresyon uygulandı.

Bulgular: Makale tarafından alınan ortalama alıntı sayısı ve altmetrik puan sırasıyla 44,6 (0-475) ve 19,2 (0-665) idi. Makalelerin çoğu en az bir alıntı (%98,3) ve altmetrik puan (%98,2) içeriyordu. Regresyon analizinde atıf sayısı dergi [Annals of Surgery (IRR= 1.93), JAMA Surgery (IRR= 1,76)] ve finanse edilmeyen araştırma (IRR= 0,83) ile anlamlı şekilde ilişkiliydi. Altmetrik puan ise ülke ile anlamlı bir şekilde ilişkiliydi. İlgili yazar (ABD) (IRR= 1,3), çalışma alt konusu, dergi [JAMA Surgery (IRR= 2,33)], finanse edilmeyen (IRR= 0,74) ve açık erişim olmayan yayın (IRR= 0,44) ile ilişkiliydi.

Sonuç: Makale ölçümleri; belirli çalışma alt konuları, ilgili yazarın ülkesi, finansman durumu, açık erişimli yayın ve dergi ile ilişkilendirildi. Bu sonuçlar editörlerin, hakemlerin ve yazarların daha etkili çalışmalar üretmesine, incelemesine ve yayımlamasına yardımcı olabilir. Gelecekte benzer bir çalışma, akademik yayıncılığın değişen dinamiklerinin daha iyi anlaşılmasına katkıda bulunabilir.

Anahtar Kelimeler: Atıf sayısı, altmetrik dikkat puanı, bibliyometri, genel cerrahi, negatif binom regresyonu

DOİ: 10.47717/turkjsurg.2024.6201

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (2): 154-160

The role of microbes and parasites in recurrent pyogenic cholangitis

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ABSTRACT

Objective: Recurrent pyogenic cholangitis (RPC) and ascariasis are prevalent in eastern India. Exact pathogenesis of RPC is still a matter of controversy. Hepatobiliary Ascaris infestation has been considered one of the causative factors in Eastern Asia, but conclusive evidence from India is lacking. RPC is associated with multi-drug-resistant (MDR) bacteria, which is a significant source of morbidity and mortality. This study aimed to assess the role of hepatobiliary ascariasis in pathogenesis of RPC and to study microbial profile and their implications in managing RPC patients.

Material and Methods: Consecutive patients with biliary stones who underwent surgery between March 2020 and December 2021 in a tertiary centre in eastern India were divided into RPC and non-RPC groups. Surgically retrieved samples of bile and biliary stones were sent for bacterial culture and microscopic and histopathological examination to identify the evidence of ascariasis in both groups and to study the microbial profile in RPC group.

Results: Eight out of 54 patients (14.8%) in the RPC group had evidence of hepatobiliary ascariasis. None of the patients in non-RPC group showed evidence of ascariasis. *Klebsiella* was the most common bacterial pathogen on bile culture, and 79% of bacterial isolates were MDR pathogens. Carbapenem group of antibiotics showed the highest sensitivity (66.6%) against bacterial culture growth in RPC patients.

Conclusion: This study showed a higher prevalence of hepatobiliary ascariasis in patients with RPC, but a conclusive etiological role is still lacking. RPC is associated with high incidence of MDR bacteria. Carbapenems may be considered the empirical antibiotic of choice in RPC.

Keywords: Ascariasis, cholangitis, multidrug resistance

INTRODUCTION

Recurrent pyogenic cholangitis (RPC) is characterised by repeated infections of the biliary system with the formation of stones and strictures. The exact pathogenesis of RPC is still a matter of controversy. Chronic bacterial infection and helminthic infestation remain the most likely possibilities. Clonorchis sinensis (CS) and Ascaris lumbricoides (AL) are the most commonly associated parasites with RPC (1). A study from Hong Kong has suggested the role of CS (2). AL is highly endemic in the Indian subcontinent, whereas CS is uncommon. Few studies indicate that parasites, their fragments, or ova can act as a physical nidus or nucleus, around which bile components can crystallise and form stones (3). Another perspective argues that the observed association between parasites and choledocholithiasis might be coincidental, especially in areas with high parasite prevalence (4). The geographic distribution of parasites and hepatobiliary stones might be relevant, as certain regions have a higher prevalence of both (3). Only a few studies from India have explored the etiological role of AL in RPC (5,6). This study aimed to identify the role of hepatobiliary ascariasis in the pathogenesis of RPC in Eastern India.

MATERIAL and METHODS

This prospective study included consecutive patients with hepatobiliary stones due to RPC and other aetiologies who underwent surgery between March 2020 and December 2021 in a tertiary care centre in Eastern India. The Institutional Ethics Committee approved this study. Written informed consent was obtained from all participants. The diagnosis of RPC was based on the clinical history of recurrent cholangitis, characteristics abnormalities on imaging, and soft brown pigment stones in intrahepatic ducts with or without stones in the common bile duct or gall bladder. Positive evidence of persisting or past hepatobiliary ascariasis was based on the identification of adult ascariasis on imaging or their recovery at surgery, histological examination showing worm fragments or ova forming the

Cite this article as: Ansari Z, Ray S, Das S, Mandal TS. The role of microbes and parasites in recurrent pyogenic cholangitis. Turk J Surg 2024; 40 (2): 154-160.

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Received: 01.03.2024
Accepted: 18.06.2024
Available Online Date: 28.06.2024

DOI: 10.47717/turkjsurg.2024.6364

nidus of surgically retrieved hepatobiliary stones or bile specimen on light microscopy containing ova of AL. Patients with brown pigment stones in the intrahepatic or extrahepatic bile duct due to causes other than RPC were included in the non-RPC group. Patients with only gallbladder stones or cholesterol stones were excluded from the study. All recent and past medical records were gathered and analysed for evidence of recent and past hepatobiliary ascariasis. Bile samples (5 mL) were collected from the intrahepatic or extrahepatic bile duct during surgery. Bile sample was sent to the department of microbiology on the same day for culture for aerobic organisms and sensitivity against antibiotics. Multi-drug-resistant (MDR) was defined as antimicrobial resistance shown by a species of microorganism to at least one antimicrobial drug in three or more antimicrobial categories (7). Bile was centrifuged and examined under light microscopy for ova of AL by a team of microbiologists. Stones were retrieved from the extrahepatic or intrahepatic biliary tree at the time of surgery or ex vivo from the resected liver specimen. A senior operating surgeon visually inspected the stones to confirm their pigmented nature. Stones removed intact were sent to the pathology department in a clean, sterile container with 10% formalin solution. Stones were split into two to analyse the appearance and structure of the nucleus. Stones were treated with ethylenediamine tetra-acetic acid (EDTA) solution to decalcify stones. Serial sections were cut and stained with hematoxylin and eosin. Multiple sections were examined for worm ova or worm fragments.

Statistics

Continuous data were reported as medians with interquartile ranges or as mean with standard deviation (SD). Categorical data were shown as frequency and percentages. Differences between categorical data were analysed using Fisher's exact or Chi-square test. $P< 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS, version 20 (IBM Corporation, Chicago, United States of America).

RESULTS

This study included 54 RPC patients and 39 non-RPC patients. In the RPC group, there were 16 men and 38 women with a mean age of 39.5 ± 12.01 years. The initial presenting features of the patients with RPC are shown in Table 1. Median duration of the illness was 30 months. A total of 24 patients (44.4%) had undergone previous biliary surgery. A total of 24 patients (44.4%) had undergone previous Endoscopic retrograde cholangiopancreatography (ERCP), and three patients (5.6%) had undergone percutaneous radiological intervention for liver abscess in the past. Overall, 38 patients (70.4%) had undergone some biliary intervention in the past. Disease distribution was bilobar in 55.6% of the patients. The disease was confined to the left liver lobe in 37% of the patients (Figure 1). Only 7.4% of the patients had isolated right lobe RPC (Table 2). Liver resection was performed in a total of 30 patients (55.5%) (Table 3). Histological results were available in all RPC patients who underwent hepatectomy. All of them showed features of RPC.

Table 1. Clinical presentation in RPC patients

	n= 54 (%)
Abdominal pain	54 (100%)
Acute cholangitis	38 (70.3%)
Fever	35 (64.8%)
Jaundice	25 (46.2%)
Vomiting	17 (31.4%)

Microbial Profile of RPC Patients

Bile was analysed for aerobic bacterial culture in 44 of 54 RPC patients. Culture results were positive in 33 patients (75%). The most common bacteria isolated on culture was *Klebsiella* in 42.4% of patients, followed by *Escherichia coli* in 39.3%. Types of organisms are shown in Table 4. In patients with a positive culture, MDR bacteria were found in 78.7%. Bacterial growths were most susceptible to carbapenem groups of antibiotics in 66.6%, followed by colistin in 63.6%. The lowest sensitivity was observed against the quinolones (27%) and cephalosporin (27%) group of antibiotics.

Etiological Evidence of Ascaris Lumbricoides

The primary indication of surgery in non-RPC patients is shown in Table 5. Biliary stones retrieved from RPC and non-RPC patients were brown pigment stones in all cases (Figure 2). Bile was analysed for the evidence of ascariasis in 36 patients in the RPC group and 32 patients in the non-RPC group. Unfertilised AL ova was found in two patients in the RPC group (Figure 3). On bile examination, no evidence of AL ova was seen in the non-RPC group. None of the patients in the RPC or non-RPC groups had evidence of AL on pathological examination of stones. Five patients in the RPC group had evidence of dead AL

Figure 1. MRCP of a patient with RPC showing left liver lobe disease.

Table 2. Demographic data of RPC patients

	n= 54 (%)
Sex	
Male	16 (26.9%)
Female	38 (70.4%)
Age (years)	39.5 (21-62)
Duration of illness (months)	30 (2-264)
Previous hepatobiliary interventions	
Previous biliary surgery	24 (44.4%)
Cholecystectomy	16
CBD exploration	8
Previous ERCP and biliary stenting	24 (44.4%)
Previous image-guided percutaneous catheter drainage of liver abscess	3 (5.6%)
Disease distribution in liver	
Bilobar	30 (55.6%)
Left lobe	20 (37%)
Right lobe	4 (7.4%)

CBD: Common bile duct, ERCP: Endoscopic retrograde cholangiopancreatography.

Table 3. Types of surgery performed in RPC patients

Surgery	n= 54 (%)
HJ	24 (44.54%)
Left hepatectomy	8 (14.8%)
Left lateral sectionectomy	3 (5.6%)
Right hepatectomy	1 (1.9%)
Right posterior sectionectomy	1 (1.9%)
Left hepatectomy + HJ	4 (7.4%)
Left lateral sectionectomy + HJ	5 (9.3%)
Right hepatectomy + HJ	4 (7.4%)
Left hepatectomy + CBD exploration + T-Tube drainage	2 (3.7%)
Left lateral sectionectomy + CBD exploration + T-Tube drainage	2 (3.7%)

HJ: Hepaticojejunostomy, CBD: Common bile duct.

on review of previous imaging. Out of five patients, two patients had evidence of AL exclusively on abdominal ultrasound, one patient exclusively on MRCP, and two patients on both abdominal ultrasound and MRCP (Figure 4,5). One patient in the RPC group was found to have a history of biliary ascariasis 25 years ago based on a written clinical record. In contrast, none of the patients in the non-RPC group had a history of hepatobiliary ascariasis. Overall, 8 (14.8%) patients in the RPC group had evidence of hepatobiliary ascariasis, while no patient had evidence of biliary ascariasis in the non-RPC group (p= 0.019) (Table 6).

DISCUSSION

Management of RPC requires a multidisciplinary team approach. Basic principles of treatment include (i) complete removal of all stones, (ii) resecting the non-functioning segments of liver, and (iii) establishing adequate biliary drainage. Both operative and non-operative interventions are described for the management of RPC. Non-operative procedures include percutaneous transhepatic cholangioscopic lithotripsy and, endoscopic retrograde cholangiopancreatography (ERCP) and stone extraction (8,9). Surgical treatment of RPC generally gives better results than non-operative techniques (10). RPC involving the first-order bile ducts is usually treated by biliary enteric bypass procedures. Whereas, associated liver abscesses, liver atrophy, third-order ductal stones, and intrahepatic cholangiocarcinoma are best treated with liver resection. In the current study, left sided liver involvement was more common (93%) and isolated right-sided involvement was only (7%), which is in concordance

Table 4. Microbial profile of bile culture in RPC patients	
Bacterial growth present	33 (75%)
Types of bacteria	
Klebsiella	14 (32%)
E. coli	13 (30%)
Acinetobacter baumannii	5 (11%)
Staphylococcus	1 (2%)
MDR	26 (79%)
Sensitivity to antibiotics	
Carbapenem*	22 (67%)
Colistin	21 (64%)
Aminoglycoside#	19 (57.5%)
Polymyxin	15 (45%)
Penicillins$	10 (30%)
Quinolones**	9 (27%)
Cephalosporins***	9 (27%)

MDR: Multidrug resistant.
*Carbapenem includes meropenem, imipenem.
**Quinolones include ciprofloxacin, levofloxacin.
***Cephalosporin include ceftriaxone, cefepime, ceftazidime.
$Penicillins include amoxicillin, piperacillin.
#Aminoglycosides includes amikacin, gentamycin.

Table 5. Indication of surgery in non-RPC patients	
Diagnosis	**n= 39**
Choledocholithiasis	18
Choledochal cyst with cystolithiasis	14
Hepaticojejunostomy site stricture with hepatolithiasis	5
Post-cholecystectomy biliary stricture with hepatolithiasis	2

Figure 2. Multiple brown pigment stones with intrahepatic biliary ductal dilatations are seen in the left lobe of the liver.

with recent studies (11,12). Left hepatectomy was the most common resection procedure performed in the present study (26%), which is in concordance with the recent study (13).

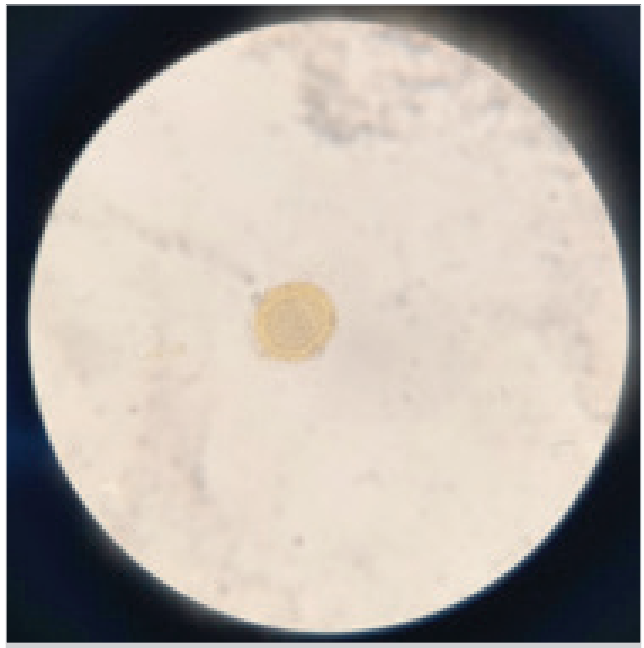

Figure 3. Unfertilised Ascaris ova is seen in bile on light microscopy in the RPC patient.

Figure 4. Ultrasound of the abdomen showed linear hyperechoic density in CBD (arrow), which suggests dead AL.

Figure 5. MRCP showed the linear filling defect (arrow) in CBD, suggesting AL.

Table 6. Evidence of hepatobiliary ascariasis in RPC and non-RPC groups

AL Detection Method	RPC (n= 54)	non-RPC (n= 39)	p
Evidence of hepatobiliary ascariasis in imaging	5	0	0.071
Ultrasonography only	2	0	
MRCP only	1	0	
Combined ultrasonography and MRCP	2	0	
Documented history of previous hepatobiliary ascariasis	1	0	1.000
Stone analysis	45	34	1.000
Stone positive for AL	0	0	
Bile analysis	36	32	0.494
Bile positive for AL	2	0	
Overall evidence for ascariasis	8	0	0.019

Causative factors described in the development of the RPC disease include primary bacterial infection of bile ducts, parasitic infections, and a diet containing high carbohydrates, low protein, and low saturated fat (14,15). Khuroo et al. have reported the only etiological study on RPC from northern India, and the authors have demonstrated the evidence of hepatobiliary ascariasis in 24 out of 30 patients with RPC in which the authors have compared the RPC group with a group of 30 patients with gallstones and found only one patient had evidence of AL (6). Twenty-two out of 30 patients had evidence of AL on pathological examination of biliary stones, three patients had positive evidence on microscopy of bile, and five patients had a history of hepatobiliary ascariasis. The authors suggested that fragments of dead worms or ova form nidus of brown pigment stones in RPC and play a key role in initiating subsequent bacterial infection and stricture formation. Similar conclusions have also been reported in studies from China and the Philippines (16,17). In the present study, we may divide the evidence into hard evidence, such as parasite fragment or egg as stone nidus and soft evidence, including the presence of ova in bile or the presence of radiological presence of hepatobiliary ascariasis. The presence of parasite fragments or ova in stone is logically the most robust evidence to prove the etiological role of AL in disease pathogenesis; however, in the present study, the stone analysis failed to demonstrate the AL ova or fragment as a nidus for stone formation. Two possible explanations may contribute to the variable detection of parasitic infection in patients with RPC across the studies. First, inter-study variations in diagnostic methodologies, with inherent differences in sensitivity, contribute to challenges in establishing a definitive prevalence for ascariasis. Second, the infection may have resolved after initiating the disease without leaving detectable evidence of the inciting cause. In support of the latter hypothesis, there are studies in which the analysis of stones and bile have shown proof of ascariasis, such as debris and ova, which may have served as a nidus for stone formation and biliary strictures (6,14,16). In the present study, MDR isolates were found in 78.7% of the patients with positive culture in RPC patients, which is significantly higher than the reported incidence of 20-30% in acute cholangitis (17). The development of MDR biliary pathogens in cholangitis has been attributed to previous antibiotic use within 90 days and previous biliary intervention, among other factors (18). In the present study, the high incidence of MDR pathogens can be attributed to previous biliary intervention in the majority of patients, including biliary stenting and biliary surgery, due to repeated use of antibiotics for previous cholangitis episodes, empirical use of antibiotics when bile culture is not possible or available and frequent change of antibiotic group to treat cholangitis empirically. MDR pathogens have been attributed to adverse surgical outcomes in RPC patients (19,20). In cases of acute cholangitis, effective treatment of bile duct obstruction is paramount. Regarding the choice of antibiotics in community-acquired cholangitis, the guidelines are based on 3rd-generation cephalosporin, associated with an anaerobic agent in cases involving biliary enteric anastomosis (19,21). However, given the high rates of resistance in RPC, a different approach to antibiotic management may be required. In the present study, the carbapenem group showed the highest sensitivity (66.6%) against bacterial culture growth, followed by colistin (63.6%), while quinolones (27%) and cephalosporin groups showed the lowest sensitivity (27%). Carbapenems may be considered empirical antibiotics of choice in RPC patients with severe cholangitis and require an aggressive treatment approach when the bacteria culture and antibiotic sensitivity pattern are unavailable. Cephalosporin and quinolone groups of antibiotics should be avoided to empirically treat severe cholangitis in RPC before culture reports become available. Finally, antimicrobial therapy must be secondarily adapted to bacteriological test results to reduce the risk of emergent MDR pathogens. This is one of the few studies from India and the first from Eastern India evaluating the role of AL in RPC. The prevalence of RPC is high in Eastern India compared to other parts of the country; therefore, further studies with a much

larger sample size are required to identify the exact aetiology of this region-specific disease.

CONCLUSION

The present study showed a higher prevalence of hepatobiliary ascariasis in patients with RPC. However, the exact mechanism of ascariasis in forming biliary stones or initiating the disease is still unclear. RPC is a disease with a high incidence of MDR pathogens; therefore, judicial use of antibiotics is required during treatment. Carbapenems may be considered the empirical antibiotic of choice in RPC patients with severe cholangitis.

Ethics Committee Approval: This study was obtained from Institute of Postgraduate Medical Education and Research Ethics Committee (Decision no: IPGME&IEC/2020/221, Date: 11.03.2020).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – SR; Design – SR, ZA; Supervision – All of authors; Data Collection and/or Processing – ZA; Analysis and/or Interpretation – ZA; Literature Search – All of authors; Writing Manuscript – ZA; Critical Reviews – ZA.

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

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (2): 154-160

Tekrarlayan piyojenik kolanjitte mikrop ve parazitlerin rolü

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ÖZET

Giriş ve Amaç: Tekrarlayan piyojenik kolanjit (TPK) ve askariyazis Hindistan'ın doğusunda yaygındır. TPK'nin kesin patogenezi hala tartışma konusudur. Hepatobiliyer Askaris enfestasyonu Doğu Asya'da TPK'nin nedenlerinden biri olarak kabul edilmiştir, ancak Hindistan'dan bu konuda kesin kanıtlar eksiktir. TPK, önemli bir morbidite ve mortalite kaynağı olan çoklu ilaca dirençli (ÇİD) bakterilerle ilişkilidir. Bu çalışmanın amacı, hepatobiliyer askariyazisin TPK patogenezindeki rolünü değerlendirmek ve mikrobiyal profili ile bunların TPK hastalarının yönetimindeki etkilerini incelemektir.

Gereç ve Yöntem: Hindistan'ın doğusunda bulunan üçüncü basamak bir merkezde, Mart 2020-Aralık 2021 tarihleri arasında ardışık ameliyat edilen safra taşı hastaları TPK olan ve TPK olmayan olarak iki gruba ayrıldı. Cerrahi olarak alınan safra ve safra taşı örnekleri, her iki grupta askariyazis kanıtlarını belirlemek ve TPK grubundaki mikrobiyal profili incelemek için bakteri kültürü, mikroskopik ve histopatolojik inceleme yapılmak üzere gönderildi.

Bulgular: TPK grubundaki 54 hastanın sekizinde (%14,8) hepatobiliyer askariyazis bulguları tespit edildi. TPK olmayan gruptaki hastaların hiçbirinde askariyazis bulgusuna rastlanmadı. *Klebsiella*, safra kültüründe en sık görülen bakteriyel patojendi ve bakteriyel izolatların %79'u çoklu ilaca dirençli (ÇİD) patojenlerdi. Karbapenem grubu antibiyotikler, TPK hastalarında bakteri kültürü üremesine karşı en yüksek duyarlılığı (%66,6) gösterdi.

Sonuç: Bu çalışma, TPK'li hastalarda hepatobiliyer askariyazis prevalansının daha yüksek olduğunu göstermiştir, ancak kesin bir kanıt hala eksiktir. TPK, yüksek ÇİD bakteri insidansı ile ilişkilidir. Karbapenemler TPK'de tercih edilen ampirik antibiyotik olarak düşünülebilir.

Anahtar Kelimeler: Askariyazis, kolanjit, çoklu ilaç direnci

DOİ: 10.47717/turkjsurg.2024.6364

ORIGINAL ARTICLE
Turk J Surg 2024; 40 (2): 161-167

How to manage difficult duodenal defects? Single center experience

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ABSTRACT

Objective: The aim of this study was to investigate the surgical treatment methods and outcomes of difficult duodenal defects due to perforation.

Material and Methods: Data of patients who had undergone surgery for difficult duodenal defect between January 2012 and November 2022 were collected. Duodenal defect size of 2 cm or more was defined as difficult duodenal defect. Characteristics of the patients, the etiology of perforation, American Society of Anesthesiology (ASA) scores, Mannheim peritonitis index (MPI), surgical treatment, need for re-operation, and morbidity and mortality were evaluated.

Results: Nineteen patients were detected. Etiology was peptic ulcer perforation in 12 (63.1%) patients, aortaduodenal fistula in 2 (10.5%), tumor implant in 2 (10.5%), cholecystoduodenal fistula in 1 (5.2%), endoscopic retrograde cholangio pancreatography (ERCP) in 1 (5.2%), and cholecystectomy related injury in 1 (5.2%) patient. The first surgical procedure was duodenoraphy + omentopexy in 8 (42.1%), Graham repair in 5 (26.3%), duodenal segment 3-4 resection and Roux-en-Y side to side duodenojejunostomy in 4 (21.0%), Roux-en-Y side to side duodenojejunostomy in 1 (0.5%), and 1 (0.5%) subtotal gastrectomy + duodenum 1st part resection + Roux-en-Y gastroenterostomy, cholecystectomy and external biliary drainage via cystic duct. Four patients who had previously undergone Graham repair (3) and duodenoraphy + omentopexy (1) required salvage surgery. As a salvage surgery; 1 end-to-side and 3 side-to-side Roux-en-Y duodenojejunostomies were performed. Overall, mortality occurred in 6 (31.6%) patients. High ASA score and MPI were considered as significant risk factors for mortality (p= 0.015, p= 0.002).

Conclusion: Primary repair techniques can be used in the surgical treatment of difficult duodenal defects when peritonitis is not severe and tension-free repair is possible. Otherwise, duodenojejunostomy may be preferred as a fast, easy, and safe technique for both initial and salvage surgeries.

Keywords: Duodenum, peptic ulcer perforation, surgery, peritonitis

INTRODUCTION

Duodenal perforations are rare, but potentially fatal conditions. Mortality rate is reported to vary between 8-25% (1-3). Despite developments in medical treatment, the most common cause of duodenal perforations is complicated peptic ulcer (4). In addition to peptic ulcer, duodenal perforations may occur due to penetrating and blunt injuries, aortaduodenal or cholecystoduodenal fistula or iatrogenic causes (4).

Knutsson was first to define ulcer perforations over 2 centimeters (cm) as "giant duodenal ulcer" (5). In the current literature, defects in the duodenum over 2 cm, especially peptic ulcer perforations, are referred to as "giant duodenal ulcer" or "difficult duodenal defect" (6-9).

In addition to the unique anatomical structure of the duodenum, accompanying severe peritonitis makes surgical treatment of difficult duodenal defects challenging. The incidence of leakage and mortality rate are high (6-8). Despite the variety of recommended techniques, there is no clear consensus in the literature about which method is more appropriate for a specific situation (4,9). In this study, we aimed to share our own clinical experience.

MATERIAL and METHODS

Surgical treatment methods and clinical outcomes of difficult duodenal defects caused by non-blunt and non-penetrating factors were investigated. Duodenal defects of 2 cm or more were defined as "difficult duodenal defects". The study was first approved by the Non-Invasive Research Ethics Committee. We then

Cite this article as: Egeli T, Çavdaroğlu Ö, Ağalar C, Derici S, Aksoy S, Yılmaz İ, et al. How to manage difficult duodenal defects? Single center experience. Turk J Surg 2024; 40 (2): 161-167.

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Received: 10.06.2024
Accepted: 27.06.2024
Available Online Date: 28.06.2024

DOI: 10.47717/turkjsurg.2024.6476

retrospectively analyzed the cases who underwent surgery due to difficult duodenal defects between January 2012 and December 2022. Hospital electronic data processing system and patient files were used. Age, sex, American Society of Anesthesiologists (ASA) score, Mannheim peritonitis index (MPI), etiology of the defect, surgical repair technique, need for re-operation, type of salvage surgery, morbidity and mortality were evaluated (10,11).

The data were analyzed in IBM SPSS Statistics 22® package program. Non-parametric data were statistically evaluated with Chi-square test and parametric data with t-test. For both, $p< 0.05$ was considered significant.

RESULTS

Difficult duodenal defect was detected in 19 patients. Fourteen (73.7%) of these patients were males, and the rest 5 (26.3%) were females. Mean age of the patients was 65.84 ± 2.04 years. Difficult duodenal defect etiology included ulcer perforation in 12 (63.1%) patients, aortaduodenal fistula in 2 (10.5%), tumor implant in 2 (10.5%), cholecystoduodenal fistula in 1 (5.2%), injury during endoscopic retrograde cholangio pancreatography (ERCP) in 1 (5.2%), and cholecystectomy related injury in 1 (5.2%) patient. Intraoperative view of the difficult duodenal defect is seen in Figure 1.

American Society of Anesthesiologists Classification scores were 1 in 6 (31.5%) patients, 2 in 7 (36.8%) patients and 3 in 6 (31.3%) patients. Median MPI score was 26 (5-37). The first surgical intervention was duodenoraphy + omentopexy in 8 (42.1%) patients. Five (26.3%) patients had Graham repair, 4 (21.0%) patients had duodenal segment 3-4 resection and Roux-en-Y side to side duodenojejunostomy, one patient (0.5%) had Roux-en-Y side to side duodenojejunostomy, one patient (0.5%) had distal subtotal gastrectomy, first part resection of the duodenum, Roux-en-Y gastroenterostomy, cholecystectomy and external biliary drainage via common bile duct catheterization through the cystic duct, and feeding jejunostomy. Four patients died within the first week after surgery secondary to intra-abdominal sepsis.

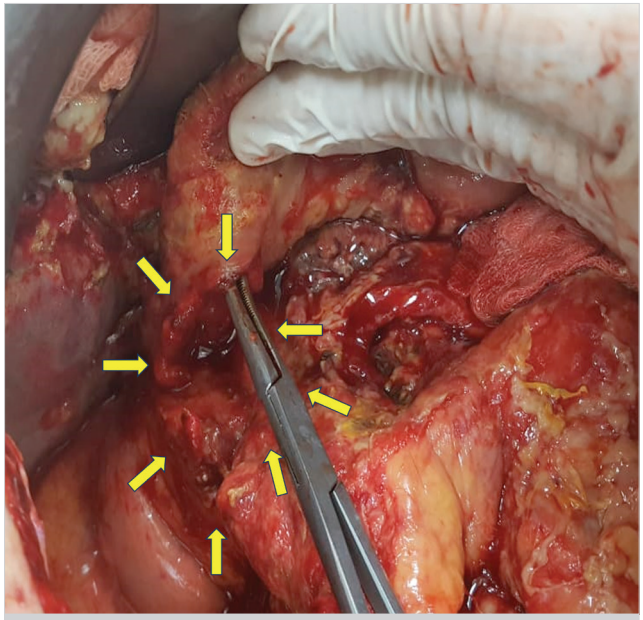

Figure 1. Intra-operative view of difficult duodenal defect. Yellow arrows indicate defect borders.

Leakage developed in 3 (16%) patients who underwent Graham repair and 1 (0.5%) patient who underwent duodenoraphy + omentopexy. Those 4 (22%) patients required second surgical intervention. Second surgical interventions were end-to-side Roux-en-Y duodenojejunostomy in one patient and side-to-side Roux-en-Y duodenojejunostomy in three patients. Additionally, biliary drainage catheter via cystic duct placed one of these three patients to divert the bile. Two of the patients who underwent second intervention died due to sepsis in the early post-operative period. Overall, 6 (31.6%) mortality occurred. Median MPI value was 35 (32-37) in patients with mortality. There was a correlation between the severity of intra-abdominal sepsis and mortality. Morbidity was observed in five patients, including surgical site infection in three and pulmonary infection in two patients. No mortality occurred in these patients. The details of the patients are summarized in Table 1.

In univariate analysis, higher ASA score ($p= 0.015$) was found to be statistically significant in terms of mortality (Table 2). When the relation between MPI elevation and mortality was evaluated statistically significant difference was found between MPI ($p= 0.002$). The cut-off value was determined as "28.5" using the Youden index.

Furthermore, patients were divided into two groups as high and low MPI scores. Although the number of patients in the data set was small, all patients who developed leakage after primary surgery were in the high MPI score group. Statistically, the risk of leak development after primary surgical repair techniques (duodenoraphy + omentopexy and Graham) increased significantly in patients with high MPI scores ($p= 0.002$).

DISCUSSION

Difficult duodenal defects are lesions that usually develop as a result of complicated duodenal ulcer perforation. Surgical treatment is problematic. The main reasons for the difficulty in surgical management are as follows: The anatomical location of the duodenum, severe inflammation, and edema due to accompanying peritonitis. Especially in delayed cases, surgical recovery becomes difficult due to generalized peritonitis and abdominal sepsis, and morbidity and mortality increase (4-9). In addition, the large size of the defect and edematous tissues make surgical repair difficult. Furthermore, high intraluminal pressure after defect repair increases the risk of disruption in

Table 1. Features of patients and details of performed surgical interventions

Number of Patients	Age	Sex	Duodenal Defect Etiology	Defect Location	ASA Score	MPI	Initial Surgery	Failure	Salvage Surgery	Mortality
1	82	F	Ulcer perforation	2. part	2	26	Duodenoraphy + Omentopexy			
2	44	M	Ulcer perforation	2. part	1	20	Duodenoraphy + Omentopexy			
3	54	M	Ulcer perforation	2. part	1	21	Duodenoraphy + Omentopexy			
4	72	M	Ulcer perforation	2. part	2	21	Duodenoraphy + Omentopexy			
5	62	F	Ulcer perforation	2. part	3	37	Duodenoraphy + Omentopexy			+
6	61	M	Ulcer perforation	2. part	1	25	Duodenoraphy + Omentopexy			
7	68	M	Ulcer perforation	2. part	2	32	Graham technique	+	Roux-en-Y End to side jejunojejunostomy	
8	58	M	Ulcer perforation	2. part	1	21	Graham technique			
9	62	F	Ulcer perforation	2. part	1	26	Graham technique			
10	74	M	Ulcer perforation	2. part	2	32	Graham technique	+	Roux-en-Y Side to side jejunojejunostomy	+
11	59	M	Ulcer perforation	2. part	2	32	Graham technique	+	Roux-en-Y Side to side jejunojejunostomy	
12	69	M	Ulcer perforation	1-2. part	2	32	Distal subtotal gastrectomy + duodenum 1. part resection + Roux-en-Y gastroenterostomy + cholecystectomy + external biliary drainage via cystic duct cathater + feeding jejunostomy			
13	65	F	ERCP injury	2-3. part	3	37	Roux-en-Y side to side duodenojejunostomy			+
14	75	M	Injury after cholecystectomy	2-3. part	1	32	Duodenoraphy	+	Side to side duodenojejunostomy + external biliary drainage via cystic duct cathater	+
15	76	F	Cholecystoduodenal fistula	2. part	2	10	Duodenoraphy + Omentopexy			
16	63	M	Aortaduodenal fistula	3-4. part	3	5	Duodenum segment 3-4 resection + side to side duodenojejunostomy			
17	68	M	Aortaduodenal fistula	3-4. part	2	5	Duodenum segment 3-4 resection + side to side duodenojejunostomy			
18	65	M	Tumor implant perforation	3-4. part	3	36	Duodenum segment 3-4 resection + side to side duodenojejunostomy			+
19	74	M	Tumor implant perforation	3-4. part	3	36	Duodenum segment 3-4 resection + side to side duodenojejunostomy			+

Table 2. Univariate analysis for mortality (p< 0.05, statistical significance)

Parameter	p
Sex	0.637
ASA score	**0.015**
Age	0.965
Mannheim peritonitis index (MPI)	**0.002**

the repair line. Advanced age of the patients, comorbidities and sepsis-induced hypoperfusion in delayed cases are other crucial issues that cause healing problems. The fact that some of the recommended surgical techniques are complicated, require experience and take a long time also might lead difficulties. In such cases, Graham repair, duodenoraphy and omentopexy, duodenoraphy and tube duodenostomy, duodenoraphy and triple ostomy, pyloric exclusion, jejunal serosal patch, duodenojejunostomy, duodenal diverticulization, repair with organic or synthetic patch, and in some cases, proximal pancreaticoduodenectomy (Whipple procedure) can be performed (4-9). However, due to the factors mentioned above, there is still no consensus on which type of surgical procedure is more appropriate in difficult duodenal defects.

Primary repair and omentopexy of the defect in duodenal perforations were defined by Cellan Jones in 1929, and repair of the defect by filling with a free omental flap was described by Graham in 1937 (12,13). These two methods are the most commonly applied primary surgical repair techniques in the treatment of duodenal perforations. However, the use of these primary repair techniques in the repair of difficult duodenal defects is often not ideal, mainly due to the following reasons: Large size of the perforation, the inflamed, edematous, and necrotic tissue edges, the risk of high intraluminal pressure to disrupt the repair line, and the inability to provide optimal omental grafts (4,9). Therefore, surgical treatments which are technically more complicated are recommended in such cases. However, complicated surgical procedures require experience; additionally, they have significant disadvantages such as prolonging the operation time in septic and hemodynamically unstable patients. In cases of difficult duodenal defect secondary to delayed perforation, leak rates of 10% and mortality rates between 10% and 65% are reported after complicated surgical procedures (7,14,15). Among the complicated surgical procedures, the pyloric exclusion method is relatively easier and faster to apply. Repair of the duodenum is done by gastrotomy, closure of the pylorus and gastrojejunostomy, and it is one of the most frequently used methods in the repair of difficult duodenal defects (4). Nevertheless, there are publications reporting that frequent complications develop after pyloric exclusion and that the length of hospital stay is prolonged (16-18).

Muhammed Ali et al. have reported the "triple ostomy" technique, which is relatively easier and faster to perform, as an alternative for patients who are not suitable for primary surgical repair. The authors have reported that complication rates were lower and successful results were obtained after this technique (9). For patients who are hemodynamically unstable and those complicated surgical procedures cannot be performed on, it is recommended to rapidly remove intra-abdominal contamination, place a large tube into the defect, suture and close the defect, and perform tube duodenostomy (4,19). The goal is to create a controlled duodenal fistula. Some centers recommend distal gastrectomy, gastrojejunostomy and feeding jejunostomy to maintain nutrition in addition to tube duodenostomy in hemodynamically stable patients (20).

Another method recommended for the repair of difficult duodenal defects is end-to-side or side-to-side duodenojejunostomy. We prefer duodenojejunostomy in cases for whom primary repair techniques are not possible as it is technically easy and rapidly applicable. Even though edematous and inflamed perforation line seems to be a disadvantage for anastomosis in duodenojejunostomy, we think that a healthy jejunal edge with good perfusion eliminates this handicap and has a positive effect on anastomotic healing. Furthermore, circumferential debriding of the perforation line provides duodenal tissue with good perfusion and optimizes anastomotic healing. In their recent publication, Gan et al. have reported successful results with retrocolic loop side-to-side duodenojejunostomy repair in four patients with giant duodenal defects caused by ulcer perforation (21). In support of our view, the authors have reported that well-blooded jejunal edge and debrided ulcer edges on duodenal side optimizes anastomotic healing. In our technique, unlike that of Gan et al, we prefer to perform duodenojejunostomy in the Roux-en-Y fashion. The primary reason for this preference is because, unlike in loop anastomosis, the nutrient contents do not return to the anastomotic line in Roux-en-Y fashion. It is thought that the return of the nutrient contents back to the anastomosis line forces the anastomosis line and may cause complications such as passage problems, gastric reflux and risk for anastomotic dehiscence.

However, it should be kept in mind that a second anastomosis is required in Roux-en-Y reconstruction, and there may be additional complications related to this. Also, according to the surgeon's preference, cholecystectomy, cystic stump cannulation, and external drainage of the bile can be added to Roux-en-Y duodenojejunostomy in order to reduce intraluminal pressure (Figure 2). In such cases, the application of post-operative percutaneous transhepatic biliary drainage can be considered as an alternative option.

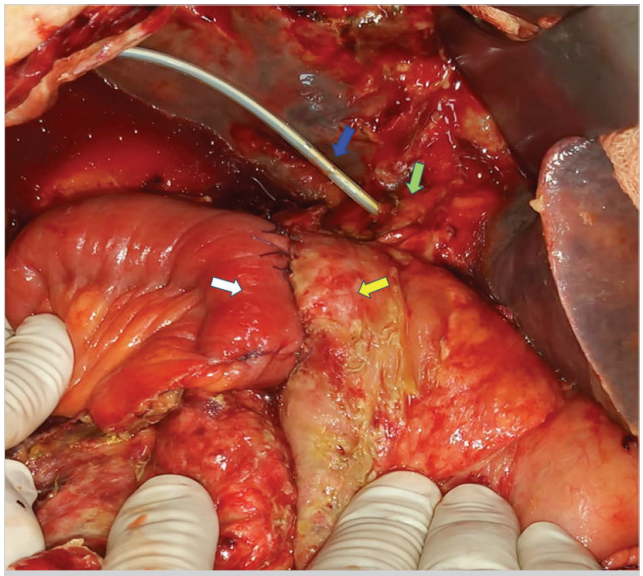

Figure 2. Salvage surgery due to leakage after initial primary repair. Side-to-side Roux-en-Y duodenojejunostomy and biliary drainage catheter via cystic duct was performed.

Yellow arrow: Duodenum, White arrow: Jejunum, Green arrow: Common bile duct, Blue arrow: Biliary drainage catheter via cystic duct.

In our clinic, primary repair techniques of duodenoraphy and Graham repair were performed on 13 patients with difficult duodenal defects. One of these patients died due to postoperative sepsis. In 4 (30%) of the other 12 patients, leakage developed after primary repair, and a second surgical intervention was required. Statistical analysis showed that the risk of post-repair leakage increased in patients with high MPI score. The second surgical interventions were duodenojejunostomies, 1 end-to-side and 3 side-to-side. In two of these four cases, early mortality developed owing to septic complications after the second surgical intervention. In other cases where severe peritonitis or tension-free primary repair techniques were not possible, direct side-to-side duodenojejunostomy was preferred. Since most of these cases had aortaduodenal fistula and perforation on the basis of tumor implant, resections of the 3rd and 4th parts of the duodenum were also performed. In one case, the first part of the duodenum and the distal part of the stomach were necrotic on the basis of a large ulcer. Therefore, surgical treatment was provided by distal subtotal gastrectomy and duodenal 1st part resection. As can be seen in Table 1, primary repair techniques can be applied with acceptable success rates in cases with difficult duodenal defects, if peritonitis is not severe, and there is a possibility of tension-free repair with primary repair techniques. Otherwise, duodenojejunostomy is more appropriate. Consistent with the literature, higher MPI and ASA scores were statistically associated with mortality (p= 0.002, p= 0.015). The MPI cut-off value for mortality was determined as 28.5. Additionally, the risk of leakage was found to increase in patients with high MPI score. Moreover, according to the data of our study, we concluded that linear duodenal defects can be safely repaired with primary repair techniques in cases which are not accompanied by severe peritonitis, regardless of size. We believe that duodenal defects should be considered as two-dimensional rather than one-dimensional, unlike how it is often portrayed in many publications; the suitability of tension-free repair should be evaluated by considering both dimensions of the defect.

While it is crucial to ensure the safety of the ampulla of Vater, the application of segmental duodenal resection is feasible for treating defects affecting the 3rd or 4th segments of duodenum. Duodenojejunostomy provides gastrointestinal continuity after resection. On the contrary, segmental resection cannot be used to treat defects in or affecting the 2nd segment of the duodenum; the only applicable resectional procedure is proximal pancreaticoduodenectomy. Thus, particularly for treating defects affecting segment 2nd, duodenojejunostomy is very important as an alternative technique. Because in these cases, duodenojejunomy provides duodenal defect repair beside enabling gastrointestinal continuity.

There are certain classifications for duodenal defects, but they mostly describe trauma-related injuries or are used by endoscopists to classify injuries in ERCP procedure, and these classifications are not suitable for the optimal identification of difficult duodenal defects on the basis of perforation and for the determination of the surgical approach (20,22). Therefore, considering the above-mentioned criteria, it is necessary to establish a new scoring system for standard definition of difficult duodenal defects.

The small number of cases and retrospective design can be considered as weaknesses of our study. These cases are not common; thus, multicenter studies are needed for effective research with a larger number of cases. Such studies will help to develop scoring and surgical treatment algorithms for difficult duodenal defects secondary to perforation.

CONCLUSION

In conclusion, we point out that primary repair techniques can be successful in difficult duodenal defects that have low risk factors and have a chance of tension-free repair. Otherwise, duodenojejunostomy may be preferred as a fast, easy and safe technique for both initial and salvage surgeries.

Ethics Committee Approval: This study was obtained from Dokuz Eylül University Faculty of Medicine Non-Interventional Research Ethics Committee (Decision no: 2020/23-09, Date: 28.09.2020).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - TE, ÖÇ, CA, SD; Design - TE, ÖÇ, CA, SD, SA; Supervision - TE, TÜ, MÖ; Data Collection and/or Processing - ADÇ, İY, ÖÇ, TE; Analysis and/or Interpretation - TE, ÖÇ, SD, TÜ, MÖ; Literature Search - TE, ADÇ, İY, TB, BM; Writing Manuscript - TE, ÖÇ, CA; Critical Reviews - TE, TÜ, MÖ.

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

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (2): 161-167

Zor duodenal defektler nasıl yönetilmeli? Tek merkez deneyimi

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ÖZET

Giriş ve Amaç: Perforasyon nedeniyle meydana gelen zor duodenal defektlerde uygulanan cerrahi tedavi yöntemleri ve sonuçlarının araştırılmasıdır.

Gereç ve Yöntem: Kliniğimizde Ocak 2012 ve Kasım 2022 tarihleri arasında perforasyona bağlı zor duodenal defekt nedeniyle cerrahi tedavi uygulanan hastaların verileri toplandı. Duodenal defekt boyutu 2 cm ve üzeri olgular zor duodenal defekt olarak tanımlandı. Hastaların karakteristik özellikleri, perforasyon etiyolojisi, Amerikan Anesteziyoloji Birliği (AAB) skorları, Mannheim peritonit indeksleri (MPİ), uygulanan cerrahi tedavi, tekrar cerrahi girişim gereksinimi, morbidite ve mortalite bilgileri değerlendirildi.

Bulgular: Zor duodenal defekt nedeniyle cerrahi uygulanan 19 hasta saptandı. Zor duodenal defekt etiyolojisi hastaların; 12 (%63,1)'sinde peptik ülser perforasyonu, 2 (%10,5)'sinde aortaduodenal fistül, 2 (%10,5)'sinde tümör implantı, 1 (%5,2)'inde kolesistoduodenal fistül, 1 (%5,2)'inde endoskopik retrograd kolanjio pankreatografi (ERCP) ve 1 (%5,2)'inde kolesistektomi kaynaklı yaralanmaydı. İlk cerrahi işlem hastaların; 8 (%42,1)'inde duodenorafi + omentopeksi, 5 (%26,3)'inde Graham onarım, 4 (%21,0)'ünde duodenum segment 3-4 rezeksiyonu ve Roux-en-Y yan yana duodenojejunostomi, 1 (%0,5)'inde Roux-en-Y yan yana duodenojejunostomi, 1 (%0,5)'inde subtotal gastrektomi, duodenum birinci kıta rezeksiyonu, Roux-en-Y gastroenterostomi, kolesistektomi ve ana safra kanalına sistik kanal üzerinden eksternal biliyer drenajdı. Öncesinde Graham onarım (3) ve duodenorafi + omentopeksi (1) uygulanan dört hastaya ikinci cerrahi gerekti. İkinci cerrahi birinci hastada uç-yan, üç hastada yan yana Roux-en-Y duodenojejunostomiydi. Toplamda 6 (%31,6) hasta kaybedildi. Yüksek AAB skoru ve MPİ mortalite gelişimi açısından anlamlı risk faktörü olarak belirlendi (p= 0,015, p= 0,002).

Sonuç: Zor duodenal defektlerin cerrahi tedavisinde, peritonit şiddeti yüksek olmayan ve gerginliksiz onarımın mümkün olduğu olgularda primer onarım teknikleri uygulanabilir. Aksi durumlarda duodenojejunostomi gerek ilk gerekse kurtarma cerrahisinde hızlı, kolay ve güvenli bir teknik olarak tercih edilebilir.

Anahtar Kelimeler: Duodenum, peptik ülser perforasyonu, cerrahi, peritonit

DOİ: 10.47717/turkjsurg.2024.6476

CASE SERIES
Turk J Surg 2024; 40 (2): 168-173

Challenges in managing duodenal intussusception: A rare cause of gastric outlet obstruction in adults

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ABSTRACT

Intussusception is a rare occurrence in adults and only 5% being adults. Ileocolic intussusception is the most common type in adults whereas duodenal intussusception (DI) is the rarest subtype due to natural retroperitoneal fixation of the duodenum. There are only a few case-reports available in the literature. Here, we aimed to present our experience of five cases with DI in adults, there operative challenges and strategies to deal with the same. Age of presentation ranged from 18-45 years, and four out of five were females. Most common presentation was partial of recurrent gastric outlet obstruction (GOO) along with weight loss. They were all diagnosed on contract-enhanced-CT scan of abdomen, and all had a lead point in form of a benign polypoidal mass arising from duodenum. Two patients were managed with local excision of polyp and retroperitoneal fixation of redundant duodenum, whereas pancreaticoduodenectomy and segmental duodenal resection was required for the other two patients. One patient was lost to follow-up without definitive treatment as was minimally symptomatic. All four operated patients had uneventful recovery post-operatively and are doing well in follow-up. DI is an infrequent occurrence and a rare etiology of GOO in adults. Most of them having benign lead point, require surgical excision of lead point with fixation of duodenum to retroperitoneum. Anatomical proximity of important structures like CBD and pancreatic duct especially at perivaterian location makes surgical resection challenging. With thorough anatomical knowledge and appropriate management, this condition can be managed well.

Keywords: Duodenal intussusception, duodenal polyps, intussusception, gastric outlet obstruction

INTRODUCTION

Intussusception, i.e., invagination of a portion of the intestine into another segment in a telescope-like fashion. It is a rare occurrence in adults, with an incidence of 5% and represents 1-5% of all causes of small bowel obstruction in adults (1,2). Duodenal intussusception (DI) is an exceedingly rare entity due to its retroperitoneal fixation and only a few case reports are available in the literature, mostly describing a single case (3,4). It is a challenging situation due to rarity, non-specific symptoms, and difficult anatomic considerations. Here, we aimed to present our experience with DI in adults, operative challenges, and strategies to deal with the same (Table 1).

Case 1

Thirty-year-old female patient presented with recurrent episodes of postprandial colicky left upper abdominal pain, distension and bloating sensation for two months with significant unintentional weight loss, but no anorexia. She had an episode of obstructive jaundice, which resolved spontaneously with resolution of pain. Physical examination did not reveal any significant findings. Her serum alkaline phosphatase level was elevated (700 IU/L). Magnetic resonance cholangiopancreatography (MRCP) revealed medial stretching of the duodenum, common bile duct (CBD), and pancreas, as well as elongated duodeno-jejunal (DJ) flexure. Bilobar intrahepatic biliary radicals and CBD were dilated. Further imaging with contrast enhanced computer tomography (CECT) confirmed DI, but lead point was not identified. Ultrasonography aided in visualization of the polypoidal mass as lead point. On exploration, duodenum and proximal jejunum were dilated with an intussuscepted bowel segment into the proximal jejunum in left upper abdomen. After reduction, duodenotomy was made on lateral wall of the 2nd part

Cite this article as: Kaw P, Malage S, Singh A, R R, Gosh NK, Sharma S, et al. Challenges in managing duodenal intussusception: A rare cause of gastric outlet obstruction in adults. Turk J Surg 2024; 40 (2): 168-173.

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Received: 20.04.2024
Accepted: 19.06.2024
Available Online Date: 28.06.2024

DOI: 10.47717/turkjsurg.2024.6411

Table 1. Patient profile

Age (Years)	Sex	Presentation	Lead Point Location	Surgery	Histopathology	Post-op	Outcome (Follow-up Period)
30	Female	Recurrent GOO, Jaundice, Weight loss	D2*	Local resection of polyp and duodenal fixation to retroperitoneum	Adenomatous polyp	Uneventful	Doing well (six months)
45	Female	Recurrent GOO	D2*	Pancreaticoduodenectomy	Hamartomatous polyp	Uneventful	Doing well (two years)
32	Male	Recurrent GOO, Weight loss	D4*	Segmental resection of intussuscepted bowel with polyp	Adenomatous polyp	Uneventful	Doing well (three years)
18	Female	Recurrent GOO, Weight loss	D2*	Local resection of polyp and duodenal fixation to retroperitoneum	Hyperplastic polyp	Post-op gastroparesis, resolved with conservative management	Doing well (five years)
27	Female	Mild dyspeptic symptoms	D1*	Denied surgery	Adenomatous polyp	Denied surgery	Lost to follow up

*D: Duodenum, Number: Part of duodenum.

of duodenum (D2). Lead point was a 6 x 5 cm perivaterian polyp. Since the opening of the papilla was not clearly defined, cholecystectomy was done, and papilla was identified by flushing saline via cystic duct, which was 1.5 cm away from polypoidal mass. Excised polypoidal mass, including 1 cm margin all around was sent for frozen section and reported as tubulo-villous adenomatous polyp low-grade dysplasia with clear margins. Duodenotomy was closed, and duodenum was fixed to the retroperitoneum. Post-operative course was uneventful. Oral contrast study on 5th-post-operative-day (POD) revealed no leakage of contrast and free flow from duodenum to the jejunum. The patient was discharged on the 7th-POD. She is doing well at six months of follow-up (Figure 1A-H).

Case 2

Forty five-year-old female patient presented with recurrent episodes of postprandial abdominal bloating and fullness for 10 years. Palpation revealed a 5 x 4 cm non-tender lump in right hypochondrium. Ultrasonography suggested possibility of intussusception with a polypoidal lead point. Further evaluation with CECT revealed intussusception of D2 along with pancreatic head, dilated CBD and pancreatic duct (PD), into the 3rd and 4th parts of the duodenum (D3, D4), reaching up to DJ flexure. A 5 x 4 cm polyp was noted as lead point. On exploration, stomach and D2 were distended, with DI noted in right upper abdomen. After reduction of intussusception, duodenotomy was made and a large polypoidal mass noted arising from medial wall of papilla acting as lead point. CBD was dilated. As the mass was arising from ampulla, pancreaticoduodenectomy was performed. Histopathological examination (HPE) revealed a hamartamatous polyp. Post-operative course was uneventful, and the patient was discharged on 10th-POD. The patient is doing well after two years of follow-up (Figure 2A-C).

Case 3

Thirty two-year-old male patient had recurrent episodes of small amounts of bilious vomiting 2-3 hours after food intake for one year, along with significant unintentional weight loss, but no anorexia. Physical examination was normal. CECT revealed distended stomach and D2, along with DJ intussusception. On exploration, DJ-flexure was found intussuscepting retrogradely into D3 and D4. Segmental resection of the intussuscepted bowel loop was done, and continuity restored with side-to-side duodenojejunal anastomosis. On cutting the specimen, a solitary sessile polyp measuring 4.5 x 4 cm was noted in the D3, 3 cm away from the resected ends. HPE revealed adenomatous polyp with low-grade dysplasia. Post-operative course was uneventful, and the patient was discharged on 6th-POD. The patient is doing well after three years of follow-up.

Case 4

Eighteen-year-old female patient had recurrent episodes of postprandial epigastric pain, fullness, large volume gastric vomiting, and melena every 1-2 months for 2-3 days for two years and suffered significant unintentional weight loss without anorexia. Physical examination was normal. Oesophagogastroscopy revealed large lobulated growth arising close to the papilla; biopsy was inconclusive. Further evaluation with CECT

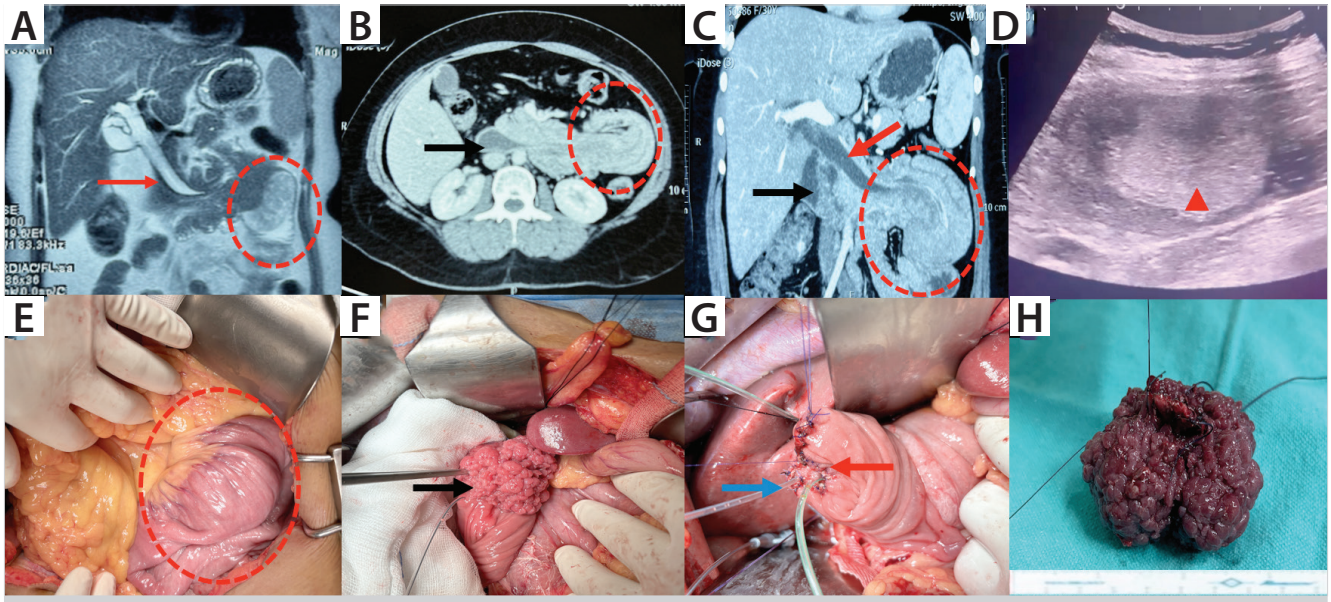

Figure 1. Case 1: **A.** Magnetic resonance cholangiopancreatography (MRCP) Coronal section depicts an elongated, dilated CBD (red arrow) tapering towards left of midline with central intrahepatic biliary radical dilatation and a suspicious clumped up bowel loops (marked with dotted circle). **B.** Computed Tomography (CT) scan of the abdomen, axial section of suggests dilated 2nd part of duodenum (black arrow), collapsed 3rd part of duodenum with duodenojejunal intussusception (dotted circle). **C.** Coronal section of the CT scan suggests dilated common bile duct (red arrow) pulled across midline to left side, dilated 2nd part of duodenum (black arrow), collapsed 3rd part of duodenum with duodenojejunal intussusception (marked by dotted circle). **D.** Ultrasonography of the abdomen showing the polypoidal mass as lead point (red arrow head). On exploration **E.** Intussusception of duodenum was noted into jejunum (red dotted circle), intussusception was reduced. **F.** A polypoidal mass in perivaterian region (black arrow) was identified as lead point on lateral duodenotomy. **G.** Choledocoduodenostomy done. **H.** Gross specimen of the excised polyp.

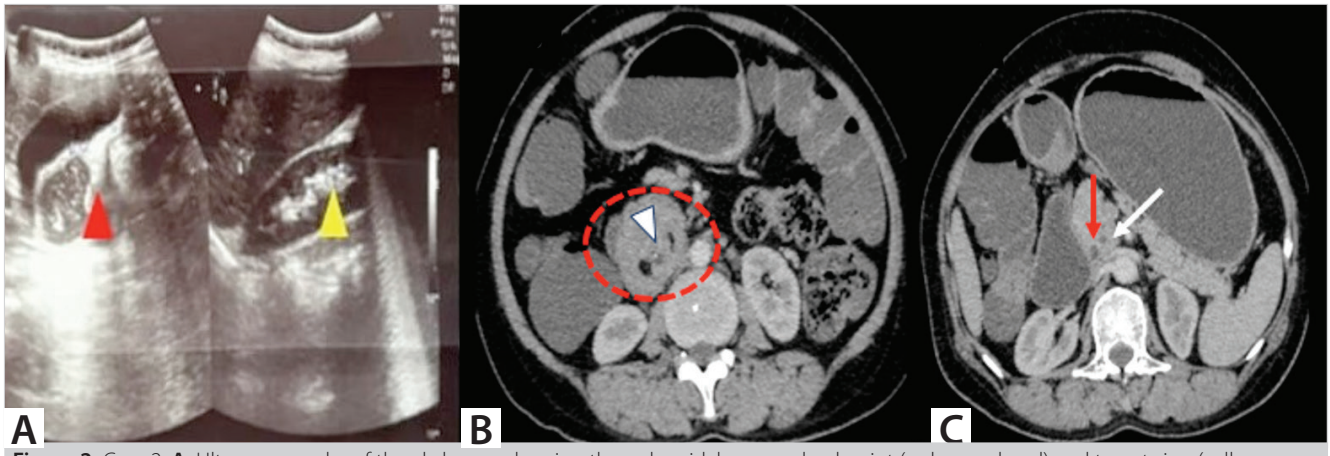

Figure 2. Case 2: **A.** Ultrasonography of the abdomen showing the polypoidal mass as lead point (red arrow head) and target sign (yellow arrow head) suggesting intussusception of bowel. **B.** Axial section of the CT scan suggests duodenoduodenal intussusception (dotted circle) and the lead point (white arrow head) **C.** Further sections on CT scan suggest dilated CBD (red arrow) and pancreatic duct (white arrow).

revealed DI in D2 and prominent CBD. On exploration, 1st part of the duodenum (D1) was dilated, and DI was noted from the D2 up to the proximal jejunum, which was reduced, and duodenotomy made on lateral wall of D2. Papilla and a perivaterian polypoid growth of size 3 x 3 cm were identified. Polyp was excised circumferentially, with a 5 mm margin safeguarding the papilla. Duodenotomy closed, and the redundant duodenum was fixed to the retroperitoneum and parities. HPE revealed hyperplastic polyp. Postoperatively, the patient had gastroparesis, requiring medical management. The patient tolerated solid food by 10th POD and was discharged on 13th-POD. At five years of follow-up, the patient is doing well (Figure 3A,B).

Case 5

Twenty seven-year-old female patient was evaluated for primary infertility and was found to have possibility of small

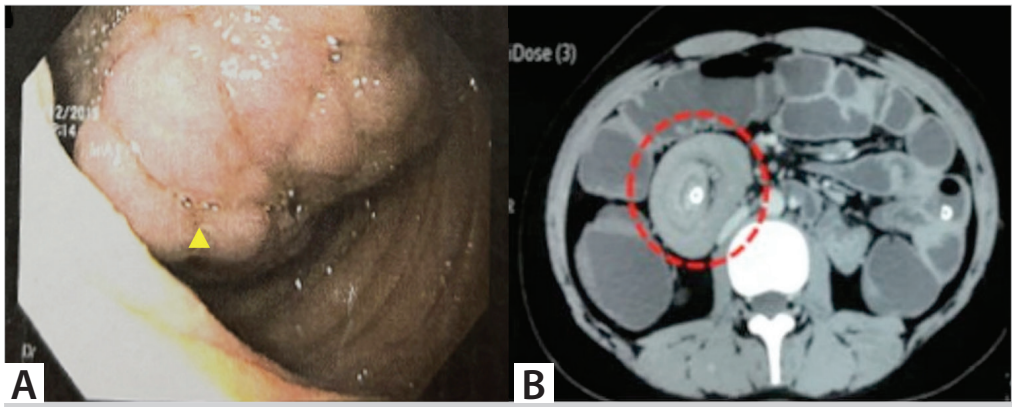

Figure 3. Case 4: **A.** Oesophagogastroscopy revealed a large lobulated growth (arrow head) arising close to the papilla. **B.** Axial section of the CT scan shows target sign suggesting duodenoduodenal intussusception (dotted circle) with NJ in situ.

bowel intussusception. Other than mild dyspeptic symptoms, she was asymptomatic. CECT revealed distended stomach and herniation of D1 into the D2 and D3, with a pedunculated polyp arising from the D1 as lead point. Oesophagogastroscopy confirmed the presence of 4 x 6 cm pedunculated polyp. HPE revealed an adenomatous polyp with low-grade dysplasia. The atient was offered surgical management, but she denied as she had minimal symptoms and was lost to follow-up (Figure 4).

DISCUSSION

Intussusception, disease of the childhood, occurs with a frequency of only 5% in adults (5). Ileocolic intussusception is the most common, whereas DI is the rarest subtype in adults (6). It is probably due to retroperitoneum fixity of the duodenum and rarity of mass in this region (7,8). In adults, DI is frequently seen in young and middle-aged women (9). In our series, the age ranged from 18-45 years, with a median of 31 years, and the female-to-male ratio was 4:1. Usual presentation is with features of recurrent or partial gastric outlet obstruction, including colicky abdominal pain, bloating, nausea, and vomiting, which may vary from being subtle to severe in intensity, as seen in our series as well (10). Biliary and pancreatic systems are generally not involved unless the mass is located in perivaterian region, dragging the CBD and PD along with intussusceptum, leading to their dilatation, which may or may not manifest clinically (11). In our series, four patients had features of recurrent GOO, while one had minimal dyspeptic symptoms. Additionally, three patients had dilated CBD; however, only one had obstructive jaundice due to perivaterian tubulovillous adenomatous polyps dragging the CBD into intussusception. Another patient had palpable lump on physical examination. Patients may also present with history of weight loss due to long-term partial or recurrent GOO, as in our series, three out of five patients had significant weight loss. Diagnosing DI is important as there is high risk of life-threatening complications associated with it, such as ischemia, obstruction, or intraluminal bleeding, requiring emergency treatment. Due to non-specific and often chronic or recurrent symptoms, diagnosis is usually missed or delayed. Hence, clinicians should be suspicious of intussusception if presentation is of partial or recurrent GOO, pancreatitis, or obstructive jaundice along with weight loss, in young females. CECT is the most reliable investigation for preoperative diagnosis (sensitivity: 71.4-87.5%; specificity: 100%) for DI showing 'target' or 'doughnut' signs, as well as a sausage-shaped mass or pitchfork image (12). In our series, all patients were diagnosed preoperatively with CT scan. Additionally, CT also helps in identification of lead-point lesions. A well-defined lead point is seen in >90% of adult intussusception (AI), most of which are benign (>70%) (13). Lead point is present in almost all cases of DI in the form of

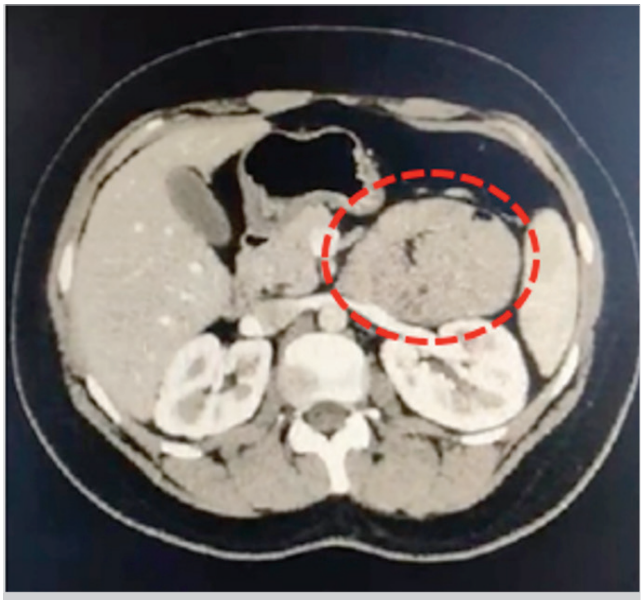

Figure 4. Case 5: Axial section of the CT scan shows target sign suggesting duodenoduodenal intussusception (dotted circle).

polypoidal mass, which may differ in histopathology. We could identify benign polyps as lead points in all cases. Three were tubulo-villous adenomatous polyps with low-grade dysplasia; one was hamartamatous polyp, and another one was hyperplastic polyp. Next investigation offered is upper GI endoscopy to find out the lead point, if possible, with biopsy to confirm histopathology. Although there is no consensus guideline for managing DI, surgical management is the preferred treatment modality considering the presence of lead point in most cases and chances of associated complications (9,14). Anatomical fixity and location of lead point close to ampulla in DI, makes surgery challenging. Perivaterian mass, located within 2 cm of the papilla, have an increased risk of CBD and PD injury. In general, a widely accepted approach is the reduction of the intussusception, excision of lead point if benign, and fixation of redundant segments of bowel to avoid recurrence (15). In case of suspected or known malignancy, radical excision is required. Most of the lead points in adult enteric intussusception are benign and only <30% are malignant (16). Hence, a more conservative surgical approach should be chosen to prevent mortality and morbidity of major resections after confirming benign pathology on frozen section histopathology. In our series, two patients underwent reduction of intussusception with local excision of polyp, one patient having polyp arising from papilla, abetting local polypectomy, underwent pancreaticoduodenectomy and one required segmental duodenal resection for polyp arising from D3. All patients had smooth post-operative course and are doing fine in follow-up, except one whose further course is not known, as patient lost follow-up without definitive treatment.

CONCLUSION

Duodenal intussusception is an infrequent occurrence and a rare aetiology of gastric outlet obstruction in adults. Most of them have a benign lead point, requiring surgical excision of the lead point with fixation of the duodenum to the retroperitoneum. Anatomical proximity of important structures like CBD and pancreatic duct especially at perivaterian location makes surgical resection challenging. With thorough anatomical knowledge and appropriate management, the condition can be managed well.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - AS; Design - All of authors; Supervision - AS; Data Collection and/or Processing - PK, SM; Analysis and/or Interpretation - All of authors; Literature Search - PK, SM, AS; Writing Manuscript - PK, SM, AS; Critical Reviews - All of authors.

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

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

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OLGU SERİSİ-ÖZET
Turk J Surg 2024; 40 (2): 168-173

Duodenal intussusepsiyon tedavisinde zorluklar: Yetişkinlerde gastrik çıkış obstrüksiyonunun nadir bir nedeni

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ÖZET

İntussepsiyon/invajinasyon yetişkinlerde nadir görülen bir durumdur ve sadece %5'i yetişkinlerde görülür. İleokolik invajinasyon erişkinlerde en sık görülen tip iken duodenal invajinasyon (Dİ) duodenumun doğal retroperitoneal fiksasyonu nedeniyle en nadir görülen alt tiptir. Literatürde sadece birkaç olgu sunumu mevcuttur. Burada yetişkinlerde Dİ'li beş olguya ilişkin deneyimlerimizi, karşılaşılan ameliyat zorluklarını ve bunlarla başa çıkma stratejilerini sunmayı amaçladık. Başvuru yaşları 18-45 arasında değişmekteydi ve beş olgunun dördü kadındı. En sık başvuru şekli kilo kaybı ile birlikte kısmi tekrarlayan gastrik çıkış obstrüksiyonu (GÇO) idi. Hepsine kontrastlı karın bilgisayarlı tomografisi taramasında tanı konuldu ve hepsinde duodenumdan kaynaklanan benign polipoidal kütle şeklinde bir öncü nokta vardı. İki hasta polipin lokal eksizyonu ve duodenumun retroperitoneal fiksasyonu ile tedavi edilirken, diğer iki hasta için pankreatoduodenektomi ve segmental duodenal rezeksiyon gerekti. Bir hasta minimal semptomatik olduğu için kesin tedavi uygulanamadan takipten çıktı. Ameliyat edilen dört hastanın tümü ameliyat sonrası sorunsuz iyileşti ve takiplerinde sorun görülmedi. Dİ nadir görülen bir durumdur ve yetişkinlerde GÇO'nun nadir bir etiyolojisidir. Çoğu benign sürükleyici lezyona sahip olan bu hastalarda, duodenumun retroperitona fiksasyonu ile birlikte sürükleyici lezyonun cerrahi eksizyonu gerekmektedir. Özellikle ampulla çevresi lokalizasyonda koledok ve pankreatik kanal gibi önemli yapıların anatomik yakınlığı cerrahi rezeksiyonu zorlaştırmaktadır. Kapsamlı anatomik bilgi ve uygun yönetim ile bu durum iyi bir şekilde yönetilebilir.

Anahtar Kelimeler: Duodenal intussusepsiyon, duodenal polipler, intussusepsiyon, gastrik çıkış obstürksiyonu

DOİ: 10.47717/turkjsurg.2024.6411

CASE REPORT
Turk J Surg 2024; 40 (2): 174-177

Radiofrequency ablation of metastatic lymph nodes in a patient requiring secondary operation for papillary thyroid carcinoma metastasis

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ABSTRACT

Radiofrequency ablation is a minimally invasive modality performed as an alternative to surgery in patients with benign thyroid nodules and recurrent thyroid cancers. As far we know there is scant data regarding the safety of radiofrequency ablation for metastatic lymph nodes. In this report, our aim was to evaluate the safety and efficacy of radiofrequency ablation for metastatic lymph nodes in patients with recurrent papillary thyroid cancer metastasis. A 63-year old man, who underwent bilateral total thyroidectomy procedure in a different hospital with the diagnosis of papillary thyroid cancer one year ago, was diagnosed to have papillary thyroid cancer metastasis in single lymph nodes bilaterally in his follow-up. He underwent percutaneous radiofrequency ablation under ultrasound guidance. He was discharged home on post-operative day one uneventfully and his first control ultrasonography revealed a decrease in nodule size larger than 50% in right side of the neck and also the nodule in the left side disappeared. In conclusion, radiofrequency ablation is a safe and feasible technique for the treatment of metastatic lymph nodes in patients requiring secondary surgery due to papillary thyroid cancer metastasis.

Keywords: Radiofrequency ablation, recurrent thyroid cancer, lymph node, thyroid cancer metastases, ultrasound, complication

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy and post-operative recurrence rates vary between 15% and 67% depending on the stage of the disease and the type of tumor. Cervical lymph node metastases are seen in up to 30% of patients with differentiated thyroid carcinoma (1). The treatment modalities for lymph node metastasis include surgical excision, irradiation, chemical injection and thermal ablation techniques (2). However, the literature is inconsistent as to which treatment is more effective for local recurrence or metastasis of thyroid carcinoma. Due to increased risk of damaging recurrent laryngeal nerves and parathyroid glands in secondary operations, it has been showed that, radiofrequency ablation (RFA) can be used alternative to surgery for treating thyroid cancers. In addition to less invasiveness and reduction of morbidity, it has been noted that even repeated RFA did not increase the complication rate (3).

The aim of this case report is to evaluate the safety and effectiveness of RFA in the treatment of metastatic lymph nodes in patients with metastatic papillary thyroid cancer.

CASE REPORT

A 63- year-old male patient underwent bilateral total thyroidectomy for the papillary thyroid cancer in another hospital. There was multicentric papillary cancer detected one cm in right lobe and 0.6 cm in the left lobe with thyroid capsule invasion. His thyroglobulin (TG) level was 0.057 ng/mL after surgery. He did not take radioactive iodine treatment (RAI) after surgery. One year later, during his follow-up imaging studies, ultrasonography (US) revealed a 12.8 x 10.4 x 9.2 mm sized patho-

Cite this article as: Öner G, Özçınar B, Ağcaoğlu O, Aksakal N, Salmaslıoğlu A, Yücel C, et al. Radiofrequency ablation of metastatic lymph nodes in a patient requiring secondary operation for papillary thyroid carcinoma metastasis. Turk J Surg 2024; 40 (2): 174-177.

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Received: 11.10.2019
Accepted: 07.06.2020
Available Online Date: 20.01.2023

DOI: 10.47717/turkjsurg.2023.4631

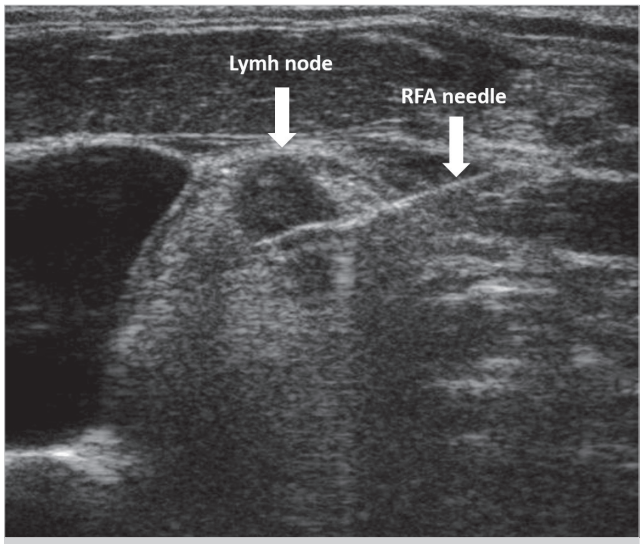

Figure 1. Ultrasonography image showing the metastatic lymph node that was adjacent to the jugular vein and radiofrequency needle.

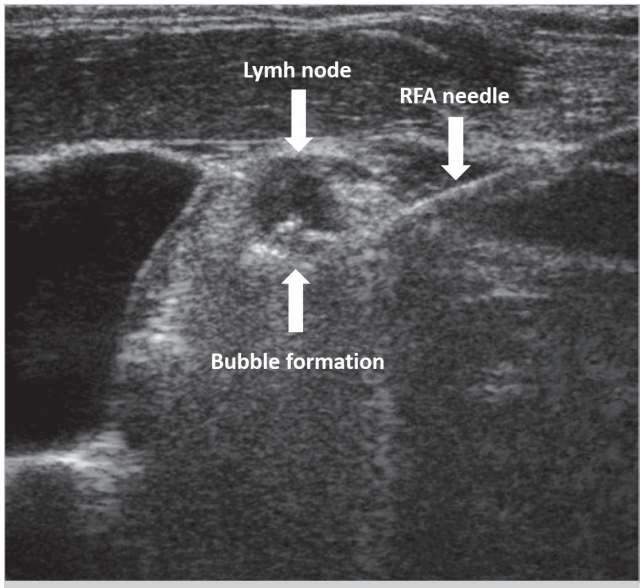

Figure 2. Ultrasonography image showing the bubbling effect due to ablation on the inferior part of the lymph node that was adjacent to the jugular vein.

logic lymph node in left neck region 4-5b junction. In addition, a 9.8 mm diameter pathologic lymph node that was adjacent to the jugular vein was detected in the right side of the neck. Fine needle aspiration biopsy result revealed papillary thyroid cancer metastasis. His TG level was 0.052 ng/mL and anti Tg level was 608 IU/mL. The risk and complications were discussed with the patient for bilateral central and lateral lymph node dissection and RFA was performed because the patient did not accept the surgery. He underwent radiofrequency ablation under ultrasound guidance and discharged home on the first day after

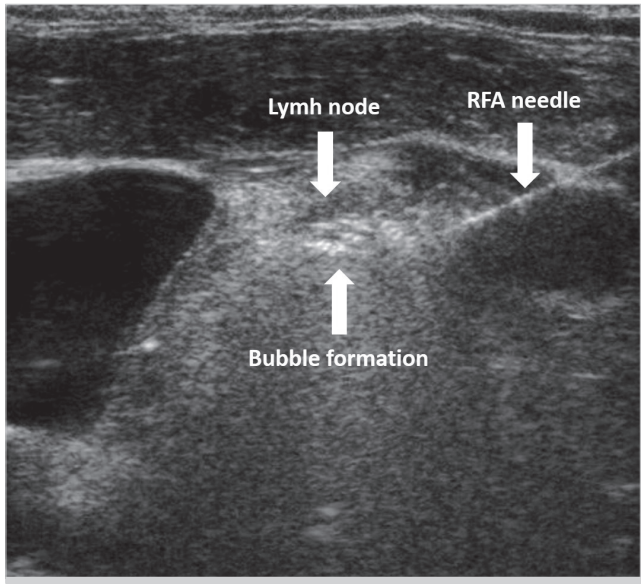

Figure 3. Ultrasonography image showing the complete ablation of the lymph node.

RFA uneventfully, there was no voice change or loss after the procedure and in his first control US revealed that the nodules disappeared. His last TG level was 0.04 ng/mL.

RFA Technique

RFA was performed by an interventional radiologist experienced in RFA procedures. During the ablation process an RF generator (Viva RF System-StarMed/Korea) and an 18 G, 7 mm RF electrode (star RF electrode-StarMed/Korea) were used (Figure 1-3). No complications were observed during or after the procedure. The control US performed one month after the procedure showed that the nodule on the right side of the neck decreased more than 50%, while the nodule on the left side of the neck completely disappeared. Thyroglobulin level was measured as 0.04 ng/mL. Both pathological lymph nodes disappeared completely during the follow-up after RFA.

DISCUSSION

Surgical resection is the gold standard for the treatment of malignant tumors but surgical resection is not always a preferable option for patients such as metastatic disease or in whom resection is associated with a high morbidity and mortality. Recently, a variety of minimally invasive local ablative methods, including chemical (ethanol, acetic acid) and thermal ablation (laser ablation, cryoablation, radiofrequency ablation, and microwave ablation) have been used as treatment options to eliminate cancer cells. The first use of ethanol ablation as an alternative treatment modality was reported by Rozman et al. in 1989 (4). Ethanol ablation is an effective method for the treatment of cystic nodules, but is less effective for solid nodules. Previous studies have reported that the efficacy of ethanol ablation was 85-98% in cystic nodules and 38-47% in solid nodules (5).

In addition, multiple treatment sessions have associated with an increased risk of complications. Laser ablation is another method of choice for the treatment of thyroid nodules. However, when RFA and laser ablation techniques compared to each other, the safety and long-term volume reduction rate of RFA was superior to that of laser ablation. This is 90% in RFA versus 48% in laser ablation, as reported in the three-year follow-up data of two studies in the literature (6).

RFA was first used in the treatment of thyroid nodules in 2006. Due to its minimal invasive access and low complication rate, RFA is increasingly used for the treatment of benign and malignant thyroid cancers including recurrent thyroid cancers in the operation bed and lymph nodes (7).

The term radiofrequency refers to alternating electric current including low frequency (460-480 kHz) and long wavelength, which causes thermal coagulation necrosis by generating heat within a tumor mass. RFA differs from other local minimally invasive techniques. High frequency electrical currents are passed through an electrode in the needle and the electrode stimulates the ions in the tissue to produce frictional heat in RFA. As a result, clotting necrosis occurs.

The results of studies after RFA have shown mean nodule volume reduction of 56-93%, complete nodule disappearance of 42-58%, and decrease in the serum thyroglobulin level in the majority of the cases (3,8). Jeong et al. reported for 236 patients who underwent RFA for thyroid nodules a volume reduction of >50% in 91% and complete disappearance of nodules in 28% of the cases (9). On the other hand, incomplete treatments have been reported because of increased pain during the procedure, anterior calcifications of the nodule and closeness of the nodule to vagus nerve (3,8). Park et al. also indicated that the RFA procedure was not effective when the ablation area was surrendered by vascular sheath or there was massive calcification in a nodule (8). In addition, despite incomplete treatment, recurrence rates have been reported in 0 to 25% of patients in the literature (3).

US imagining is relevant for the characterization of the nodule and the evaluation of the surrounding important anatomical structures. Each diameter of a nodule should be measured by US in order to calculate nodule volume. Thermal damage of laryngeal nerve during the procedure should be checked by talking with patient during the procedure. In literature, reported complications related with RFA include pain, hemorrhage, voice change, skin burn, infection and nodule rupture. In our case we did not encounter any of these complications. In RFA of thyroid nodules, 1-2% lidocaine is used in most treatment centers without any premedication. On the other hand, Monchik et al. have reported the intravenous use of combination of fentanyl citrate and midazolam as a possible anesthetic (10). However, we believe that painkillers and anesthesia will delay early detection of complications by masking some symptoms during the procedure. Especially within lateral neck region, vagus nerve is one of the most important structures. The location of the nerve is usually posterior-lateral to common carotid artery and posteromedial to internal jugular vein that can easily detect by US. In our case, the metastatic lymph nodes were away from vagus nerve. In addition, we used the hydro-dissection technique during the procedure to prevent complications due to any variation in the nerve. The recurrent tumors in central neck region are usually close to, or attached to the trachea, esophagus or recurrent laryngeal nerve, so it is more difficult to perform RFA in central area than lateral region (3). In the literature, no complications were reported in the esophagus and trachea following RFA for recurrent thyroid cancer. In our case, RFA was easily applied because pathological lymph nodes were located in the bilateral neck region.

We recommend that the patients should be followed-up at the first, the sixth and the 12th month after RFA depending on the treated metastatic lymph nodes. The efficacy of RFA can be evaluated by volume reduction of the nodule and serum thyroglobulin concentrations (8,10).

CONCLUSION

In conclusion, we believe that RFA can be as effective as surgery with less risk of complications in selected patients for thyroid cancer treatment. RFA may be preferred as an alternative treatment option to surgery for eligible patients.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - GÖ, BÖ, OA, NA, YE; Design - GÖ, BÖ, AS; Supervision - YE, CY, NA, BÖ; Materials - GÖ, BÖ, YE; Data Collection and/or Processing - GÖ, BÖ, OA, AS, NA; Analysis and/or Interpretation - GÖ, BÖ, OA; Literature Search - GÖ, BÖ, OA; Writing Manuscript - All of authors; Critical Reviews - All of authors.

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

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

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OLGU SUNUMU-ÖZET
Turk J Surg 2024; 40 (2): 174-177

Papiller tiroid karsinomi metastazlı hastada ikincil ameliyat yerine metastatik nodlarının radyofrekans ile ablasyonu

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ÖZET

Radyofrekans ablasyonu, iyi huylu tiroid nodülü ve tekrarlayan tiroid kanserli hastalarda ameliyata alternatif olarak uygulanan minimal invaziv bir yöntemdir. Metastatik lenf nodları için radyofrekans ablasyon tedavisinin etkinliğine ilişkin az veri bulunmaktadır. Bu yazı, tekrarlayan papiller tiroid kanseri metastazı olan hastalarda metastatik lenf nodları için radyofrekans ablasyonun güvenliğini ve etkinliğini değerlendirmektedir. Bir yıl önce papiller tiroid kanseri tanısıyla farklı bir hastanede bilateral total tiroidektomi işlemi uygulanan 63 yaşında bir erkek hastanın kontrolleri sırasında bilateral lenf nodlarında papiller tiroid kanseri metastazı saptandı. Ultrason eşliğinde perkütan radyofrekans ablasyonu yapıldı. Hasta postoperatif birinci günde sorunsuz bir şekilde taburcu edildi ve ilk kontrol ultrasonografisinde nodül boyutunda boynun sağ tarafında %50'den daha büyük bir azalma olduğu ve sol taraftaki nodülün kaybolduğu görüldü. Sonuç olarak, radyofrekans ablasyon, papiller tiroid kanseri metastazı nedeniyle sekonder cerrahi gerektiren hastalarda metastatik lenf nodlarının tedavisi için güvenli ve uygulanabilir bir tekniktir.

Anahtar Kelimeler: Radyofrekans ablasyonu, nüks tiroid kanseri, lenf nodu, tiroid kanseri metastazı, ultrason, komplikasyon

DOİ: 10.47717/turkjsurg.2023.4631

CASE REPORT
Turk J Surg 2024; 40 (2): 178-182

Juvenile papillomatosis: A case report

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ABSTRACT

Juvenile papillomatosis (JP) is a very rare benign proliferative breast disease, especially in young women under 30 years of age. Its etiology is not clear yet. Although some patients have breast cancer in their family history, up to 10% breast cancer can develop in the follow-up of JP patients. In this pathology, which is diagnosed with biopsy, history, clinical and radiological findings help in diagnosis. In this case report, a 37-year-old patient diagnosed with JP will be discussed in the light of the literature.

Keywords: Juvenil papillomatosis, proliferative lesion, malignancy

INTRODUCTION

Juvenile papillomatosis (JP) is a rare benign mass-like lesion which is pre-dominantly seen in young women under 30 years old. It can confuse with fibroadenoma which is multinodular mass on breast examination, but JP lesions are generally are larger than fibroadenomas. Radiological and histopatological examinations play key role in certain diagnosis.

CASE REPORT

A 37-year-old female patient with no known cancer history and additional disease in her family was referred to the radiology clinic after she applied to the general surgery outpatient clinic with a spontaneous discharge from the left. As a result of this mammography examination, asymmetric fibroglandular tissue density in the right midline posterior of the right breast was detected and ductal dilatations with secretion content were detected in bilateral retroareolar areas in both breasts that did not exceed one cm in both breasts (Figure 1A-1B, 2A-C). Since the nipple discharge of the patient could not be explained with defined mammographic and sonographic findings, a dynamic contrast-enhanced MR examination was performed in order to solving problem. In breast MRI examination; In the right breast at 12 o'clock, a lesion with a posterior location of 18 x 15 mm, which is hardly differentiated from the breast parenchyma, which contains millimetric cysts, was observed in the post-contrast series, with peripheral-weighted heterogeneous contrast, and in the late series, contrast loss was observed.In addition, in the subtraction images, non-mass heterogeneous segmental enhancements were recorded in an area of approximately 5 x 4.5 x 2.5 cm, including the neighborhood of the defined lesion, in the upper right outer quadrant of the right breast. The findings were evaluated in the category suspected for malignancy (Figure 3A-3B, 4A-4B). Corre biopsy was performed by correlating the lesion with the second aspect US, and the result of pathology was reported as ductal epithelial hyperplasia, sclerosing adenosis. The pathology result of the excisional biopsy performed for the lesion due to radiological-pathological incompatibility; It has been evaluated as "juvenile papillomatosis"

Cite this article as: Güneş YC, Öztekin PS, Değirmenci T, Uçar F, Uysal Ramadan S, Nercis Koşar P, et al. Juvenile papillomatosis: A case report. Turk J Surg 2024; 40 (2): 178-182.

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Received: 23.04.2020
Accepted: 07.06.2020
Available Online Date: 28.06.2024

DOI: 10.47717/turkjsurg.2022.4745

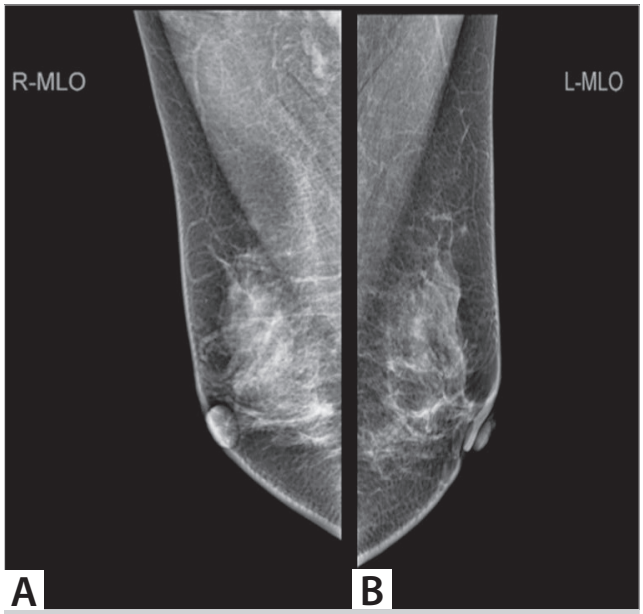

Figure 1. A,B. Asymmetric fibroglandular tissue density observed in the midline posterior on the right breast MLO view.

containing atypical ductal hyperplasia areas (Figure 5A-C, 6A-C). The lesion causing the left nipple discharge of the patient was also detected by breast MRI and it was understood that it was a benign intraductal papilloma located at retroareolar location.

DISCUSSION

JP is a pathology that was defined by Rosen et al. between 1947 and 1980 as a series of 37 cases. In the case series that was first described, the average age of the patients was 19 and mostly consist of Caucasian patients (1,2). Considering the general cases in the literature, it has been reported that 70% of the presented cases are under the age of 26, but this spectrum has expanded until the age of 40 (3,4). Although histopathological examinations may have different findings, the most common findings are accumulation with papillomatosis of ductus with or without JP epithelial atypia, papillary apocrine hyperplasia, sclerosing adenosis and stasis in ducts (5). In JP, which is also named in the literature as the Swiss cheese disease of the breast, the reason for this naming is that there are many cysts and ducts in the dense stromal areas in the microscopic images (6). JP may rarely be associated with severe atypia and focal epithelial necrosis. Patients with such histopathological characteristics generally display premalignant features and have been observed in elderly female patients (7). In the clinic, patients are usually presented with a well-circumscribed, rigid and mobile mass in the upper outer quadrant of the breast but not causing discharge from the nipple. Although the exact diagnosis of JP is made by biopsy, imaging modalities are used in the pre-operative diagnosis and follow-up of patients.In the ultrasound image, it is observed as hypoechoic mass, which is not generally well-circumscribed, and multiple small-sized weighted peripheral localized cysts (8). While the findings of the lesion are generally not observed in mammograms, rarely, asymmetric densities can be observed with pleomorphic and amorphous microcalcifications (8,9). Contrast-enhanced T1-weighted fat saturated images are useful in the evaluation of lesion contours and internal matrix. In T1-weighted images, a lobule contoured mass image is observed in the hypointense view; T2-weighted images, on the other hand, are the most helpful sequence in diagnosis since they show many small cysts (10). Since JP has active proliferative hyperplastic epithelial tissue, it shows involvement in contrast-enhanced MRI examinations. Contrast media involvement patterns are in the form of type 1 and type 2 curves, such

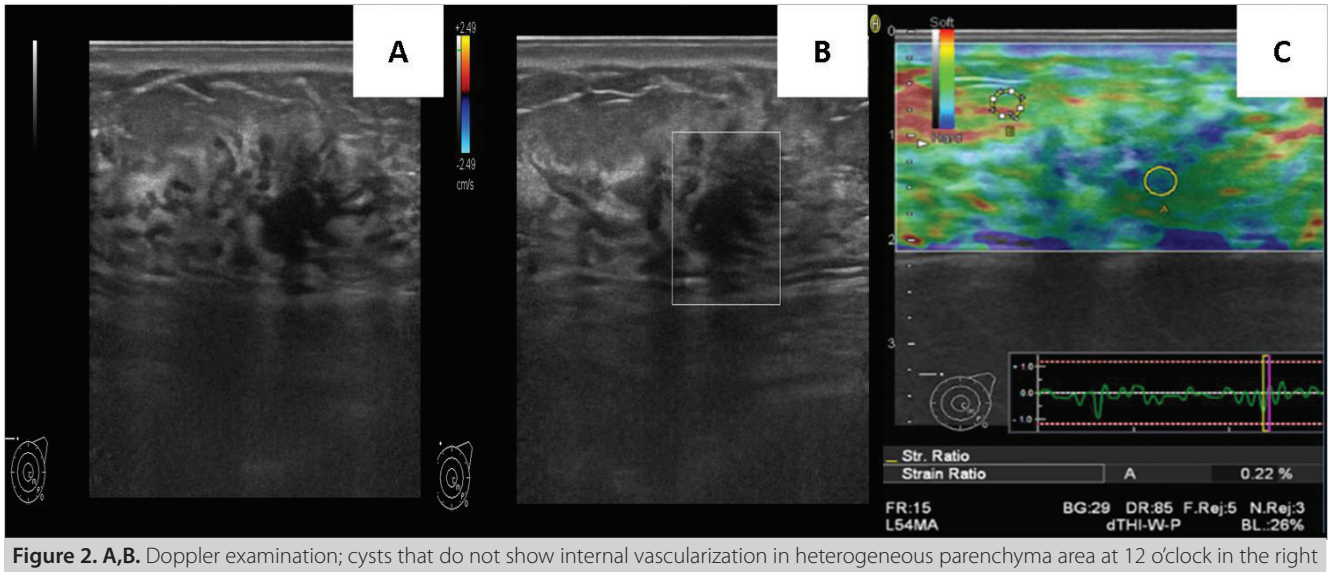

Figure 2. A,B. Doppler examination; cysts that do not show internal vascularization in heterogeneous parenchyma area at 12 o'clock in the right breast. **C.** The lesion is observed in medium stiffnes in elastography examination.

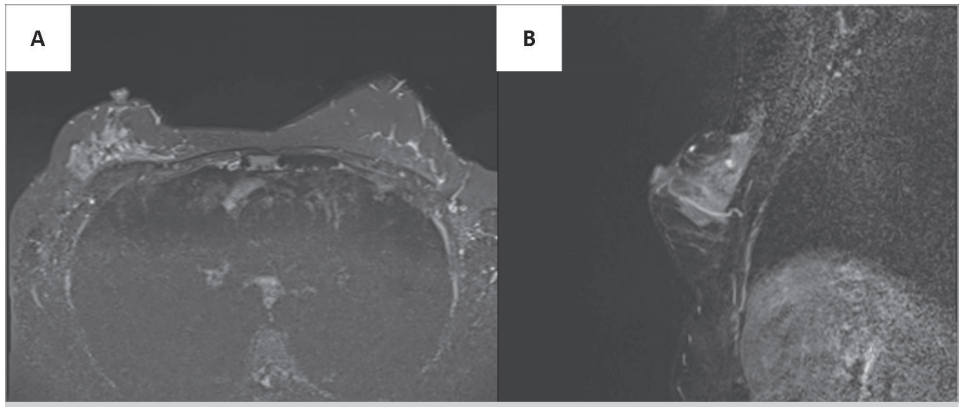

Figure 3. A. T2-weighted fat saturated axial MR image **B.** T2-weighted fat saturated sagittal MR image - Lesion with millimeter cysts approximately 2 cm from the nipple at 12 o'clock.

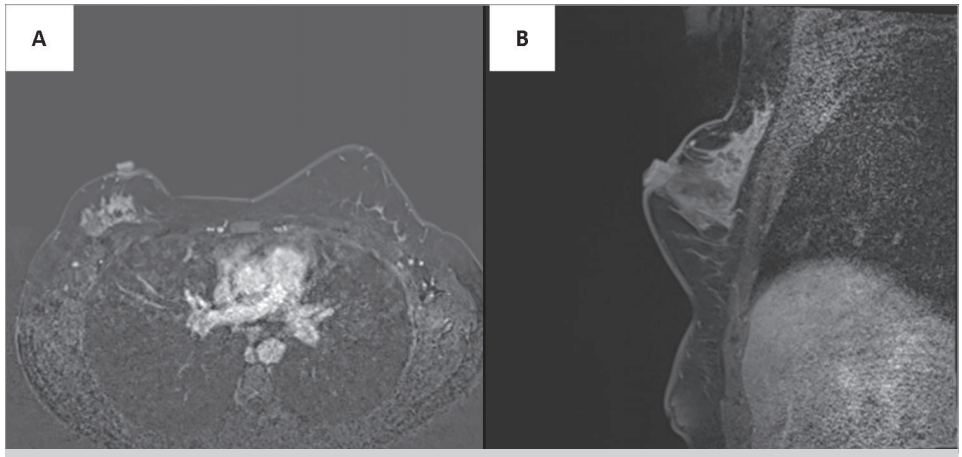

Figure 4. A. T1-weighted fat saturated axial MR image. **B.** T1-weighted post-contrast sagittal MR image - Peripheral enhancement at the lesion and adjacent non-mass segmental enhancements are observed.

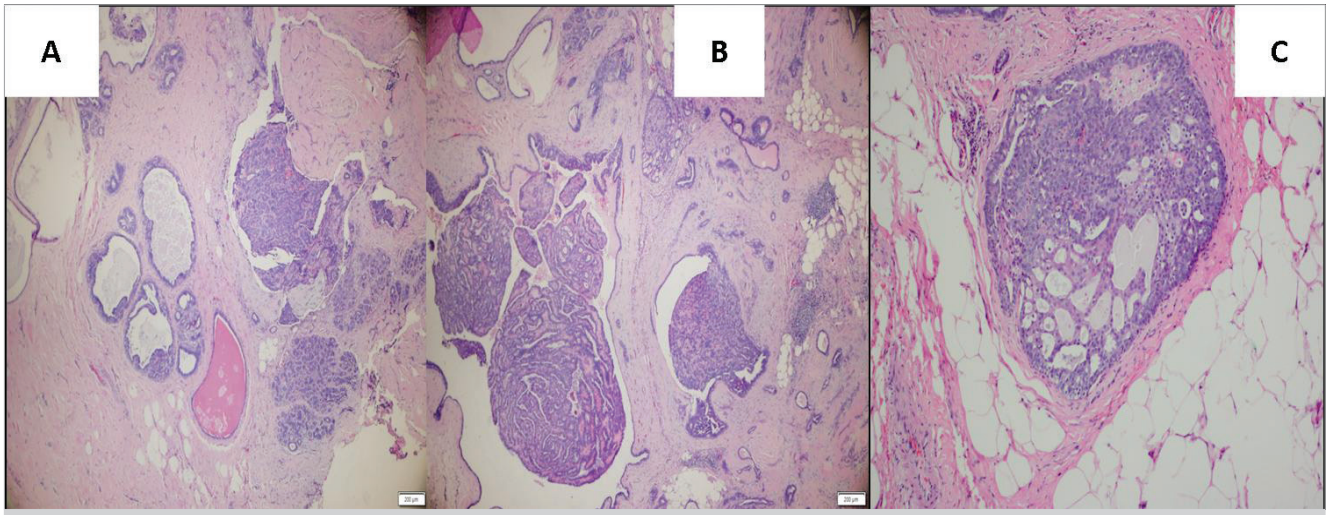

Figure 5. A,B. Papilloma areas (HE x 40) characterized by papilla-like structures in the ductus lumens within the breast parenchyma (HE x 40). **C.** Atypical epithelial hyperplasia areas (HE x 40).

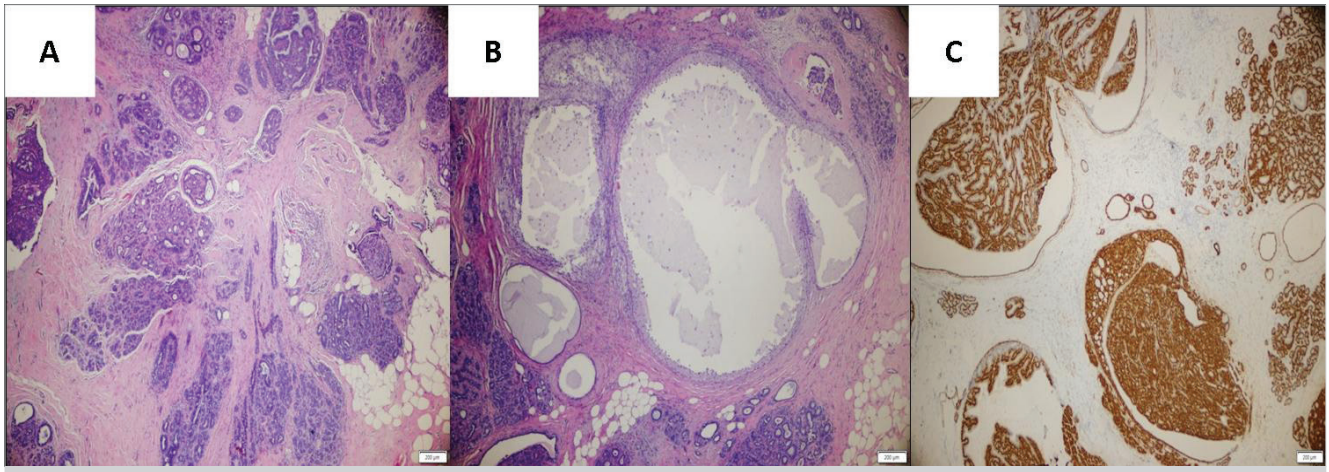

Figure 6. A. Sclerosing adenosis areas (HE x 40). **B.** Cystic enlarged ducts (HE x 40). **C.** Immunhistochemical calponin positivity around the ducts (HE x 40).

as benign diseases (11,12). Despite its benign nature, there is an increased risk of breast cancer in JP cases. In 4-15% patients, JP and breast cancer co-exist at the time of diagnosis. Although JPs are generally associated with intraductal papillomas, they can also co-exist with invasive ductal, invasive lobular and secretory cancers of the breast (13). In addition, approximately 10% of patients with JP have a risk of developing breast cancer in their follow-up (13). Since incomplete surgical excision causes recurrences, extensive surgical excision and clinical follow-up are the most common treatment options in JP cases. In patients with bilateral, multifocal and recurrent family history, the frequency of follow-up should be increased since the risk of breast cancer increases (7-14).

CONCLUSION

JP is a benign proliferative lesion of the breast, which is frequently observed at a young age. Clinically, radiologically it can be confused with malignancy, requiring histopathological examination for a definitive. In terms of breast cancer that can accompany and occur during follow-up, extensive surgical excision, multiple sampling and clinical follow-up are recommended.

Informed Consent: Yes.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - YCG, FU, TD, HÜ; Supervision - PSÖ, SUR, SE, PNK; Literature Search - All of authors; Writing Manuscript - All of authors; Critical Reviews - YCG, PSÖ.

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

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

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OLGU SUNUMU-ÖZET
Turk J Surg 2024; 40 (2): 178-182

Juvenil papillomatozis: Olgu sunumu

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ÖZET

Juvenil papillomatozis (JP) özellikle 30 yaş altında genç kadınlarda izlenen oldukça nadir görülen benign proliferatif meme hastalığıdır. Etiyolojisi henüz net olarak bilinmemektedir. Hastaların bir kısmında aile öyküsünde meme kanseri bulunmakla birlikte, JP hastaların takiplerinde %10 kadar meme kanseri gelişebilmektedir. Kesin tanısı biyopsi ile konan bu patolojide öykü, klinik ve radyolojik bulgular tanı konulmasında yardımcı olmaktadır. Bu olgu sunumunda 37 yaşında JP tanısı alan hasta literatürdeki veriler ışığında tartışılacaktır.

Anahtar Kelimeler: Juvenil papillomatozis, proliferatif lezyon, malignite

DOİ: 10.47717/turkjsurg.2022.4745