ISSN 1948-9366 (online)

# World Journal of

# *Gastrointestinal Surgery*

*World J Gastrointest Surg* 2022 December 27; 14(12): 1320-1437

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 14 Number 12 December 27, 2022

*World Journal of Gastrointestinal Surgery*

**Monthly Volume 14 Number 12 December 27, 2022**

## Contents

*World Journal of Gastrointestinal Surgery*

**Monthly Volume 14 Number 12 December 27, 2022**

# Contents

## ABOUT COVER

Peer Reviewer of *World Journal of Gastrointestinal Surgery*, Giuseppe Currò, MD, Professor, Surgeon, Department of Health Science, University Magna Graecia of Catanzaro, Catanzaro 88100, Calabria, Italy. currog@unicz.it

## AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGS* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc.*

## INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJGS* as 2.505; IF without journal self cites: 2.473; 5-year IF: 3.099; Journal Citation Indicator: 0.49; Ranking: 104 among 211 journals in surgery; Quartile category: Q2; Ranking: 81 among 93 journals in gastroenterology and hepatology; and Quartile category: Q4.

## RESPONSIBLE EDITORS FOR THIS ISSUE



**NAME OF JOURNAL**

*World Journal of Gastrointestinal Surgery*

**ISSN**

ISSN 1948-9366 (online)

**LAUNCH DATE**

November 30, 2009

**FREQUENCY**

Monthly



**PUBLICATION DATE**

December 27, 2022

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 December 27; 14(12): 1320-1328

DOI: 10.4240/wjgs.v14.i12.1320

ISSN 1948-9366 (online)

*MINIREVIEWS*

# Timing of individualized surgical intervention in Crohn's disease

Kai Xia, Ren-Yuan Gao, Xiao-Cai Wu, Lu Yin, Chun-Qiu Chen

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Jha P, United States; Zha B, China

**Received:** September 1, 2022
**Peer-review started:** September 1, 2022
**First decision:** October 20, 2022
**Revised:** October 24, 2022
**Accepted:** December 1, 2022
**Article in press:** December 1, 2022
**Published online:** December 27, 2022

**Kai Xia, Ren-Yuan Gao, Xiao-Cai Wu, Lu Yin, Chun-Qiu Chen,** Diagnostic and Treatment Center for Refractory Diseases of Abdomen Surgery, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China

**Corresponding author:** Chun-Qiu Chen, Doctor, Chief Doctor, Professor, Diagnostic and Treatment Center for Refractory Diseases of Abdomen Surgery, Shanghai Tenth People's Hospital, Tongji University School of Medicine, No. 301 Yanchang Middle Road, Shanghai 200072, China. chenchunqiu6@126.com

## Abstract

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract with an increasing incidence worldwide. Comprehensive therapy for CD focuses on symptom control and healing the intestinal mucosa to improve the quality of life and prevent complications. Surgical intervention plays a vital role in comprehensive therapy. However, deciding the optimal timing for surgical intervention has long been a focus of controversy. This review provides insights into the timing of surgery for CD and guides clinicians in daily treatment.

**Key Words:** Crohn's disease; Surgical intervention; Timing of surgery; Individualization; Therapy



**Core Tip:** Surgical intervention plays an important role in the comprehensive treatment of Crohn's disease (CD). However, the timing of surgery has always been a major controversial point. This review focuses on the main surgical indications for CD and the clinical factors that may influence surgical timing decisions. We also emphasize the value of early surgery in treating CD.

**Citation:** Xia K, Gao RY, Wu XC, Yin L, Chen CQ. Timing of individualized surgical intervention in Crohn's disease. *World J Gastrointest Surg* 2022; 14(12): 1320-1328
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i12/1320.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i12.1320

## INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease that can affect the entire digestive tract, especially the terminal ileum and proximal colon[1,2]. The course of CD is protracted, characterized by alternating active and remission stages. The epidemiologic patterns of CD depict that the prevalence and hospitalization rates are currently rising gradually worldwide, contributing to an increasing burden on healthcare systems[3-6]. The underlying cause of CD is still unknown but includes a variety of factors, including genetic susceptibility, environmental triggers, immune regulation, and gut microbial imbalance[7-9]. CD is prone to various complications due to penetrating and chronic intestinal inflammatory response, including intestinal obstruction, bowel perforation, fistula, or intra-abdominal abscess [10,11]. After diagnosis, approximately 50% and 70% of CD patients develop complications within 5 or 10 years, respectively[12,13].

Recently, the launch of new biological agents has breathed new life into the clinical treatment of CD, while surgical intervention still plays an indispensable role[14-16]. The cumulative surgery rate for CD patients is 16.6%, 35.4%, 53%, and 94.5% for 1, 5, 10, and 30 years, respectively, after the onset of the disease[17]. The choice of optimal timing for surgical intervention has always been a focus of controversy. Some scholars advocate for early surgical intervention if drugs fail to achieve good results. Nevertheless, the recurrence after surgery is almost inevitable, and approximately 40% of CD patients require reoperation[18]. Other scholars prefer to avoid early surgery only if it is necessary to resect the intestinal segments that cause complications following the principle of intestinal conservation. However, postoperative complications significantly increase due to poor nutritional status and severe abdominal infection[19]. This review mainly focuses on the choice of individualized surgical intervention timing for CD patients.

## SURGICAL INDICATIONS FOR CD

According to the relevant literature and clinical experience, we summarize the main surgical indications for CD, which involve serious complications of CD (Figure 1), failure of medical therapy, and growth retardation in children.

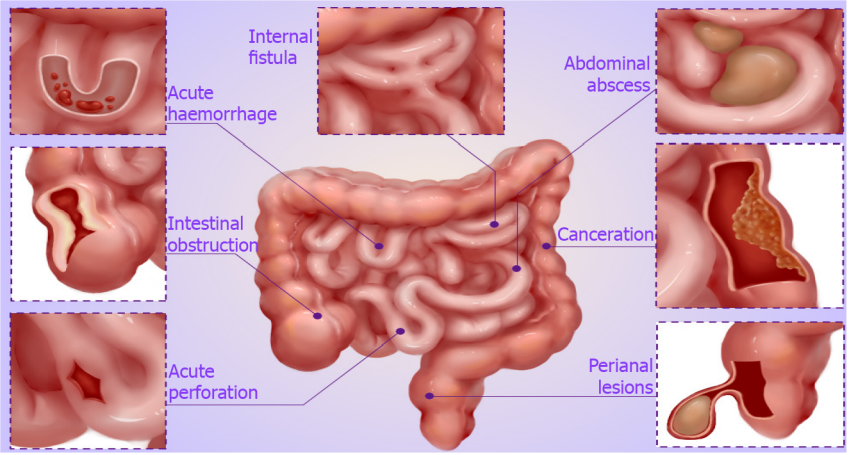
### *Serious complications of CD*

**Intestinal obstruction:** Intestinal obstruction is a common and serious complication of CD, especially fibrosis-associated intestinal stricture[20]. Lin *et al*[21] revealed that approximately 70% of CD patients inevitably develop fibrosis-associated intestinal stricture a decade following diagnosis. Medical treatment is frequently ineffective in patients who develop intestinal obstruction, and surgical resection is primarily required in that case[22,23]. Certainly, with the development of endoscopic technology, endoscopic balloon dilation is also an appropriate treatment option when the length of strictures is ≤ 5 cm, non-angulated, and with a sizeable intestinal cavity large enough to allow balloon dilators in the absence of contraindications such as the presence of fistula, abscess, or malignancy[24,25]. Furthermore, acute inflammatory obstruction can be frequently relieved by medical therapy. If conservative therapy is ineffective, surgical intervention should be considered to relieve the obstruction.

**Intra-abdominal abscess:** Intra-abdominal abscess is an important clinical complication of CD, the cause of which may be spontaneous or secondary to surgery[26,27]. The current first-line therapy for CD complicated by intra-abdominal abscess, is percutaneous abscess drainage with systemic antibiotics[28,29]. However, surgical intervention should be considered actively if the symptoms of sepsis do not improve after drainage, abscess ruptures with severe peritonitis, or multiple abscesses cannot be drained. Intestine resection appears to be inevitable in most CD patients presenting intra-abdominal abscess[30,31].

**Fistula:** Therapy for fistula has always been a complex clinical challenge. Simple enteral fistula without infection and clinical symptoms can be healed by a medical treatment such as enteral nutrition or biological agents[32,33]. For other complex enteral fistulae, including spontaneous enteroenteral or enteroexternal fistula formed after abscess drainage, the possibility of self-healing is low, and surgery should be adopted[34,35]. CD patients with severe fistula are often accompanied by loss of digestive fluid, resulting in disturbance of internal environmental balance, secondary infection, and malnutrition. Therefore, the infection should be readily controlled, and adequate nutritional support provided before elective surgery[36,37]. Yzet *et al*[38] recently reported successful cases of endoscopic treatment for enteroexternal fistula, which was feasible with short-term effectiveness.

**Perianal lesions:** Perianal lesions are common complications of CD, with perianal fistula and abscess being one of the most common[39,40]. The management of symptomatic simple perianal fistula and complex perianal fistula employs a multidisciplinary approach, which includes antibiotics, biological therapies, and surgery[41,42]. Furthermore, stem cell therapy is also an effective option for complex perianal fistula in CD patients[43,44]. As for the treatment of perianal abscess, surgical drainage and




**DOI:** 10.4240/wjgs.v14.i12.1320 

**Figure 1 Major categories of Crohn's disease complications, including intestinal obstruction, fistula, intra-abdominal abscess, perianal lesions, massive bleeding, perforation, and canceration.**

antibiotic therapy are preferred.

**Perforation, massive bleeding, or canceration:** The incidence of CD complicated by acute perforation is low. However, emergency surgical intervention is often required if it occurs[45]. When complicated by massive bleeding, the location of bleeding should be identified, and treatments such as drug, endoscopic, or interventional hemostasis should be actively adopted. Emergency surgery is required if the above treatments fail and massive bleeding continues[46,47]. In addition, CD complicated by canceration is an absolute indication for surgery[48].

**Failure of medical therapy:** Surgical intervention may be considered when drug therapy fails, and symptoms such as intolerance to severe side effects and ineffectiveness to various biological agents are difficult to control.

**Growth retardation in children:** Pediatric CD often presents as a triad of abdominal pain, diarrhea, and weight loss, characterized by growth retardation[49,50]. Therefore, the pediatric treatment of CD induces and maintains clinical remission of the disease and optimizes nutrition and growth as soon as possible[51]. Surgery should be performed before puberty for prepubertal or early pubertal patients with severe malnutrition resulting in growth arrest[52]. Since the rate of postoperative recurrence is still high, drug therapy is required to maintain remission after surgery[53].

## CLINICAL FACTORS AFFECTING TIMING OF SURGERY

Surgical intervention for CD aims to deal with complications and improve the quality of life of patients, as they tend to be in poor general conditions. Therefore, except for emergencies such as massive bleeding and acute perforation, adequate preoperative preparation should be completed to improve the efficacy of surgery. As a clinician, more attention should be paid to following the clinical factors to minimize perioperative complications.

### *Nutritional support*

Malnutrition is one of the prominent clinical manifestations of CD. Our team recently published a study indicating that CD patients were at higher nutritional risk than healthy people[54]. It can hinder wound healing and increase the risk of incision infection, hernia, and anastomotic leak[55]. Therefore, nutritional status is recognized as an independent risk factor for postoperative complications. Yamamoto *et al*[56] revealed that patients with preoperative low albumin levels (< 30 g/L) had a 2.6-fold increased incidence of postoperative complications, similar to that reported by Shah *et al*[57]. Another study indicated that preoperative optimization with nutritional support reduced the overall rate of postoperative complications of CD[58]. Thus, perioperative nutritional support is vital for CD patients, while enteral nutrition should be adopted when the intestinal state permits. Appropriate enteral nutrition can improve the nutritional status, protect the intestinal mucosal barrier, and induce clinical remission[59,60]. It is a well-established and recommended first-line induction therapy in pediatric CD with remission rates of up to 80%[61].

**Table 1 Correlations between drug factors and surgical complications of Crohn's disease**

| Ref. | Drugs | Type of study | Number of patients | Observations | Conclusion |
|---|---|---|---|---|---|
| Cohen *et al*[68], 2022 | TNFis | Prospective study | 947 | Postoperative infection rate | No correlation |
| Uchino *et al*[69], 2022 | TNFis | Retrospective study | 305 | Surgical mortality | No correlation |
| Abd El Aziz *et al*[70], 2022 | TNFis | Prospective study | 274 | Intra-abdominal septic complications | No correlation |
| Azzam *et al*[71], 2022 | Azathioprine | Retrospective study | 105 | Endoscopic recurrence rate | Negative correlation |
| Cosnes *et al*[72], 2005 | Azathioprine | Retrospective study | 2573 | Intestinal complications | No correlation |
| Nguyen *et al*[73], 2014 | Steroids | Retrospective study | 15495 | Postoperative sepsis and VTE | Positive correlation |

TNFis: Tumor necrosis factor inhibitors; VTE: Venous thromboembolism.

### *Infection control*

A recent study by Bachour *et al*[62] revealed that abdominal infection was associated with an increased risk of surgical postoperative recurrence of CD. Tzivanakis *et al*[63] indicated that the presence of preoperative abdominal abscess formation was identified as an independent predictor of anastomotic-associated complications. If the risk factor is present before surgery, the risk of anastomotic complications can be increased to 14%. Therefore, CD patients with abdominal abscesses can often be first managed with antibiotics and percutaneous drainage, while definitive surgical intervention should be performed after the infection has been controlled[64].

### *Effects of drugs*

Whether preoperative CD treatment with tumor necrosis factor inhibitors (TNFis) increases the risk of postoperative complications remains controversial. TNFis may compromise immunity, collagen production, and angiogenesis, resulting in postoperative infective complications and altered wound healing[65,66]. In addition, TNF-α is a key cytokine in collagen production and angiogenesis, with animal studies confirming its role in wound healing[67]. However, previous studies have confirmed that preoperative TNFis exposure was not correlated with postoperative infectious complications[68-70] (Table 1).

Azathioprine is commonly used as an immunosuppressant for treating CD and may not increase the risk of postoperative complications. Although azathioprine has demonstrated efficacy in preventing postoperative recurrence, there is no significant decrease in the need for surgery or intestinal complications from CD[71,72] (Table 1). Furthermore, CD patients are frequently treated with steroids before surgery. Nguyen *et al*[73] indicated that preoperative steroids were correlated with a higher risk of postoperative sepsis (Table 1). Therefore, steroids should be minimized or discontinued 6 mo before surgery.

## VALUE OF EARLY SURGICAL INTERVENTION IN TREATMENT OF CD

Early surgery for CD is commonly performed within a short time after diagnosis, while the time frame is still inconclusive[74,75]. An *et al*[76] defined early surgery as patients who had undergone upfront surgery for CD due to an acute complication and those who underwent surgery within 6 mo of diagnosis. Interestingly, this study revealed that patients with ileocolonic CD may have a better prognosis if undergoing early surgical intervention, with fewer admissions to the hospital and reduced overall operation rates. Aratari *et al*[77] also defined early surgery when performed at the time of CD diagnosis, when these patients underwent surgery for the acute or subacute presentation of CD. Meanwhile, late surgery was defined as patients with an established diagnosis of CD who underwent surgery during the course of the disease on account of intestinal complications or refractoriness to medical therapy. Early surgery may significantly prolong the time of clinical recurrence of CD compared to late surgery. Considering the lack of evidence from these retrospective studies, the conclusions warrant further verification.

Early surgical intervention may benefit patients with localized CD, which refers to intestinal CD affecting < 30 cm in extent. This usually applies to an ileocaecal location but also isolated colonic disease, or conceivably to proximal small intestinal disease[78]. Ponsioen *et al*[79] indicated that early laparoscopic surgery for localized CD could improve the overall quality of life of patients and reduce the rate of recurrence and reoperation. A long-term follow-up study by Stevens *et al*[80] during the LIR! C-trial revealed that most patients with localized CD who underwent early surgery were free of anti-TNF treatment, and none required a second surgery. Conversely, almost half of the patients who underwent anti-TNF treatment moved on to a Crohn-related resection. Furthermore, de Groof *et al*[81]

revealed that mean CD total direct healthcare costs per patient at 1 year were lower in the group who underwent early surgery compared with the anti-TNF group. Early surgical intervention is a reasonable and cost-effective treatment option for patients with localized CD.

China has a high incidence of hepatitis and tuberculosis. However, anti-TNF treatment may increase the risk of opportunistic infections[82,83]. Early surgery instead of anti-TNF treatment can reduce opportunistic infections. Additionally, early surgical resection of localized lesions may improve the response to postoperative anti-TNF treatment, the curative effect of which is better than that of the initial therapy[84,85].

## CONCLUSION

CD is a refractory disease with a high misdiagnosis rate, a tendency for lifelong recurrence, and a high rate of operation and reoperation. Surgical intervention is a key part of the comprehensive treatment of CD. Inappropriate timing of surgery may lead to catastrophic postoperative complications, increasing the risk of surgery and prolonging hospital stays. Therefore, clinicians need to evaluate the severity and type of CD as well as the effectiveness of medical therapy and choose the timing of surgical intervention based on individual circumstances to ensure the maximum benefit for CD patients. Maybe in the future, with the deepening of multi-omics researches such as radiomics, metabolomics, and microbiomics, it will provide a more favorable basis for individualized timing of CD surgery and identify the early changes of CD related acute lesions.

## ACKNOWLEDGEMENTS

We thank the medical teams of Diagnostic and Treatment Center for Refractory Diseases of Abdomen Surgery, Shanghai Tenth People's Hospital, for their support for this subject.

## FOOTNOTES

**Author contributions:** Xia K drafted the manuscript, and collected and organized the literature; Gao RY, Wu XC, Yin L, and Chen CQ contributed to manuscript modification.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.



**Country/Territory of origin:** China

**ORCID number:** Kai Xia 0000-0001-6690-0341; Ren-Yuan Gao 0000-0002-7602-0601; Xiao-Cai Wu 0000-0001-7546-6882; Lu Yin 0000-0002-9060-0178; Chun-Qiu Chen 0000-0002-4248-7414.

**S-Editor:** Wang JJ
**L-Editor:** Wang TQ
**P-Editor:** Wang JJ

## REFERENCES

1 **Cohen NA**, Micic DM, Sakuraba A. Factors associated with poor compliance amongst hospitalized, predominantly adolescent pediatric Crohn's disease patients. *Ann Med* 2022; **54**: 886-892 [PMID: 35352625 DOI: 10.1080/07853890.2022.2057582]

2 **Narula N**, Wong ECL, Dulai PS, Sengupta NK, Marshall JK, Colombel JF, Reinisch W. Comparative Efficacy and Rapidity of Action for Infliximab *vs* Ustekinumab in Biologic Naïve Crohn's Disease. *Clin Gastroenterol Hepatol* 2022; **20**: 1579-1587.e2 [PMID: 33838348 DOI: 10.1016/j.cgh.2021.04.006]

3 **Buie MJ**, Quan J, Windsor JW, Coward S, Hansen TM, King JA, Kotze PG, Gearry RB, Ng SC, Mak JWY, Abreu MT, Rubin DT, Bernstein CN, Banerjee R, Yamamoto-Furusho JK, Panaccione R, Seow CH, Ma C, Underwood FE, Ahuja V, Panaccione N, Shaheen AA, Holroyd-Leduc J, Kaplan GG; Global IBD Visualization of Epidemiology Studies in the 21st Century (GIVES-21) Research Group, Balderramo D, Chong VH, Juliao-Baños F, Dutta U, Simadibrata M, Kaibullayeva J,

Sun Y, Hilmi I, Raja Ali RA, Paudel MS, Altuwaijri M, Hartono JL, Wei SC, Limsrivilai J, El Ouali S, Vergara BI, Dao VH, Kelly P, Hodges P, Miao Y, Li M. Global Hospitalization Trends for Crohn's Disease and Ulcerative Colitis in the 21st Century: A Systematic Review With Temporal Analyses. *Clin Gastroenterol Hepatol* 2022 [PMID: 35863682 DOI: 10.1016/j.cgh.2022.06.030]

4 **Kuenzig ME**, Fung SG, Marderfeld L, Mak JWY, Kaplan GG, Ng SC, Wilson DC, Cameron F, Henderson P, Kotze PG, Bhatti J, Fang V, Gerber S, Guay E, Kotteduwa Jayawarden S, Kadota L, Maldonado D F, Osei JA, Sandarage R, Stanton A, Wan M; InsightScope Pediatric IBD Epidemiology Group, Benchimol EI. Twenty-first Century Trends in the Global Epidemiology of Pediatric-Onset Inflammatory Bowel Disease: Systematic Review. *Gastroenterology* 2022; **162**: 1147-1159.e4 [PMID: 34995526 DOI: 10.1053/j.gastro.2021.12.282]

5 **Cosnes J**, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011; **140**: 1785-1794 [PMID: 21530745 DOI: 10.1053/j.gastro.2011.01.055]

6 **Stöss C**, Berlet M, Reischl S, Nitsche U, Weber MC, Friess H, Wilhelm D, Neumann PA. Crohn's disease: a population-based study of surgery in the age of biological therapy. *Int J Colorectal Dis* 2021; **36**: 2419-2426 [PMID: 33876296 DOI: 10.1007/s00384-021-03930-w]

7 **Michaud E**, Waeckel L, Gayet R, Goguyer-Deschaumes R, Chanut B, Jospin F, Bathany K, Monnoye M, Genet C, Prier A, Tokarski C, Gérard P, Roblin X, Rochereau N, Paul S. Alteration of microbiota antibody-mediated immune selection contributes to dysbiosis in inflammatory bowel diseases. *EMBO Mol Med* 2022; **14**: e15386 [PMID: 35785473 DOI: 10.15252/emmm.202115386]

8 **Ananthakrishnan AN**, Kaplan GG, Bernstein CN, Burke KE, Lochhead PJ, Sasson AN, Agrawal M, Tiong JHT, Steinberg J, Kruis W, Steinwurz F, Ahuja V, Ng SC, Rubin DT, Colombel JF, Gearry R; International Organization for Study of Inflammatory Bowel Diseases. Lifestyle, behaviour, and environmental modification for the management of patients with inflammatory bowel diseases: an International Organization for Study of Inflammatory Bowel Diseases consensus. *Lancet Gastroenterol Hepatol* 2022; **7**: 666-678 [PMID: 35487235 DOI: 10.1016/S2468-1253(22)00021-8]

9 **Kong C**, Yan X, Liu Y, Huang L, Zhu Y, He J, Gao R, Kalady MF, Goel A, Qin H, Ma Y. Ketogenic diet alleviates colitis by reduction of colonic group 3 innate lymphoid cells through altering gut microbiome. *Signal Transduct Target Ther* 2021; **6**: 154 [PMID: 33888680 DOI: 10.1038/s41392-021-00549-9]

10 **Xia K**, Gao R, Wu X, Ruan Y, Wan J, Wu T, Wang F, Lin Y, Yin L, Chen C. Crohn's Disease Complicated by Rare Types of Intestinal Obstruction: Two Case Reports. *Front Med (Lausanne)* 2022; **9**: 895202 [PMID: 35572975 DOI: 10.3389/fmed.2022.895202]

11 **Yao J**, Jiang Y, Ke J, Lu Y, Hu J, Zhi M. A Validated Prognostic Model and Nomogram to Predict Early-Onset Complications Leading to Surgery in Patients With Crohn's Disease. *Dis Colon Rectum* 2021; **64**: 697-705 [PMID: 33315712 DOI: 10.1097/DCR.0000000000001881]

12 **Rieder F**, Zimmermann EM, Remzi FH, Sandborn WJ. Crohn's disease complicated by strictures: a systematic review. *Gut* 2013; **62**: 1072-1084 [PMID: 23626373 DOI: 10.1136/gutjnl-2012-304353]

13 **Louis E**, Collard A, Oger AF, Degroote E, Aboul Nasr El Yafi FA, Belaiche J. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut* 2001; **49**: 777-782 [PMID: 11709511 DOI: 10.1136/gut.49.6.777]

14 **Sands BE**, Irving PM, Hoops T, Izanec JL, Gao LL, Gasink C, Greenspan A, Allez M, Danese S, Hanauer SB, Jairath V, Kuehbacher T, Lewis JD, Loftus EV Jr, Mihaly E, Panaccione R, Scherl E, Shchukina OB, Sandborn WJ; SEAVUE Study Group. Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with moderately to severely active Crohn's disease: a multicentre, randomised, double-blind, parallel-group, phase 3b trial. *Lancet* 2022; **399**: 2200-2211 [PMID: 35691323 DOI: 10.1016/S0140-6736(22)00688-2]

15 **Hindson J**. First-line infliximab for children with Crohn's disease. *Nat Rev Gastroenterol Hepatol* 2021; **18**: 150 [PMID: 33594271 DOI: 10.1038/s41575-021-00429-1]

16 **Bouhnik Y**, Carbonnel F, Laharie D, Stefanescu C, Hébuterne X, Abitbol V, Nachury M, Brixi H, Bourreille A, Picon L, Bourrier A, Allez M, Peyrin-Biroulet L, Moreau J, Savoye G, Fumery M, Nancey S, Roblin X, Altwegg R, Bouguen G, Bommelaer G, Danese S, Louis E, Zappa M, Mary JY; GETAID CREOLE Study Group. Efficacy of adalimumab in patients with Crohn's disease and symptomatic small bowel stricture: a multicentre, prospective, observational cohort (CREOLE) study. *Gut* 2018; **67**: 53-60 [PMID: 28119352 DOI: 10.1136/gutjnl-2016-312581]

17 **Gao X**, Yang RP, Chen MH, Xiao YL, He Y, Chen BL, Hu PJ. Risk factors for surgery and postoperative recurrence: analysis of a south China cohort with Crohn's disease. *Scand J Gastroenterol* 2012; **47**: 1181-1191 [PMID: 22845663 DOI: 10.3109/00365521.2012.668931]

18 **Bernell O**, Lapidus A, Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. *Ann Surg* 2000; **231**: 38-45 [PMID: 10636100 DOI: 10.1097/00000658-200001000-00006]

19 **Brouquet A**, Blanc B, Bretagnol F, Valleur P, Bouhnik Y, Panis Y. Surgery for intestinal Crohn's disease recurrence. *Surgery* 2010; **148**: 936-946 [PMID: 20363010 DOI: 10.1016/j.surg.2010.02.001]

20 **Ou W**, Xu W, Liu F, Guo Y, Huang Z, Feng T, Liu CY, Du P. Increased expression of yes-associated protein/YAP and transcriptional coactivator with PDZ-binding motif/TAZ activates intestinal fibroblasts to promote intestinal obstruction in Crohn's disease. *EBioMedicine* 2021; **69**: 103452 [PMID: 34186485 DOI: 10.1016/j.ebiom.2021.103452]

21 **Lin XX**, Qiu Y, Zhuang XJ, Liu F, Wu XM, Chen MH, Mao R. Intestinal stricture in Crohn's disease: A 2020 update. *J Dig Dis* 2021; **22**: 390-398 [PMID: 34014617 DOI: 10.1111/1751-2980.13022]

22 **Schulberg JD**, Wright EK, Holt BA, Hamilton AL, Sutherland TR, Ross AL, Vogrin S, Miller AM, Connell WC, Lust M, Ding NS, Moore GT, Bell SJ, Shelton E, Christensen B, De Cruz P, Rong YJ, Kamm MA. Intensive drug therapy versus standard drug therapy for symptomatic intestinal Crohn's disease strictures (STRIDENT): an open-label, single-centre, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2022; **7**: 318-331 [PMID: 34890567 DOI: 10.1016/S2468-1253(21)00393-9]

23 **Hayashi Y**, Nakase H. The Molecular Mechanisms of Intestinal Inflammation and Fibrosis in Crohn's Disease. *Front Physiol* 2022; **13**: 845078 [PMID: 35222098 DOI: 10.3389/fphys.2022.845078]

24 **Bettenworth D**, Gustavsson A, Atreja A, Lopez R, Tysk C, van Assche G, Rieder F. A Pooled Analysis of Efficacy,

Safety, and Long-term Outcome of Endoscopic Balloon Dilation Therapy for Patients with Stricturing Crohn's Disease. *Inflamm Bowel Dis* 2017; **23**: 133-142 [PMID: 28002130 DOI: 10.1097/MIB.0000000000000988]

25 **Chen M**, Shen B. Endoscopic Therapy in Crohn's Disease: Principle, Preparation, and Technique. *Inflamm Bowel Dis* 2015; **21**: 2222-2240 [PMID: 26284298 DOI: 10.1097/MIB.0000000000000433]

26 **Levartovsky A**, Barash Y, Ben-Horin S, Ungar B, Soffer S, Amitai MM, Klang E, Kopylov U. Machine learning for prediction of intra-abdominal abscesses in patients with Crohn's disease visiting the emergency department. *Therap Adv Gastroenterol* 2021; **14**: 17562848211053114 [PMID: 34707689 DOI: 10.1177/17562848211053114]

27 **Clancy C**, Boland T, Deasy J, McNamara D, Burke JP. A Meta-analysis of Percutaneous Drainage Versus Surgery as the Initial Treatment of Crohn's Disease-related Intra-abdominal Abscess. *J Crohns Colitis* 2016; **10**: 202-208 [PMID: 26512133 DOI: 10.1093/ecco-jcc/jjv198]

28 **Celentano V**, Giglio MC, Pellino G, Rottoli M, Sampietro G, Spinelli A, Selvaggi F; Italian Society of Colorectal Surgery SICCR. High complication rate in Crohn's disease surgery following percutaneous drainage of intra-abdominal abscess: a multicentre study. *Int J Colorectal Dis* 2022; **37**: 1421-1428 [PMID: 35599268 DOI: 10.1007/s00384-022-04183-x]

29 **Collard MK**, Benoist S, Maggiori L, Zerbib P, Lefevre JH, Denost Q, Germain A, Cotte E, Beyer-Berjot L, Corté H, Desfourneaux V, Rahili A, Duffas JP, Pautrat K, Denet C, Bridoux V, Meurette G, Faucheron JL, Loriau J, Souche R, Vicaut E, Panis Y, Brouquet A. A Reappraisal of Outcome of Elective Surgery After Successful Non-Operative Management of an Intra-Abdominal Abscess Complicating Ileocolonic Crohn's Disease: A Subgroup Analysis of a Nationwide Prospective Cohort. *J Crohns Colitis* 2021; **15**: 409-418 [PMID: 33090205 DOI: 10.1093/ecco-jcc/jjaa217]

30 **Waked B**, Holvoet T, Geldof J, Baert F, Pattyn P, Lobatón T, Hindryckx P. Conservative management of spontaneous intra-abdominal abscess in Crohn's disease: Outcome and prognostic factors. *J Dig Dis* 2021; **22**: 263-270 [PMID: 33742782 DOI: 10.1111/1751-2980.12984]

31 **Buisson A**, Cannon L, Umanskiy K, Hurst RD, Hyman NH, Sakuraba A, Pekow J, Dalal S, Cohen RD, Pereira B, Rubin DT. Factors associated with anti-tumor necrosis factor effectiveness to prevent postoperative recurrence in Crohn's disease. *Intest Res* 2022; **20**: 303-312 [PMID: 34333909 DOI: 10.5217/ir.2021.00018]

32 **Klek S**, Sierzega M, Turczynowski L, Szybinski P, Szczepanek K, Kulig J. Enteral and parenteral nutrition in the conservative treatment of pancreatic fistula: a randomized clinical trial. *Gastroenterology* 2011; **141**: 157-163, 163.e1 [PMID: 21439962 DOI: 10.1053/j.gastro.2011.03.040]

33 **Kucharski MA**, Wierzbicka A, Tsibulski A, Sotiri E, Dobrowolska A, Mańkowska-Wierzbicka D. Parenteral and Enteral Nutrition: A Bridge to Healing and Biological Therapy in a Patient With Enterocutaneous Fistula and Sepsis Complicated Crohn's Disease. *JPEN J Parenter Enteral Nutr* 2021; **45**: 430-433 [PMID: 32386252 DOI: 10.1002/jpen.1875]

34 **Gong J**, Wei Y, Gu L, Li Y, Guo Z, Sun J, Ding C, Zhu W, Li N, Li J. Outcome of Surgery for Coloduodenal Fistula in Crohn's Disease. *J Gastrointest Surg* 2016; **20**: 976-984 [PMID: 26718702 DOI: 10.1007/s11605-015-3065-z]

35 **Ghimire P**. Management of Enterocutaneous Fistula: A Review. *JNMA J Nepal Med Assoc* 2022; **60**: 93-100 [PMID: 35199684 DOI: 10.31729/jnma.5780]

36 **Papa A**, Lopetuso LR, Minordi LM, Di Veronica A, Neri M, Rapaccini G, Gasbarrini A, Papa V. A modern multidisciplinary approach to the treatment of enterocutaneous fistulas in Crohn's disease patients. *Expert Rev Gastroenterol Hepatol* 2020; **14**: 857-865 [PMID: 32673498 DOI: 10.1080/17474124.2020.1797484]

37 **Abdalla S**, Benoist S, Maggiori L, Zerbib P, Lefevre JH, Denost Q, Germain A, Cotte E, Beyer-Berjot L, Corte H, Desfourneaux V, Rahili A, Duffas JP, Pautrat K, Denet C, Bridoux V, Meurette G, Faucheron JL, Loriau J, Guillon F, Vicaut E, Panis Y, Brouquet A; GETAID Chirurgie group. Impact of preoperative enteral nutritional support on postoperative outcome in patients with Crohn's disease complicated by malnutrition: Results of a subgroup analysis of the nationwide cohort registry from the GETAID Chirurgie group. *Colorectal Dis* 2021; **23**: 1451-1462 [PMID: 33624371 DOI: 10.1111/codi.15600]

38 **Yzet C**, Brazier F, Sabbagh C, Le Mouel JP, Hakim S, Nguyen-Khac E, Fumery M. Endoscopic Treatment of Enterocutaneous Fistulas in Crohn's Disease. *Dis Colon Rectum* 2022; **65**: 721-726 [PMID: 33990501 DOI: 10.1097/DCR.0000000000001995]

39 **Flacs M**, Collard M, Doblas S, Zappa M, Cazals-Hatem D, Maggiori L, Panis Y, Treton X, Ogier-Denis E. Preclinical Model of Perianal Fistulizing Crohn's Disease. *Inflamm Bowel Dis* 2020; **26**: 687-696 [PMID: 31774918 DOI: 10.1093/ibd/izz288]

40 **Mak WY**, Mak OS, Lee CK, Tang W, Leung WK, Wong MTL, Sze ASF, Li M, Leung CM, Lo FH, Lam BCY, Chan KH, Shan EHS, Tsang SWC, Hui AJ, Chow WH, Chan FKL, Sung JJY, Ng SC. Significant Medical and Surgical Morbidity in Perianal Crohn's Disease: Results from a Territory-Wide Study. *J Crohns Colitis* 2018; **12**: 1392-1398 [PMID: 30165543 DOI: 10.1093/ecco-jcc/jjy120]

41 **de Las Casas SG**, Alvarez-Gallego M, Martínez JAG, Alcolea NG, Serrano CB, Jiménez AU, Arranz MDM, Martín JLM, Migueláñez IP. Management of perianal fistula in inflammatory bowel disease: identification of prognostic factors associated with surgery. *Langenbecks Arch Surg* 2021; **406**: 1181-1188 [PMID: 33515317 DOI: 10.1007/s00423-021-02100-4]

42 **Biemans VBC**, van der Meulen-de Jong AE, van der Woude CJ, Löwenberg M, Dijkstra G, Oldenburg B, de Boer NKH, van der Marel S, Bodelier AGL, Jansen JM, Haans JJL, Theeuwen R, de Jong D, Pierik MJ, Hoentjen F. Ustekinumab for Crohn's Disease: Results of the ICC Registry, a Nationwide Prospective Observational Cohort Study. *J Crohns Colitis* 2020; **14**: 33-45 [PMID: 31219157 DOI: 10.1093/ecco-jcc/jjz119]

43 **Panés J**, García-Olmo D, Van Assche G, Colombel JF, Reinisch W, Baumgart DC, Dignass A, Nachury M, Ferrante M, Kazemi-Shirazi L, Grimaud JC, de la Portilla F, Goldin E, Richard MP, Diez MC, Tagarro I, Leselbaum A, Danese S; ADMIRE CD Study Group Collaborators. Long-term Efficacy and Safety of Stem Cell Therapy (Cx601) for Complex Perianal Fistulas in Patients With Crohn's Disease. *Gastroenterology* 2018; **154**: 1334-1342.e4 [PMID: 29277560 DOI: 10.1053/j.gastro.2017.12.020]

44 **Schwandner O**. Stem cell injection for complex anal fistula in Crohn's disease: A single-center experience. *World J Gastroenterol* 2021; **27**: 3643-3653 [PMID: 34239275 DOI: 10.3748/wjg.v27.i24.3643]

45 **Chiarello MM**, Pepe G, Fico V, Bianchi V, Tropeano G, Altieri G, Brisinda G. Therapeutic strategies in Crohn's disease in

an emergency surgical setting. *World J Gastroenterol* 2022; **28**: 1902-1921 [PMID: 35664965 DOI: 10.3748/wjg.v28.i18.1902]

46 **Goldstone RN**, Steinhagen RM. Abdominal Emergencies in Inflammatory Bowel Disease. *Surg Clin North Am* 2019; **99**: 1141-1150 [PMID: 31676053 DOI: 10.1016/j.suc.2019.08.007]

47 **De Simone B**, Davies J, Chouillard E, Di Saverio S, Hoentjen F, Tarasconi A, Sartelli M, Biffl WL, Ansaloni L, Coccolini F, Chiarugi M, De'Angelis N, Moore EE, Kluger Y, Abu-Zidan F, Sakakushev B, Coimbra R, Celentano V, Wani I, Pintar T, Sganga G, Di Carlo I, Tartaglia D, Pikoulis M, Cardi M, De Moya MA, Leppaniemi A, Kirkpatrick A, Agnoletti V, Poggioli G, Carcoforo P, Baiocchi GL, Catena F. WSES-AAST guidelines: management of inflammatory bowel disease in the emergency setting. *World J Emerg Surg* 2021; **16**: 23 [PMID: 33971899 DOI: 10.1186/s13017-021-00362-3]

48 **Porter RJ**, Arends MJ, Churchhouse AMD, Din S. Inflammatory Bowel Disease-Associated Colorectal Cancer: Translational Risks from Mechanisms to Medicines. *J Crohns Colitis* 2021; **15**: 2131-2141 [PMID: 34111282 DOI: 10.1093/ecco-jcc/jjab102]

49 **Agrawal M**, Spencer EA, Colombel JF, Ungaro RC. Approach to the Management of Recently Diagnosed Inflammatory Bowel Disease Patients: A User's Guide for Adult and Pediatric Gastroenterologists. *Gastroenterology* 2021; **161**: 47-65 [PMID: 33940007 DOI: 10.1053/j.gastro.2021.04.063]

50 **Heuschkel R**, Salvestrini C, Beattie RM, Hildebrand H, Walters T, Griffiths A. Guidelines for the management of growth failure in childhood inflammatory bowel disease. *Inflamm Bowel Dis* 2008; **14**: 839-849 [PMID: 18266237 DOI: 10.1002/ibd.20378]

51 **Zimmerman L**, Bousvaros A. The pharmacotherapeutic management of pediatric Crohn's disease. *Expert Opin Pharmacother* 2019; **20**: 2161-2168 [PMID: 31574236 DOI: 10.1080/14656566.2019.1659778]

52 **Fehmel E**, Teague WJ, Simpson D, McLeod E, Hutson JM, Rosenbaum J, Oliver M, Alex G, King SK. The burden of surgery and postoperative complications in children with inflammatory bowel disease. *J Pediatr Surg* 2018; **53**: 2440-2443 [PMID: 30244938 DOI: 10.1016/j.jpedsurg.2018.08.030]

53 **Yerushalmy-Feler A**, Assa A. Pharmacological Prevention and Management of Postoperative Relapse in Pediatric Crohn's Disease. *Paediatr Drugs* 2019; **21**: 451-460 [PMID: 31628665 DOI: 10.1007/s40272-019-00361-7]

54 **Xia K**, Gao R, Wu X, Sun J, Wan J, Wu T, Fichna J, Yin L, Chen C. Characterization of Specific Signatures of the Oral Cavity, Sputum, and Ileum Microbiota in Patients With Crohn's Disease. *Front Cell Infect Microbiol* 2022; **12**: 864944 [PMID: 35493739 DOI: 10.3389/fcimb.2022.864944]

55 **Yamamoto T**, Shimoyama T, Umegae S, Kotze PG. Impact of Preoperative Nutritional Status on the Incidence Rate of Surgical Complications in Patients With Inflammatory Bowel Disease With Vs Without Preoperative Biologic Therapy: A Case-Control Study. *Clin Transl Gastroenterol* 2019; **10**: e00050 [PMID: 31136361 DOI: 10.14309/ctg.0000000000000050]

56 **Yamamoto T**, Allan RN, Keighley MR. Risk factors for intra-abdominal sepsis after surgery in Crohn's disease. *Dis Colon Rectum* 2000; **43**: 1141-1145 [PMID: 10950014 DOI: 10.1007/BF02236563]

57 **Shah RS**, Bachour S, Jia X, Holubar SD, Hull TL, Achkar JP, Philpott J, Qazi T, Rieder F, Cohen BL, Regueiro MD, Lightner AL, Click BH. Hypoalbuminaemia, Not Biologic Exposure, Is Associated with Postoperative Complications in Crohn's Disease Patients Undergoing Ileocolic Resection. *J Crohns Colitis* 2021; **15**: 1142-1151 [PMID: 33388775 DOI: 10.1093/ecco-jcc/jjaa268]

58 **Yamamoto T**, Nakahigashi M, Shimoyama T, Umegae S. Does preoperative enteral nutrition reduce the incidence of surgical complications in patients with Crohn's disease? *Colorectal Dis* 2020; **22**: 554-561 [PMID: 31782874 DOI: 10.1111/codi.14922]

59 **Svolos V**, Hansen R, Nichols B, Quince C, Ijaz UZ, Papadopoulou RT, Edwards CA, Watson D, Alghamdi A, Brejnrod A, Ansalone C, Duncan H, Gervais L, Tayler R, Salmond J, Bolognini D, Klopfleisch R, Gaya DR, Milling S, Russell RK, Gerasimidis K. Treatment of Active Crohn's Disease With an Ordinary Food-based Diet That Replicates Exclusive Enteral Nutrition. *Gastroenterology* 2019; **156**: 1354-1367.e6 [PMID: 30550821 DOI: 10.1053/j.gastro.2018.12.002]

60 **Sohouli MH**, Fatahi S, Farahmand F, Alimadadi H, Seraj SS, Rohani P. Meta-analysis: efficacy of exclusive enteral nutrition as induction therapy on disease activity index, inflammation and growth factors in paediatric Crohn's disease. *Aliment Pharmacol Ther* 2022; **56**: 384-395 [PMID: 35748390 DOI: 10.1111/apt.17109]

61 **Di Caro S**, Fragkos KC, Keetarut K, Koo HF, Sebepos-Rogers G, Saravanapavan H, Barragry J, Rogers J, Mehta SJ, Rahman F. Enteral Nutrition in Adult Crohn's Disease: Toward a Paradigm Shift. *Nutrients* 2019; **11** [PMID: 31540038 DOI: 10.3390/nu11092222]

62 **Bachour SP**, Shah RS, Rieder F, Qazi T, Achkar JP, Philpott J, Lashner B, Holubar SD, Lightner AL, Barnes EL, Axelrad J, Regueiro M, Click B, Cohen BL. Intra-abdominal septic complications after ileocolic resection increases risk for endoscopic and surgical postoperative Crohn's disease recurrence. *J Crohns Colitis* 2022; **16**: 1696-1705 [PMID: 35705188 DOI: 10.1093/ecco-jcc/jjac078]

63 **Tzivanakis A**, Singh JC, Guy RJ, Travis SP, Mortensen NJ, George BD. Influence of risk factors on the safety of ileocolic anastomosis in Crohn's disease surgery. *Dis Colon Rectum* 2012; **55**: 558-562 [PMID: 22513434 DOI: 10.1097/DCR.0b013e318247c433]

64 **Feagins LA**, Holubar SD, Kane SV, Spechler SJ. Current strategies in the management of intra-abdominal abscesses in Crohn's disease. *Clin Gastroenterol Hepatol* 2011; **9**: 842-850 [PMID: 21679776 DOI: 10.1016/j.cgh.2011.04.023]

65 **Byrne LW**, McKay D. Does perioperative biological therapy increase 30-day post-operative complication rates in inflammatory bowel disease patients undergoing intra-abdominal surgery? *Surgeon* 2021; **19**: e153-e167 [PMID: 34581275 DOI: 10.1016/j.surge.2020.09.001]

66 **de Buck van Overstraeten A**, Wolthuis A, D'Hoore A. Surgery for Crohn's disease in the era of biologicals: a reduced need or delayed verdict? *World J Gastroenterol* 2012; **18**: 3828-3832 [PMID: 22876034 DOI: 10.3748/wjg.v18.i29.3828]

67 **Jensen JS**, Petersen NB, Biagini M, Bollen P, Qvist N. Infliximab treatment reduces tensile strength in intestinal anastomosis. *J Surg Res* 2015; **193**: 145-152 [PMID: 25156230 DOI: 10.1016/j.jss.2014.07.022]

68 **Cohen BL**, Fleshner P, Kane SV, Herfarth HH, Palekar N, Farraye FA, Leighton JA, Katz JA, Cohen RD, Gerich ME, Cross RK, Higgins PDR, Tinsley A, Glover S, Siegel CA, Bohl JL, Iskandar H, Ji J, Hu L, Sands BE. Prospective Cohort

Study to Investigate the Safety of Preoperative Tumor Necrosis Factor Inhibitor Exposure in Patients With Inflammatory Bowel Disease Undergoing Intra-abdominal Surgery. *Gastroenterology* 2022; **163**: 204-221 [PMID: 35413359 DOI: 10.1053/j.gastro.2022.03.057]

69 **Uchino M**, Ikeuchi H, Horio Y, Kuwahara R, Minagawa T, Kusunoki K, Goto Y, Beppu N, Ichiki K, Ueda T, Nakajima K, Ikeda M. Association between preoperative biologic use and surgical morbidity in patients with Crohn's disease. *Int J Colorectal Dis* 2022; **37**: 999-1010 [PMID: 35384495 DOI: 10.1007/s00384-022-04140-8]

70 **Abd El Aziz MA**, Abdalla S, Calini G, Saeed H, Stocchi L, Merchea A, Colibaseanu DT, Shawki S, Larson DW. Postoperative Safety Profile of Minimally Invasive Ileocolonic Resections for Crohn's Disease in the Era of Biologic Therapy. *J Crohns Colitis* 2022; **16**: 1079-1088 [PMID: 35045164 DOI: 10.1093/ecco-jcc/jjac012]

71 **Azzam N**, AlRuthia Y, Al Thaher A, Almadi M, Alharbi O, Altuwaijri M, Alshankiti S, Alanazi M, Alanazi A, Aljebreen A, Regueiro M. Rate and risk factors of postoperative endoscopic recurrence of moderate- to high-risk Crohn's disease patients - A real-world experience from a Middle Eastern cohort. *Saudi J Gastroenterol* 2022; **28**: 201-208 [PMID: 35042320 DOI: 10.4103/sjg.sjg_499_21]

72 **Cosnes J**, Nion-Larmurier I, Beaugerie L, Afchain P, Tiret E, Gendre JP. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. *Gut* 2005; **54**: 237-241 [PMID: 15647188 DOI: 10.1136/gut.2004.045294]

73 **Nguyen GC**, Elnahas A, Jackson TD. The impact of preoperative steroid use on short-term outcomes following surgery for inflammatory bowel disease. *J Crohns Colitis* 2014; **8**: 1661-1667 [PMID: 25107847 DOI: 10.1016/j.crohns.2014.07.007]

74 **Maruyama BY**, Ma C, Panaccione R, Kotze PG. Early Laparoscopic Ileal Resection for Localized Ileocecal Crohn's Disease: Hard Sell or a Revolutionary New Norm? *Inflamm Intest Dis* 2022; **7**: 13-20 [PMID: 35224013 DOI: 10.1159/000515959]

75 **Luglio G**, Kono T. Surgical Techniques and Risk of Postoperative Recurrence in CD: A Game Changer? *Inflamm Intest Dis* 2022; **7**: 21-27 [PMID: 35224014 DOI: 10.1159/000515372]

76 **An V**, Cohen L, Lawrence M, Thomas M, Andrews J, Moore J. Early surgery in Crohn's disease a benefit in selected cases. *World J Gastrointest Surg* 2016; **8**: 492-500 [PMID: 27462391 DOI: 10.4240/wjgs.v8.i7.492]

77 **Aratari A**, Papi C, Leandro G, Viscido A, Capurso L, Caprilli R. Early versus late surgery for ileo-caecal Crohn's disease. *Aliment Pharmacol Ther* 2007; **26**: 1303-1312 [PMID: 17848181 DOI: 10.1111/j.1365-2036.2007.03515.x]

78 **Gomollón F**, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, Peyrin-Biroulet L, Cullen GJ, Daperno M, Kucharzik T, Rieder F, Almer S, Armuzzi A, Harbord M, Langhorst J, Sans M, Chowers Y, Fiorino G, Juillerat P, Mantzaris GJ, Rizzello F, Vavricka S, Gionchetti P; ECCO. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis* 2017; **11**: 3-25 [PMID: 27660341 DOI: 10.1093/ecco-jcc/jjw168]

79 **Ponsioen CY**, de Groof EJ, Eshuis EJ, Gardenbroek TJ, Bossuyt PMM, Hart A, Warusavitarne J, Buskens CJ, van Bodegraven AA, Brink MA, Consten ECJ, van Wagensveld BA, Rijk MCM, Crolla RMPH, Noomen CG, Houdijk APJ, Mallant RC, Boom M, Marsman WA, Stockmann HB, Mol B, de Groof AJ, Stokkers PC, D'Haens GR, Bemelman WA; LIR!C study group. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. *Lancet Gastroenterol Hepatol* 2017; **2**: 785-792 [PMID: 28838644 DOI: 10.1016/S2468-1253(17)30248-0]

80 **Stevens TW**, Haasnoot L, D'Haens GR, Buskens C, de Groof EJ, Eshuis EJ, Gardenbroef TJ, Mol B, Stokkers PCF, Bemelman WA, Ponsioen CY. OP03 Reduced need for surgery and medical therapy after early ileocaecal resection for Crohn's disease: Long-term follow-up of the LIR! *J Crohns Colitis* 2020; **14**: S003-S004 [DOI: 10.1093/ecco-jcc/jjz203.002]

81 **de Groof EJ**, Stevens TW, Eshuis EJ, Gardenbroek TJ, Bosmans JE, van Dongen JM, Mol B, Buskens CJ, Stokkers PCF, Hart A, D'Haens GR, Bemelman WA, Ponsioen CY; LIR!C study group. Cost-effectiveness of laparoscopic ileocaecal resection versus infliximab treatment of terminal ileitis in Crohn's disease: the LIR! *Gut* 2019; **68**: 1774-1780 [PMID: 31233395 DOI: 10.1136/gutjnl-2018-317539]

82 **Su X**, Zheng L, Zhang H, Shen T, Liu Y, Hu X. Secular Trends of Acute Viral Hepatitis Incidence and Mortality in China, 1990 to 2019 and Its Prediction to 2030: The Global Burden of Disease Study 2019. *Front Med (Lausanne)* 2022; **9**: 842088 [PMID: 35360747 DOI: 10.3389/fmed.2022.842088]

83 **Dong Z**, Wang QQ, Yu SC, Huang F, Liu JJ, Yao HY, Zhao YL. Age-period-cohort analysis of pulmonary tuberculosis reported incidence, China, 2006-2020. *Infect Dis Poverty* 2022; **11**: 85 [PMID: 35902982 DOI: 10.1186/s40249-022-01009-4]

84 **Van Assche G**, Lewis JD, Lichtenstein GR, Loftus EV, Ouyang Q, Panes J, Siegel CA, Sandborn WJ, Travis SP, Colombel JF. The London position statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: safety. *Am J Gastroenterol* 2011; **106**: 1594-602; quiz 1593, 1603 [PMID: 21844919 DOI: 10.1038/ajg.2011.211]

85 **Bemelman WA**, Warusavitarne J, Sampietro GM, Serclova Z, Zmora O, Luglio G, de Buck van Overstraeten A, Burke JP, Buskens CJ, Colombo F, Dias JA, Eliakim R, Elosua T, Gecim IE, Kolacek S, Kierkus J, Kolho KL, Lefevre JH, Millan M, Panis Y, Pinkney T, Russell RK, Shwaartz C, Vaizey C, Yassin N, D'Hoore A. ECCO-ESCP Consensus on Surgery for Crohn's Disease. *J Crohns Colitis* 2018; **12**: 1-16 [PMID: 28498901 DOI: 10.1093/ecco-jcc/jjx061]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 December 27; 14(12): 1329-1339

DOI: 10.4240/wjgs.v14.i12.1329

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Basic Study

# Hydrogen gas and preservation of intestinal stem cells in mesenteric ischemia and reperfusion

Ryo Yamamoto, Sayuri Suzuki, Koichiro Homma, Shintaro Yamaguchi, Tomohisa Sujino, Junichi Sasaki

**Specialty type:** Critical care medicine

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Arslan M, Turkey; de Oliveira I, Brazil

**Received:** August 25, 2022
**Peer-review started:** August 25, 2022
**First decision:** September 2, 2022
**Revised:** September 11, 2022
**Accepted:** November 7, 2022
**Article in press:** November 7, 2022
**Published online:** December 27, 2022

**Ryo Yamamoto, Sayuri Suzuki, Koichiro Homma, Junichi Sasaki,** Department of Emergency and Critical Care Medicine, Keio University School of Medicine, Tokyo 1608582, Japan

**Shintaro Yamaguchi,** Division of Endocrinology, Metabolism and Nephrology, Department of Internal Medicine, Keio University School of Medicine, Tokyo 1608582, Japan

**Tomohisa Sujino,** Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo 1608582, Japan

**Corresponding author:** Koichiro Homma, MD, PhD, Assistant Professor, Department of Emergency and Critical Care Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 1608582, Japan. homma@keio.jp

## Abstract

### *BACKGROUND*

Patients with mesenteric ischemia frequently suffer from bowel necrosis even after revascularization. Hydrogen gas has showed promising effects for ischemia-reperfusion injury by reducing reactive oxygen species in various animal and clinical studies. We examined intestinal tissue injury by ischemia and reperfusion under continuous initiation of 3% hydrogen gas.

### *AIM*

To clarify the treatment effects and target cells of hydrogen gas for mesenteric ischemia.

### *METHODS*

Three rat groups underwent 60-min mesenteric artery occlusion (ischemia), 60-min reperfusion following 60-min occlusion (reperfusion), or ischemia-reperfusion with the same duration under continuous 3% hydrogen gas inhalation (hydrogen). The distal ileum was harvested. Immunofluorescence staining with caspase-3 and leucine-rich repeat-containing G-protein-coupled 5 (LGR5), a specific marker of intestinal stem cell, was conducted to evaluate the injury location and cell types protected by hydrogen. mRNA expressions of LGR5, olfactomedin 4 (OLFM4), hairy and enhancer of split 1, Jagged 2, and Neurogenic locus notch homolog protein 1 were measured by quantitative polymerase chain reaction. Tissue oxidative stress was analyzed with immunostaining for 8-hydroxy-2'-deoxyguanosine (8-OHdG). Systemic oxidative stress was evaluated by plasma 8-OHdG.

*RESULTS*

Ischemia damaged the epithelial layer at the tip of the villi, whereas reperfusion induced extensive apoptosis of the cells at the crypt base, which were identified as intestinal stem cells with double immunofluorescence stain. Hydrogen mitigated such apoptosis at the crypt base, and the LGR5 expression of the tissues was higher in the hydrogen group than in the reperfusion group. OLFM4 was also relatively higher in the hydrogen group, whereas other measured RNAs were comparable between the groups. 8-OHdG concentration was high in the reperfusion group, which was reduced by hydrogen, particularly at the crypt base. Serum 8-OHdG concentrations were relatively higher in both reperfusion and hydrogen groups without significance.

*CONCLUSION*

This study demonstrated that hydrogen gas inhalation preserves intestinal stem cells and mitigates oxidative stress caused by mesenteric ischemia and reperfusion.

**Key Words:** Hydrogen molecule; Intestinal ischemia; Ischemia-reperfusion injury; Tissue protection; Non-operative management; Leucine-rich repeat-containing G-protein-coupled 5



**Core Tip:** Distal ileum of rats was observed after 60-min mesenteric artery occlusion (ischemia), 60-min reperfusion following 60-min occlusion (reperfusion), or ischemia-reperfusion with the same duration under continuous 3% hydrogen gas inhalation (hydrogen). Immunofluorescence staining with caspase-3 and leucine-rich repeat-containing G-protein-coupled 5 (LGR5) (a specific marker of intestinal stem cell) identified ischemia damaged the epithelial layer at the tip of the villi, whereas reperfusion induced extensive apoptosis of intestinal stem cells that was mitigated by hydrogen. In addition, quantitative polymerase chain reaction revealed the LGR5 expression of the tissues was higher in rats with hydrogen inhalation than in those with reperfusion injury.

**Citation:** Yamamoto R, Suzuki S, Homma K, Yamaguchi S, Sujino T, Sasaki J. Hydrogen gas and preservation of intestinal stem cells in mesenteric ischemia and reperfusion. *World J Gastrointest Surg* 2022; 14(12): 1329-1339
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i12/1329.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i12.1329

## INTRODUCTION

Mesenteric ischemia is caused by insufficient blood flow in the mesenteric artery to meet the metabolic demand of the visceral organs[1]. Despite the relatively low incidence of mesenteric ischemia, delayed diagnosis caused by vague symptoms sometimes results in devastating complications, such as intestinal necrosis, abdominal sepsis, and mortality[1-3]. While rapid recirculation of mesenteric vessels by endovascular or surgical intervention has been critical, increasing the arterial flow would be the only method of preserving the intestines when hemodynamic instability causes mesenteric ischemia[1,4,5]. Notably, some patients develop bowel necrosis even after revascularization of the mesenteric artery[6].

In the last decades, hydrogen gas (molecular hydrogen) has emerged as an attractive medicinal agent for various diseases, specifically for ischemic diseases that require revascularization[7-9]. Some animal studies have shown that hydrogen had anti-inflammatory effects and reduced the reactive oxygen species (ROS) that are produced during ischemia-reperfusion injury[7,8,10,11]. Hydrogen inhalation was associated with the reduction of necrotic tissues in the animal model of cerebral and myocardial ischemia[7,8]. Moreover, several clinical investigations have reported that hydrogen gas inhalation was beneficial on acute myocardial infarction and out-of-hospital cardiac arrest, which are typical ischemia-reperfusion injuries[12,13].

Furthermore, studies on the safety of hydrogen gas have identified that hydrogen can be supplied to patients using a simple device without any adverse events, suggesting its high feasibility for clinical use [12-14]. Although the physiological mechanisms of the possible therapeutic benefits remain unclear, recent studies have suggested that the antioxidant effects of hydrogen would be introduced by cell signal transduction, preventing cellular apoptosis[15,16]. Another study reported that oxidation-reduction reactions that involve molecular hydrogen occur only with strong fatal ROS rather than with weak or beneficial ROS[14].

Accordingly, as mesenteric ischemia with revascularization is an ischemia-reperfusion injury, we aimed to clarify the favorable effects of hydrogen gas inhalation for mesenteric ischemia as a novel

noninvasive treatment. In this study, we examined the degree of tissue damage in the intestines following ischemia and reperfusion and the tissue-protective effects of continuous initiation of 3% hydrogen gas. Moreover, several cell markers were substantially measured for the differentiation of hydrogen-target cells to elucidate the pathophysiological mechanisms of hydrogen.

## MATERIALS AND METHODS

### Animals

The protocol used in this study was approved by the Research Council and Animal Care and Use Committee of the Research Institute of Keio University in Tokyo, Japan (approval number 21013-0) and was performed in accordance with the guidelines for the care and use of laboratory animals established by the Japanese Pharmacological Society and the National Institutes of Health.

Eight-week-old male Sprague-Dawley rats (250-270 g) were purchased from Sankyo Labo Service Corporation, Inc. (Tokyo, Japan) and kept in a temperature- and light-controlled room (20 °C, 12-h light/dark cycle). The rats had free access to food and water. Before the procedure, they were intraperitoneally anesthetized with a combination of 0.3 mg/kg medetomidine, 2.0 mg/kg midazolam, and 2.5 mg/kg butorphanol. They were appropriately anesthetized throughout the procedure.

### Hydrogen gas preparation

Hydrogen gas (3%) was prepared using a hydrogen gas supply device (Nihon Kohden Co., Tokyo, Japan)[14] and administered to rats at a rate of 0.2 L/min. The hydrogen gas stored in the device was mixed with air, and the targeted concentration was measured inside the supply device. The gas flow rate was adjusted at the output port of the device and validated with a flow meter attached to the respiratory circuit.

### Experimental protocol

The rats were allocated to three groups: ischemia (control 1), reperfusion (control 2), and hydrogen groups. The ischemia group ($n$ = 10) underwent a median laparotomy and dissection of the superior mesenteric artery. The artery was then occluded at the root by a double microclamp for 60 min. The marginal arteries of the intestines were also ligated at the ileocolic junction and at 15 cm proximal from the junction to achieve complete ischemia of the terminal ileum. The reperfusion group ($n$ = 11) similarly underwent 60-min occlusion of the superior mesenteric artery and ligation of the marginal arteries. The occlusion was then released by declamping of the mesenteric artery, and reperfusion of the intestine was observed for 60 min without closing the abdomen[17,18]. The hydrogen group ($n$ = 9) was connected to the respiratory circuit using a gas supply hood that covered the face and head of the rats, in which spontaneous respiration was maintained without using mechanical ventilation[14]. After hydrogen gas inhalation, the rats underwent the same surgical procedures as those in the reperfusion group.

In each rat, intestinal ischemia was confirmed by the paleness of the distal ileum and pulselessness of the mesenteric artery. The procedures of the tree groups were conducted simultaneously to reduce potential confounders by procedures. All animals were sacrificed immediately after the aforementioned procedures. A 2-cm-long ileum was then excised at 6 cm proximal from the ileocolic junction, which was processed for histological evaluation and ribonucleic acid (RNA) extraction. Blood samples were also obtained directly from the left ventricle[19]. Details of study protocol were not pre-registered nor published.

### Histological evaluation

Tissues were fixed in 4% neutral-buffered paraformaldehyde, and 4 μm paraffin-embedded sections were prepared. Hematoxylin and eosin (H&E) staining was performed to evaluate histopathological changes that were visually compared between the three groups (ischemia, ischemia-reperfusion, and ischemia-reperfusion under hydrogen gas inhalation).

For immunostaining, samples were deparaffinized and rehydrated, and endogenous peroxidase activity was then suppressed using 0.3% hydrogen peroxide ($H_2O_2$) in methanol. Nonspecific binding was blocked with bovine serum albumin (BSA) for 30 min. Primary rabbit antirat antibody against active caspase-3 (CST 9661S; Cell Signaling Technology, Beverly, MA, United States) or against 8-hydroxy-2'-deoxyguanosine (8-OHdG) that is an oxidized nucleoside of DNA induced by ROS (N45.1; Japan Institute for the Control of Aging, Fukuroi, Shizuoka, Japan) was applied with 1:200 dilution and then incubated overnight at 4 °C. After washing, sections were incubated with biotinylated antirabbit antibodies (Vector Laboratories, Burlingame, CA, United States) diluted to 1:200 in a blocking serum for 30 min. Sections were subjected to peroxidase along with 3,3'-diaminobenzidine-tetrahydrochloride and $H_2O_2$ (Elite ABC Kit and DAB Substrate Kit; Vector Laboratories). Slides were washed and counter-stained with Gill's hematoxylin (Accustain; Sigma-Aldrich, St. Louis, MO, United States), and samples were microphotographed at Zeiss Axioscope2 (Carl Zeiss, Oberkochen, Germany).

Frozen sections of the harvested tissues were incubated with one of the following primary antibodies diluted in 0.1% BSA/phosphate-buffered saline (PBS): LGR5 as an intestinal stem cell marker[20] (1:200, bs-1117R Bioss Antibodies Inc., MA, United States) and active caspase-3 (1:200). After washing with PBS/0.1% Tween 20 (Wako Pure Chemical Industries, Japan), sections were incubated with secondary antibodies for 1 h at room temperature using Alexa Fluor 488-conjugated (1:500, Invitrogen, CA, United States) or TAS fluorescence systems (NEL 702, PerkinElmer Life Sciences Inc., MA, United States). After counterstaining with Hoechst 33258 (94403, Sigma-Aldrich, MO, United States) to visualize nuclei, images were obtained with a BZ9000 (Keyence, Osaka, Japan).

### *RNA extraction, cDNA synthesis, polymerase chain reaction, and real-time polymerase chain reaction*

Total RNA was isolated using a miRNeasy Mini Kit (Qiagen, Valencia, CA, United States) and converted to cDNA using the High-Capacity Reverse Transcription Kit (Applied Biosystems, Carlsbad, CA, United States), according to the manufacturer's instructions. Real-time polymerase chain reaction (PCR) was performed using a QuantiFast SYBR Green PCR Kit (Qiagen), according to the manufacturer's instructions. The PCR primers used in this study were as follows: LGR5 forward, 5'-TGTCATGTGAGCTGGATGG-3' and reverse, 5'-ATGCAGGAGACTGGCAGGTA-3'; OLFM4 forward, 5'-GTGGACAGAAGGTGGTACTCTG-3' and reverse, 5'- GCTGGACATACTCCTTCACCTTA-3'; Hes1 forward, 5'-ATAAACCCTCAACTGCTCCGT-3' and reverse, 5'-CCATGATAGGCTTTGATGACTTTCT-3'; Jag2 forward, 5'-CCACACCAGATGAGGAGCTG-3' and reverse, 5'-CAGAACTTGTTGCAGGTGGC-3'; Notch1 forward, 5'-TGGTCTCAACTGCCAGAACC-3' and reverse, 5'-CACTCGCAGTG-GTACTGTGT-3'; and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) forward, 5'-TTGTGCAGT-GCCAGCCTC-3' and reverse, 5'-GGTAACCAGGCGTCCGATAC-3'. Expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method and normalized to levels of the internal control GAPDH[19,21,22]. Real-time PCR was performed by a researcher who was blinded to the group allocation.

### *Evaluation of systemic oxidative injury*

Serum samples were prepared from blood using Nanosep® Centrifugal Devices with Omega™ Membrane 10K (Pall Corporation, NY, United States), according to the manufacturer's instructions. The supernatant was used to determine 8-OHdG by a competitive enzyme-linked immunosorbent assay (Highly Sensitive 8-OHdG Check; Japan Institute for the Control of Aging, Fukuroi, Shizuoka, Japan) [20].

### *Statistical analysis*

Descriptive statistics are presented as median (interquartile range) or number (percentage). Intergroup comparisons of mRNA expressions and 8-OHdG concentrations were performed using analysis of variance with Tukey-Kramer as post-hoc test and/or Kruskal-Wallis tests, as appropriate. All statistical tests used a $\alpha$ error rate of 0.05 and were two-sided. All statistical analyses were conducted using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, United States), and Microsoft Excel (Microsoft, Redmond, WA, United States).

## RESULTS

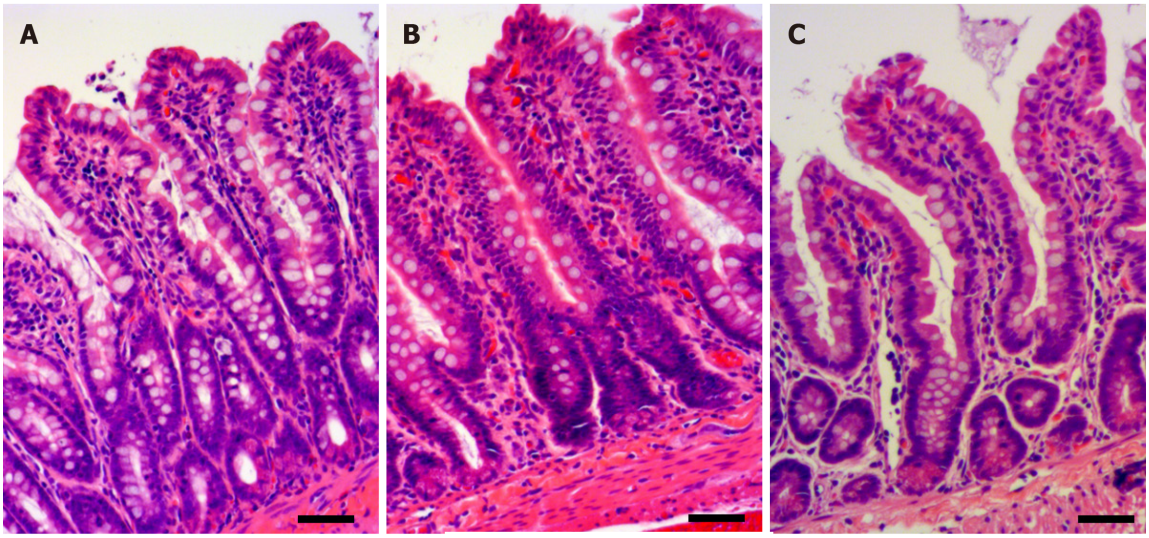
### *Intestinal mucosal injury*

Histological sections with H&E staining showed morphologic changes in the intestinal mucosa of the ischemia group (Figure 1A), in which pyknosis was observed in the epithelial layer. Mucosa was more severely injured in the reperfusion group (Figure 1B), and extensive pyknosis in the epithelial layer, denudation of the tip of the villi, and capillary congestion were observed. Conversely, the hydrogen groups showed similar degree of injury to the ischemia group (Figure 1C), with mild epithelial pyknosis and denudation of the villi.

### *Intestinal stem cell injury by ischemia-reperfusion injury*

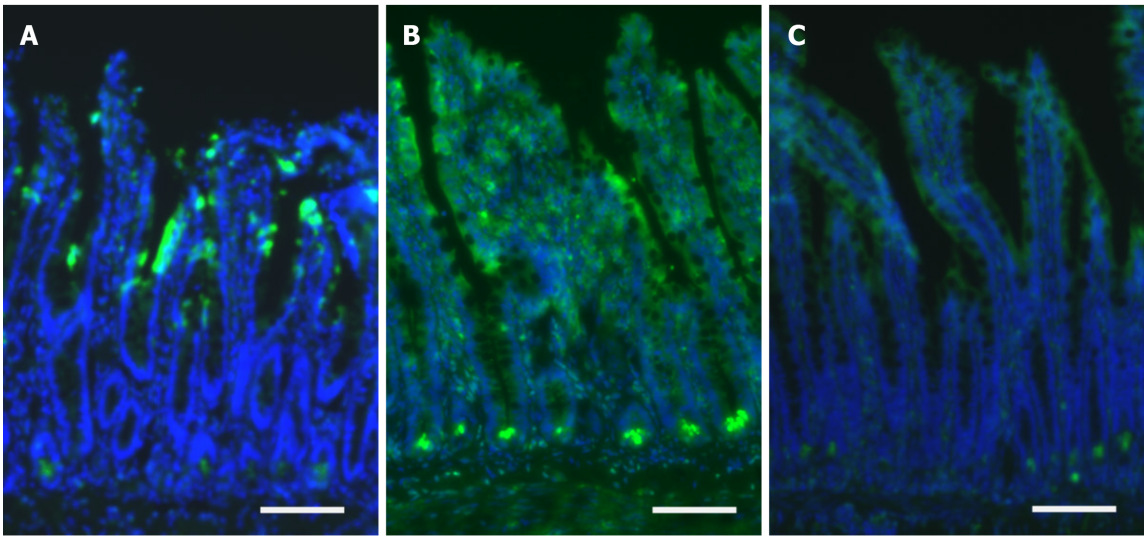
Immunofluorescence analyses with caspase-3 antibodies revealed that the intestinal mucosa of the ischemia group was mainly injured at the epithelial layer closed to the tip of the villi (Figure 2A). In the reperfusion group, apoptosis was extensively identified at the crypt base, where intestinal stem cells exist[23,24], in addition to injuries at the whole epithelial layer (Figure 2B). Apoptosis at the crypt base was limited in the hydrogen group (Figure 2C), whereas epithelial injury was observed at the villi with a half side of the digestive tract.

In the ischemia group, immunofluorescence analyses using simultaneous staining of caspase-3 and LGR5, a specific protein for intestinal stem cell, revealed that LGR5-positive cells at the crypt base did not undergo apoptosis [caspase-3 (red) and LGR5 (green) were separately stained; Figure 3A]. Conversely, multiple LGR5-positive cells underwent apoptosis after reperfusion (there were double-stained cells with caspase-3 and LGR5; Figure 3B).




**DOI:** 10.4240/wjgs.v14.i12.1329 **Copyright** ©The Author(s) 2022.

**Figure 1 Intestinal mucosal injury with ischemia-reperfusion injury.** A: Histological sections with H&E stain showed pyknosis in the epithelial layer in the ischemia group; B: Extensive pyknosis in the epithelial layer, denudation of the tip of the villi, and capillary congestion in the reperfusion group; C: Mild epithelial pyknosis and denudation of the villi in the hydrogen group. Scale bar: 50 μm.




**DOI:** 10.4240/wjgs.v14.i12.1329 **Copyright** ©The Author(s) 2022.

**Figure 2 Intestinal stem cell injury by ischemia-reperfusion injury.** A: Immunofluorescence staining with caspase-3 (green) revealed mucosal injury at the epithelial layer closed to the tip of the villi in the ischemia group; B: Extensive apoptosis was identified at the crypt base and the whole epithelial layer in the reperfusion group; C: Apoptosis at the crypt base was limited in the hydrogen group. Scale bar: 100 μm.

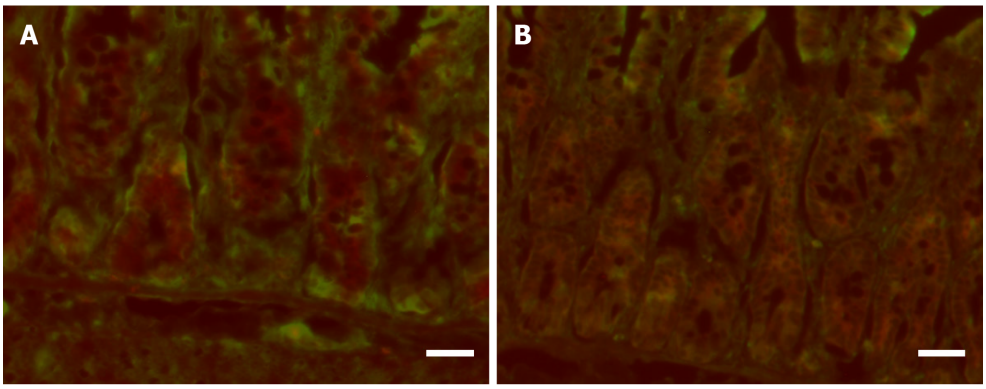
### *Quantitative analysis of RNA with RT-PCR*

Quantitative analyses of RNA in the homogenized intestinal tissues were conducted on LGR5, OLFM4, Hes1, Jag2, and Notch1, and Figure 4 summarizes these RNA expressions in the ischemia, reperfusion, and hydrogen groups. The expression of LGR5 was significantly lower in the reperfusion group than in the ischemia group, whereas the expression of LGR5 was higher in the hydrogen group than in the reperfusion group (Figure 4A). In addition, the expression of OLFM4 was relatively higher in the hydrogen group than in the reperfusion group, although the differences were not significant.

Conversely, the expression of Hes1, a transcriptional repressor of genes, was relatively high in the reperfusion group than in the ischemia and hydrogen groups (Figure 4B). Expressions of Jag2 (a ligand in Notch signaling for cell fate decision) and Notch1 (a transmembrane receptor in Notch signaling) were comparable among the ischemia, reperfusion, and hydrogen groups (Figure 4B).

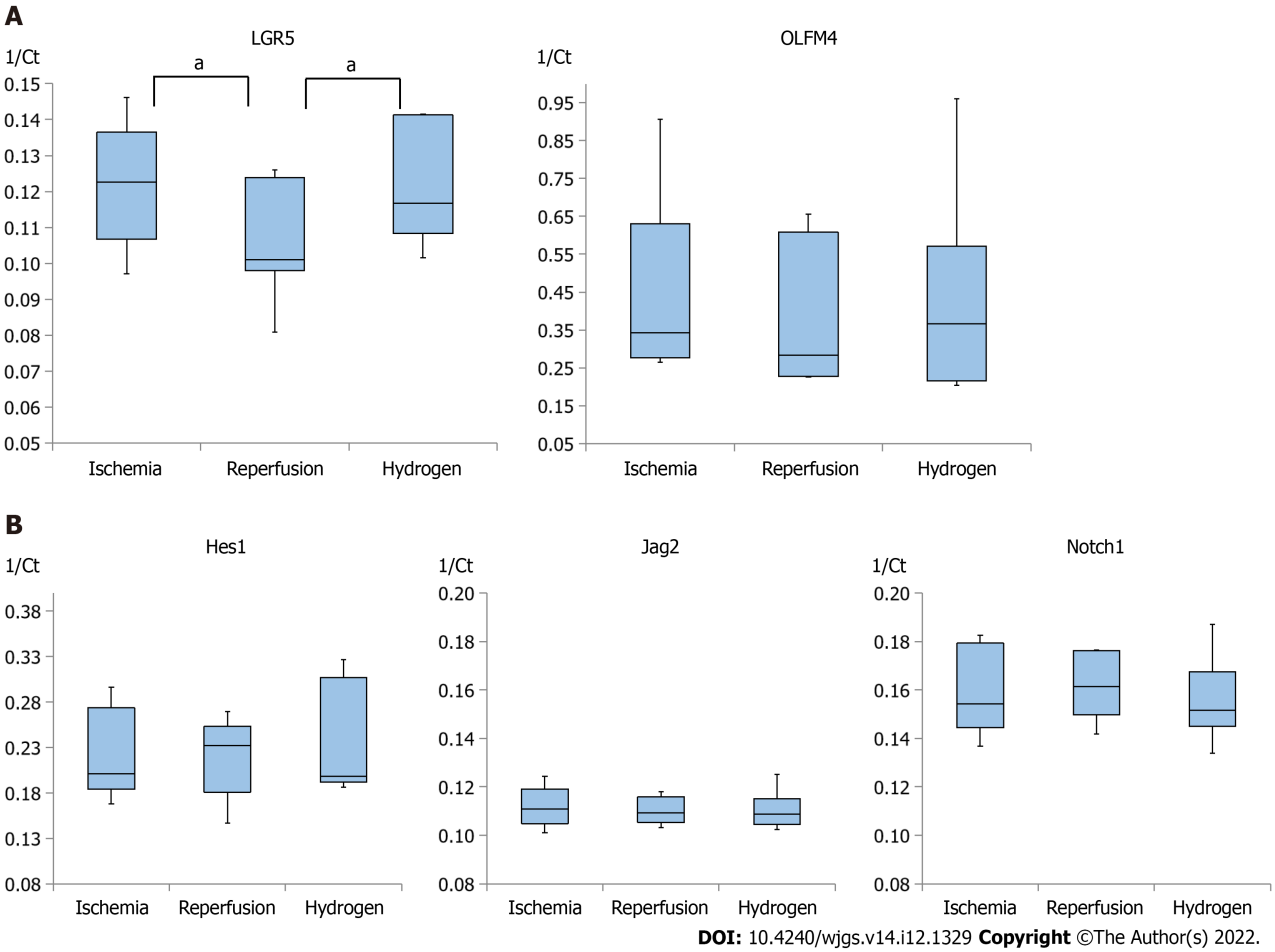
### *Mucosal and systemic oxidative injuries*

Immunostaining for 8-OHdG of intestinal tissue showed that the ischemia group had limited oxidative




**DOI:** 10.4240/wjgs.v14.i12.1329 **Copyright** ©The Author(s) 2022.

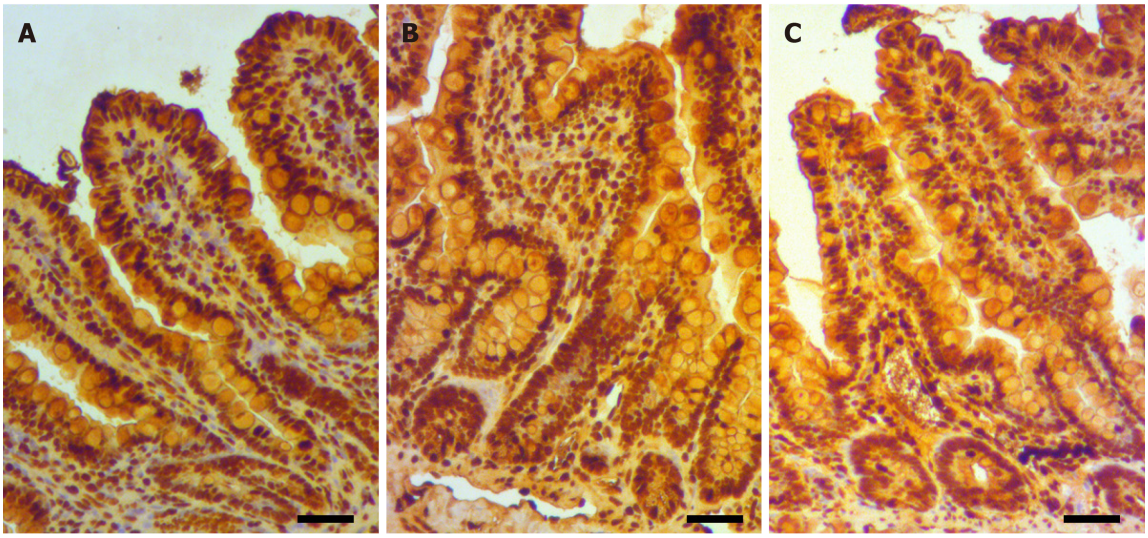
**Figure 3 Intestinal stem cell with double immunofluorescence staining.** A: Double immunofluorescence staining with caspase-3 (red) and leucine-rich repeat-containing G-protein-coupled 5 (LGR5) (green) showed that LGR5-positive cells at the crypt base did not undergo apoptosis in the ischemia group (caspase-3 and LGR5 were separately stained); B: Multiple LGR5-positive cells underwent apoptosis after reperfusion (there were double-stained cells with caspase-3 and LGR5). Scale bar: 50 μm.




**DOI:** 10.4240/wjgs.v14.i12.1329 **Copyright** ©The Author(s) 2022.

**Figure 4 Quantitative analysis of RNA.** A: Leucine-rich repeat-containing G-protein-coupled 5 expression was significantly lower in the reperfusion group than in the ischemia group, but it was significantly higher in the hydrogen group than in the reperfusion group. Olfactomedin 4 expression was also relatively higher in the hydrogen group than in the reperfusion group, although the differences were not significant; B: Hes1 expression was relatively high in the reperfusion group than in the ischemia and hydrogen groups, whereas Jag2 and Notch1 expressions were comparable between the ischemia, reperfusion, and hydrogen groups. $^{a}P < 0.05$. LGR5: Leucine-rich repeat-containing G-protein-coupled 5; OLFM4: Olfactomedin 4; Hes1: Hairy and enhancer of split 1; Jag2: Jagged 2; Notch1: Neurogenic locus notch homolog protein 1.

stress at the intestinal mucosa, although considerable pyknosis occurred in the epithelial layer, particularly at the tip of the villi (Figure 5A). Conversely, the reperfusion group had extensive oxidative injury throughout the epithelium, including at the crypt base (Figure 5B). The hydrogen group had




**DOI:** 10.4240/wjgs.v14.i12.1329 

**Figure 5 Mucosal oxidative injury in the ischemia-reperfusion model.** A: Immunostaining for 8-hydroxy-2'-deoxyguanosine showed limited oxidative stress at the mucosa in the ischemia group, although there was considerable pyknosis at the tip of the villi; B: Extensive oxidative injury throughout the epithelium, including the crypt base, in the reperfusion group; C: Mild-to-moderate oxidative injury at the mucosa of the crypt base, along with pyknosis with the denudation at the tip of the villi, in the hydrogen group. Scale bar: 50 μm.

mild-to-moderate oxidative injury at the mucosa of the crypt base, along with pyknosis with the denudation at the tip of the villi (Figure 5C).

Regarding systematic oxidative injury, the serum 8-OHdG concentrations immediately after the intervention in each group (ischemia, ischemia and reperfusion, and ischemia and reperfusion under hydrogen gas inhalation) are summarized in Figure 6. Despite the lack of significance, 8-OHdG concentration was higher in the reperfusion and hydrogen groups than in the ischemia group.

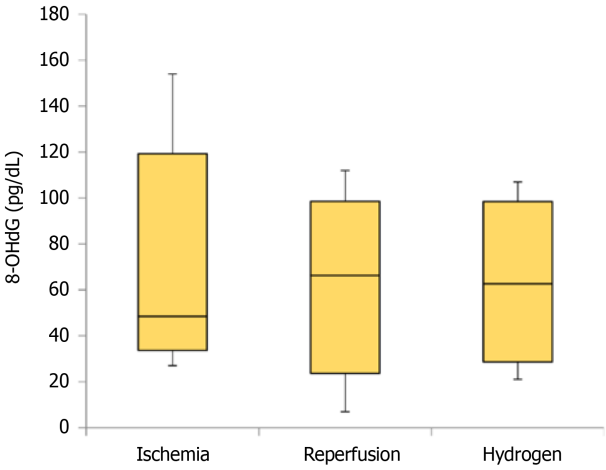
## DISCUSSION

In this study, the tissue-protective effects of continuous hydrogen gas inhalation were histologically identified in the model of ischemic-reperfusion injury at mesentery. In addition, hydrogen protected intestinal stem cells from oxidative stress following ischemia-reperfusion injury, which has not been reported as therapeutic effect of hydrogen in previous studies. Notably, the intestinal stem cells were not injured by ischemia alone (ischemia without reperfusion), and therefore, hydrogen would provide tissue-protective effect only when reperfusion happens, rather than only ischemic injury exists.

Previous clinical and animal studies have suggested that hydrogen gas has anti-oxidative and anti-inflammatory effects on several critical diseases, such as cerebral infarction, myocardial infarction, and post-cardiac arrest syndrome[7,10,12]. Although pathophysiological mechanisms underlying these therapeutic effects remain unclear, hydrogen would attenuate excessive neutrophil activation and reduce hydroxyl radicals produced following an ischemia-reperfusion injury[25,26]. In this study, fewer oxidized nucleosides of DNA (8-OHdG) were observed at the crypt base of the intestines during continuous inhalation of hydrogen gas, which suggests that hydrogen mitigated ROS toxicity.

Immunofluorescence assay using LGR5 suggested that the intestinal stem cells would be a target of the therapeutic effects of hydrogen, at least under mesenteric ischemia and reperfusion. Stem cells have unique features, one of which is self-proliferation under adequate ischemic stimuli, whereas differentiated enterocytes undergo apoptosis because of ischemia-induced energy depletion[23,27]. In a study on the association between ROS and intestinal stem cells, modest ROS following ischemia would signal proliferation and differentiation of stem cells[27]. However, the same study suggested that high levels of ROS can induce intestinal stem cell apoptosis, which is similar to the observations in this study. We showed relative preservation of intestinal stem cells with ischemic stress alone and extensive apoptosis of stem cells with reperfusion that would have introduced massive ROS. Therefore, our results might indicate that hydrogen reduces excessive ROS caused by ischemia-reperfusion stimuli and prevents apoptosis of intestinal stem cells.

The protective effects of hydrogen on intestinal stem cells are also indicated by the higher LGR5 expression with hydrogen gas inhalation in the quantitative measurement of RNA. OLFM4 is a robust marker of LGR5-positive stem cells[28], and in this study, its expression was relatively higher in the hydrogen group than in the reperfusion group. Jag2/Notch1/Hes1 expressions have been reported to increase with epithelial cell proliferation following ischemia-reperfusion injury in the intestines[19].




**DOI:** 10.4240/wjgs.v14.i12.1329 

**Figure 6 Systematic oxidative injury in the ischemia-reperfusion model.** Serum 8-hydroxy-2'-deoxyguanosine (8-OHdG) concentration immediately after each intervention (ischemia, ischemia-reperfusion, and ischemia-reperfusion under hydrogen gas inhalation) was measured. Although not significant, the 8-OHdG concentration was higher in the reperfusion and hydrogen groups than in the ischemia group. 8-OHdG: 8-hydroxy-2'-deoxyguanosine.

Expressions of Jag2 and Notch1 were comparable between the three groups, and the expression of Hes1 was slightly high in the reperfusion group, suggesting that proliferation signals at the epithelium under ischemia would be similar regardless of reperfusion or hydrogen inhalation.

Systemic oxidative stress was not different between the reperfusion and hydrogen groups. Therefore, hydrogen would not systematically affect the total amount of ROS in the body. Although hydrogen may reduce ROS in other tissues or organs in addition to the intestinal mucosa, such possible effects were not examined in this study. Moreover, the mechanisms of the reduction of ROS toxicity by hydrogen were not assessed. Future studies should focus on these topics to develop a noninvasive novel therapy using hydrogen gas.

## CONCLUSION

This study reported on the tissue-protective effects of continuous hydrogen gas inhalation in ischemia-reperfusion injury in the intestines. The target cells of hydrogen might be intestinal stem cells, which are injured by excessive ROS caused by reperfusion following ischemia rather than by ischemic stress alone. The pathophysiological mechanisms for ROS reduction by hydrogen in stem cells should be further clarified in future studies.

## ARTICLE HIGHLIGHTS

### *Research background*

Mesenteric ischemia introduces unfavorable clinical outcomes particularly when bowel necrosis is diagnosed, and it can happen even after revascularization. However, promising treatment has not been developed to prevent bowel necrosis after revascularization.

### *Research motivation*

Hydrogen gas inhalation has showed tissue preserving effects for several ischemia-reperfusion injuries by reducing reactive oxygen species (ROS) in various animal and clinical studies. In addition, the safety of hydrogen gas was shown by clinical studies that examined the efficacy of hydrogen on myocardial infarction and post-cardiac arrest syndrome. Therefore, hydrogen gas for mesenteric ischemia can be a novel noninvasive treatment.

### *Research objectives*

This study aimed to clarify the favorable effects of hydrogen gas inhalation for mesenteric ischemia and reperfusion. We hypothesized that the degree of tissue damage in the intestines following ischemia and reperfusion would be mitigated by continuous initiation of 3% hydrogen gas.

### *Research methods*

Rats were allocated to three groups: ischemia (control 1) that underwent 60-min occlusion of mesenteric artery by clamping under laparotomy, reperfusion (control 2) that underwent the ischemia procedure and 60-min release of occlusion, and hydrogen that underwent the ischemia and reperfusion under 0.3% hydrogen gas inhalation at a rate of 0.2 L/min. Then, the tissue damages at the ileum were histologically evaluated, using immunostaining against caspase-3, 8-hydroxy-2'-deoxyguanosine, and leucine-rich repeat-containing G-protein-coupled 5 (LGR5). Several mRNA, including LGR5, were quantitatively measured with RT-PCR.

### *Research results*

The reperfusion procedure introduced intestinal tissue destruction, which was mitigated by hydrogen gas inhalation. In addition, the intestinal tissue injury by the reperfusion involved intestinal stem cell that was marked by LGR5, whereas the ischemia without reperfusion did not affect the stem cell. The expression of LGR5 was significantly lower in the reperfusion group than in the ischemia group, whereas the expression of LGR5 was higher in the hydrogen group than in the reperfusion group.

### *Research conclusions*

This study reported on the tissue-protective effects of continuous hydrogen gas inhalation in the ischemia and reperfusion injury at the intestine. The target cells of hydrogen might be intestinal stem cells that are injured by excessive ROS caused by reperfusion following ischemia.

### *Research perspectives*

Hydrogen may reduce ROS in other tissues in addition to the intestinal mucosa, which should be examined in the future study. Moreover, the mechanisms of the reduction of ROS toxicity by hydrogen should be revealed to validate the hydrogen as a noninvasive novel treatment.


## FOOTNOTES


**Author contributions:** Yamamoto R, Suzuki S, Homma K, Yamaguchi S, and Sujino T designed the experiment; Yamamoto R, Suzuki S, and Homma K performed the experiment and analyzed the data; Sasaki J supervised the experiment; Yamamoto R and Suzuki S wrote the original manuscript; Yamamoto R, Suzuki S, and Homma K revised the manuscript; all authors reviewed the manuscript.

**Institutional animal care and use committee statement:** The protocol used in this study was approved by the Research Council and Animal Care and Use Committee of the Research Institute of Keio University in Tokyo, Japan (approval number 21013-0) and was performed in accordance with the guidelines for the care and use of laboratory animals established by the Japanese Pharmacological Society and the National Institutes of Health.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Data sharing statement:** Technical appendix, statistical code, and dataset available from the corresponding author at homma@keio.jp.

**ARRIVE guidelines statement:** The authors have read the ARRIVE guidelines, and the manuscript was prepared and revised according to the ARRIVE guidelines.





**Country/Territory of origin:** Japan



**ORCID number:** Tomohisa Sujino 0000-0003-0699-6577; Junichi Sasaki 0000-0002-5190-8524.



**S-Editor:** Gong ZM
**L-Editor:** A
**P-Editor:** Gong ZM

## REFERENCES


1 **Clair DG**, Beach JM. Mesenteric Ischemia. *N Engl J Med* 2016; **374**: 959-968 [PMID: 26962730 DOI: 10.1056/NEJMra1503884]
2 **Schoots IG**, Koffeman GI, Legemate DA, Levi M, van Gulik TM. Systematic review of survival after acute mesenteric ischaemia according to disease aetiology. *Br J Surg* 2004; **91**: 17-27 [PMID: 14716789 DOI: 10.1002/bjs.4459]
3 **Grootjans J**, Lenaerts K, Buurman WA, Dejong CH, Derikx JP. Life and death at the mucosal-luminal interface: New perspectives on human intestinal ischemia-reperfusion. *World J Gastroenterol* 2016; **22**: 2760-2770 [PMID: 26973414 DOI: 10.3748/wjg.v22.i9.2760]
4 **Park WM**, Gloviczki P, Cherry KJ Jr, Hallett JW Jr, Bower TC, Panneton JM, Schleck C, Ilstrup D, Harmsen WS, Noel AA. Contemporary management of acute mesenteric ischemia: Factors associated with survival. *J Vasc Surg* 2002; **35**: 445-452 [PMID: 11877691 DOI: 10.1067/mva.2002.120373]
5 **Ryer EJ**, Kalra M, Oderich GS, Duncan AA, Gloviczki P, Cha S, Bower TC. Revascularization for acute mesenteric ischemia. *J Vasc Surg* 2012; **55**: 1682-1689 [PMID: 22503176 DOI: 10.1016/j.jvs.2011.12.017]
6 **Plumereau F**, Mucci S, Le Naoures P, Finel JB, Hamy A. Acute mesenteric ischemia of arterial origin: importance of early revascularization. *J Visc Surg* 2015; **152**: 17-22 [PMID: 25677209 DOI: 10.1016/j.jviscsurg.2014.11.001]
7 **Hayashida K**, Sano M, Ohsawa I, Shinmura K, Tamaki K, Kimura K, Endo J, Katayama T, Kawamura A, Kohsaka S, Makino S, Ohta S, Ogawa S, Fukuda K. Inhalation of hydrogen gas reduces infarct size in the rat model of myocardial ischemia-reperfusion injury. *Biochem Biophys Res Commun* 2008; **373**: 30-35 [PMID: 18541148 DOI: 10.1016/j.bbrc.2008.05.165]
8 **Ohta S**. Molecular hydrogen is a novel antioxidant to efficiently reduce oxidative stress with potential for the improvement of mitochondrial diseases. *Biochim Biophys Acta* 2012; **1820**: 586-594 [PMID: 21621588 DOI: 10.1016/j.bbagen.2011.05.006]
9 **Xie K**, Yu Y, Pei Y, Hou L, Chen S, Xiong L, Wang G. Protective effects of hydrogen gas on murine polymicrobial sepsis *via* reducing oxidative stress and HMGB1 release. *Shock* 2010; **34**: 90-97 [PMID: 19997046 DOI: 10.1097/SHK.0b013e3181cdc4ae]
10 **Hayashida K**, Sano M, Kamimura N, Yokota T, Suzuki M, Ohta S, Fukuda K, Hori S. Hydrogen inhalation during normoxic resuscitation improves neurological outcome in a rat model of cardiac arrest independently of targeted temperature management. *Circulation* 2014; **130**: 2173-2180 [PMID: 25366995 DOI: 10.1161/CIRCULATIONAHA.114.011848]
11 **Homma K**, Yoshida T, Yamashita M, Hayashida K, Hayashi M, Hori S. Inhalation of Hydrogen Gas Is Beneficial for Preventing Contrast-Induced Acute Kidney Injury in Rats. *Nephron Exp Nephrol* 2015 [PMID: 25592271 DOI: 10.1159/000369068]
12 **Katsumata Y**, Sano F, Abe T, Tamura T, Fujisawa T, Shiraishi Y, Kohsaka S, Ueda I, Homma K, Suzuki M, Okuda S, Maekawa Y, Kobayashi E, Hori S, Sasaki J, Fukuda K, Sano M. The Effects of Hydrogen Gas Inhalation on Adverse Left Ventricular Remodeling After Percutaneous Coronary Intervention for ST-Elevated Myocardial Infarction - First Pilot Study in Humans. *Circ J* 2017; **81**: 940-947 [PMID: 28321000 DOI: 10.1253/circj.CJ-17-0105]
13 **Tamura T**, Hayashida K, Sano M, Suzuki M, Shibusawa T, Yoshizawa J, Kobayashi Y, Suzuki T, Ohta S, Morisaki H, Fukuda K, Hori S. Feasibility and Safety of Hydrogen Gas Inhalation for Post-Cardiac Arrest Syndrome - First-in-Human Pilot Study. *Circ J* 2016; **80**: 1870-1873 [PMID: 27334126 DOI: 10.1253/circj.CJ-16-0127]
14 **Yamamoto R**, Homma K, Suzuki S, Sano M, Sasaki J. Hydrogen gas distribution in organs after inhalation: Real-time monitoring of tissue hydrogen concentration in rat. *Sci Rep* 2019; **9**: 1255 [PMID: 30718910 DOI: 10.1038/s41598-018-38180-4]
15 **Cai J**, Kang Z, Liu WW, Luo X, Qiang S, Zhang JH, Ohta S, Sun X, Xu W, Tao H, Li R. Hydrogen therapy reduces apoptosis in neonatal hypoxia-ischemia rat model. *Neurosci Lett* 2008; **441**: 167-172 [PMID: 18603371 DOI: 10.1016/j.neulet.2008.05.077]
16 **Itoh T**, Fujita Y, Ito M, Masuda A, Ohno K, Ichihara M, Kojima T, Nozawa Y. Molecular hydrogen suppresses FcepsilonRI-mediated signal transduction and prevents degranulation of mast cells. *Biochem Biophys Res Commun* 2009; **389**: 651-656 [PMID: 19766097 DOI: 10.1016/j.bbrc.2009.09.047]
17 **Mine Y**, Fujita F, Murase T, Ito S, Takatsuki M, Ikematsu K, Eguchi S. Heat Shock Protein 70 Messenger RNA in Rat Leukocytes Elevates After Severe Intestinal Ischemia-Reperfusion. *J Surg Res* 2019; **242**: 342-348 [PMID: 31132625 DOI: 10.1016/j.jss.2019.04.074]
18 **Strumwasser A**, Bhargava A, Victorino GP. Attenuation of endothelial phosphatidylserine exposure decreases ischemia-reperfusion induced changes in microvascular permeability. *J Trauma Acute Care Surg* 2018; **84**: 838-846 [PMID: 29538229 DOI: 10.1097/TA.0000000000001891]
19 **Chen G**, Qiu Y, Sun L, Yu M, Wang W, Xiao W, Yang Y, Liu Y, Yang S, Teitelbaum DH, Ma Y, Lu D, Yang H. The jagged-2/notch-1/hes-1 pathway is involved in intestinal epithelium regeneration after intestinal ischemia-reperfusion injury. *PLoS One* 2013; **8**: e76274 [PMID: 24098462 DOI: 10.1371/journal.pone.0076274]
20 **Kim CK**, Yang VW, Bialkowska AB. The Role of Intestinal Stem Cells in Epithelial Regeneration Following Radiation-Induced Gut Injury. *Curr Stem Cell Rep* 2017; **3**: 320-332 [PMID: 29497599 DOI: 10.1007/s40778-017-0103-7]
21 **Cai Y**, Wang W, Liang H, Sun L, Teitelbaum DH, Yang H. Keratinocyte growth factor improves epithelial structure and function in a mouse model of intestinal ischemia/reperfusion. *PLoS One* 2012; **7**: e44772 [PMID: 23028616 DOI: 10.1371/journal.pone.0044772]
22 **Chen G**, Sun L, Yu M, Meng D, Wang W, Yang Y, Yang H. The Jagged-1/Notch-1/Hes-1 pathway is involved in intestinal adaptation in a massive small bowel resection rat model. *Dig Dis Sci* 2013; **58**: 2478-2486 [PMID: 23595520 DOI: 10.1007/s10620-013-2680-3]
23 **Nalapareddy K**, Nattamai KJ, Kumar RS, Karns R, Wikenheiser-Brokamp KA, Sampson LL, Mahe MM, Sundaram N, Yacyshyn MB, Yacyshyn B, Helmrath MA, Zheng Y, Geiger H. Canonical Wnt Signaling Ameliorates Aging of Intestinal Stem Cells. *Cell Rep* 2017; **18**: 2608-2621 [PMID: 28297666 DOI: 10.1016/j.celrep.2017.02.056]

24 **Sato T**, Vries RG, Snippert HJ, van de Wetering M, Barker N, Stange DE, van Es JH, Abo A, Kujala P, Peters PJ, Clevers H. Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. *Nature* 2009; **459**: 262-265 [PMID: 19329995 DOI: 10.1038/nature07935]

25 **Sano M**, Suzuki M, Homma K, Hayashida K, Tamura T, Matsuoka T, Katsumata Y, Onuki S, Sasaki J. Promising novel therapy with hydrogen gas for emergency and critical care medicine. *Acute Med Surg* 2018; **5**: 113-118 [PMID: 29657720 DOI: 10.1002/ams2.320]

26 **Shirakawa K**, Kobayashi E, Ichihara G, Kitakata H, Katsumata Y, Sugai K, Hakamata Y, Sano M. $H_2$ Inhibits the Formation of Neutrophil Extracellular Traps. *JACC Basic Transl Sci* 2022; **7**: 146-161 [PMID: 35257042 DOI: 10.1016/j.jacbts.2021.11.005]

27 **Morris O**, Jasper H. Reactive Oxygen Species in intestinal stem cell metabolism, fate and function. *Free Radic Biol Med* 2021; **166**: 140-146 [PMID: 33600942 DOI: 10.1016/j.freeradbiomed.2021.02.015]

28 **Grover PK**, Hardingham JE, Cummins AG. Stem cell marker olfactomedin 4: critical appraisal of its characteristics and role in tumorigenesis. *Cancer Metastasis Rev* 2010; **29**: 761-775 [PMID: 20878207 DOI: 10.1007/s10555-010-9262-z]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 December 27; 14(12): 1340-1349

DOI: 10.4240/wjgs.v14.i12.1340

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Microbial spectrum and drug resistance of pathogens cultured from gallbladder bile specimens of patients with cholelithiasis: A single-center retrospective study

Xiao-Ming Huang, Zong-Jin Zhang, Nan-Rong Zhang, Jian-Dong Yu, Xiang-Jun Qian, Xian-Hua Zhuo, Jia-Yu Huang, Wei-Dong Pan, Yun-Le Wan

**Specialty type:** Infectious diseases

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Janvilisri T, Thailand; Sahle Z, Ethiopia

**Received:** August 28, 2022
**Peer-review started:** August 28, 2022
**First decision:** September 12, 2022
**Revised:** September 26, 2022
**Accepted:** November 20, 2022
**Article in press:** November 20, 2022
**Published online:** December 27, 2022

**Xiao-Ming Huang, Xiang-Jun Qian, Wei-Dong Pan,** Department of Pancreatic-Hepato-Biliary-Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou 510655, Guangdong Province, China

**Xiao-Ming Huang, Zong-Jin Zhang, Jian-Dong Yu, Xiang-Jun Qian, Wei-Dong Pan, Yun-Le Wan,** Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Diseases, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou 510655, Guangdong Province, China

**Zong-Jin Zhang,** Department of Colorectal Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou 510655, Guangdong Province, China

**Nan-Rong Zhang,** Department of Anesthesiology, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou 510655, Guangdong Province, China

**Jian-Dong Yu, Yun-Le Wan,** Department of Hepatobiliary Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou 510655, Guangdong Province, China

**Xian-Hua Zhuo,** Department of Otorhinolaryngology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou 510520, Guangdong Province, China

**Jia-Yu Huang,** Department of Urology, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou 510655, Guangdong Province, China

**Corresponding author:** Yun-Le Wan, MD, PhD, Department of Hepatobiliary Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, No. 26 Yuancun Erheng Road, Guangzhou 510655, Guangdong Province, China. wanyunle@mail.sysu.edu.cn

## Abstract

*BACKGROUND*

Bacterial infection is an important cause of cholelithiasis or gallstones and interferes with its treatment. There is no consensus on bile microbial culture profiles in previous studies, and identified microbial spectrum and drug resistance is helpful for targeted preventive and therapeutic drugs in the perioperative period.

***AIM***

To analyze the bile microbial spectrum of patients with cholelithiasis and the drug susceptibility patterns in order to establish an empirical antibiotic treatment for cholelithiasis-associated infection.

***METHODS***

A retrospective single-center study was conducted on patients diagnosed with cholelithiasis between May 2013 and December 2018.

***RESULTS***

This study included 185 patients, of whom 163 (88.1%) were diagnosed with gallstones and 22 (11.9%) were diagnosed with gallstones and common bile duct stones (CBDSs). Bile culture in 38 cases (20.5%) was positive. The presence of CBDSs (OR = 5.4, 95%CI: 1.3-21.9, $P$ = 0.03) and longer operation time (> 80 min) (OR = 4.3, 95%CI: 1.4-13.1, $P$ = 0.01) were identified as independent risk factors for positive bile culture. Gram-negative bacteria were detected in 28 positive bile specimens, and *Escherichia coli* (*E. coli*) (19/28) and *Klebsiella pneumoniae* (5/28) were the most frequently identified species. Gram-positive bacteria were present in 10 specimens. The resistance rate to cephalosporin in *E. coli* was above 42% and varied across generations. All the isolated *E. coli* strains were sensitive to carbapenems, with the exception of one imipenem-resistant strain. *K. pneumoniae* showed a similar resistance spectrum to *E. coli*. *Enterococcus* spp. was largely sensitive to glycopeptides and penicillin, except for a few strains of *E. faecium*.

***CONCLUSION***

The presence of common bile duct stones and longer operation time were identified as independent risk factors for positive bile culture in patients with cholelithiasis. The most commonly detected bacterium was *E. coli*. The combination of β-lactam antibiotics and β-lactamase inhibitors prescribed perioperatively appears to be effective against bile pathogens and is recommended. Additionally, regular monitoring of emerging resistance patterns is required in the future.

**Key Words:** Bacterial infection; Drug resistance; Cholelithiasis; Gallbladder bile culture



**Core Tip:** In this work, we analyzed the microbial spectrum of the bile of cholelithiasis patients, and their drug susceptibility pattern. We found that the presence of common bile duct stones and longer operative duration were independent risk factors for positive bile culture for patients complicated with cholelithiasis. The most commonly detected bacterium was *Escherichia coli*. In addition, the combination of β-lactam antibiotics and β-lactamase inhibitors prescribed perioperatively appears to be effective against bile pathogens secondary to carbapenems or glycopeptides and is recommended, but its resistance should also be noted.

**Citation:** Huang XM, Zhang ZJ, Zhang NR, Yu JD, Qian XJ, Zhuo XH, Huang JY, Pan WD, Wan YL. Microbial spectrum and drug resistance of pathogens cultured from gallbladder bile specimens of patients with cholelithiasis: A single-center retrospective study. *World J Gastrointest Surg* 2022; 14(12): 1340-1349

**URL:** https://www.wjgnet.com/1948-9366/full/v14/i12/1340.htm

**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i12.1340

## INTRODUCTION

Bacteria can easily enter the biliary system from the duodenum; however, continuous bile secretion in the biliary system prevents their growth and colonization. Despite this, the presence of bacteria in bile has been reported in 9.5%-54.0% of patients with cholelithiasis or gallstones[1-3], and up to 70.2%-78.0% of patients with common bile duct stones (CBDSs)[4,5]. As the presence of bacteria in the biliary tract may increase the risk of postoperative septic complications[6-8], it is essential to identify the risk factors for positive bile culture during cholecystectomy and, accordingly, design a suitable antibiotic prophylaxis regimen[6,8].

The indiscriminate use of antibiotics in the last few decades has led to the emergence of multidrug-resistant (MDR) pathogenic bacteria[9], which have also been isolated from bile specimens[10]. Such

MDR microbes reduce the efficacy of empirical drugs[11,12]. Therefore, it is essential to identify the species of pathogenic bacteria found in the bile of cholelithiasis patients, as well as their drug susceptibility profile, in order to develop effective antibiotic regimens for biliary tract infections. To this end, we analyzed the distribution and drug resistance patterns of pathogens isolated from bile samples obtained from patients with cholelithiasis on the basis of bile culture and drug susceptibility test results.

## MATERIALS AND METHODS

### Study population

This study included patients with bile culture results who underwent cholecystectomy with or without common bile duct exploration, stone extraction, and T tube drainage between May 2013 and December 2018 at the Department of Hepatobiliary Surgery at The Sixth Affiliated Hospital of Sun Yat-sen University. The indications for surgical treatment were cholelithiasis and its complications. Most patients had presented with right upper abdominal pain or other discomfort at the time of admission. In all the included patients, a gallstone with acute or chronic cholecystitis was preoperatively diagnosed based on abdominal ultrasound and computed tomography (CT) imaging and confirmed after cholecystectomy. Each surgical procedure was performed by a professional hepatobiliary surgical team. Access to clinical data was approved by the Institutional Review Board of the Sixth Affiliated Hospital of Sun Yat-sen University (2022ZSLYEC-352).

### Inclusion and exclusion criteria

Inclusion criteria were patients aged ≥ 18 years, who underwent cholecystectomy indicated by cholelithiasis and its complications. All included patients had complete clinicopathological and bile culture results. Exclusion criteria were cholecystectomy indicated by other reasons ($n$ = 12), lack of bacterial culture results ($n$ = 64), and contaminated bile culture sample ($n$ = 2). Demographic characteristics, microbial spectrum and drug resistance of pathogens in patients were assessed. A total of 185 patients were included, and the clinicopathological and microbiological data were retrospectively collected from the medical record system. The research flow chart is outlined in Figure 1.

### Bile culture, identification of bacteria, and drug sensitivity tests

Bile samples (5 μL) were extracted during cholecystectomy and promptly transported in sterile containers to a microbiology laboratory for bacterial culture as per standard protocols. Bacterial identification and drug susceptibility tests were performed using the French Bio-Merieux ATB-Expression Automatic Bacterial Identification and Drug Susceptibility Test instrument. The results were evaluated according to the 2010 recommendations of the American Society for Clinical Laboratory Standardization.

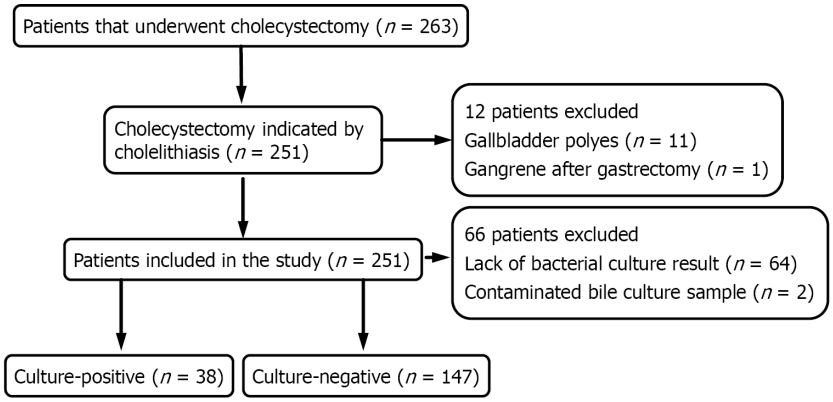
### Statistical analysis

Data analysis was performed using SPSS 24.0 for Windows (SPSS Inc., Chicago, IL, United States). Continuous variables that followed Gaussian distribution were expressed as mean ± SD, and those with non-normal distribution were expressed as the median with interquartile range. Categorical variables were described using frequencies. Data were compared using the two-tailed student $t$-test, chi-square test, Fisher's exact test, or Mann-Whitney $U$-test, as appropriate. Significant covariates identified by univariate analysis were further analyzed by multivariate logistic regression analysis to determine the independent risk factors for positive bile culture. A $P$ value < 0.05 was considered to indicate statistical significance.

## RESULTS

### Patient characteristics

Out of a total of 285 patients who underwent cholecystectomy between May 2013 and December 2018, 185 fulfilled the inclusion criteria and were included in this study. The cohort comprised 80 (43.2%) male and 105 (56.8%) female patients, and their mean age was 54.3 years (SD = 15). Twenty-two patients were diagnosed with gallstones accompanied by CBDSs, and bile cultures were positive for 17 (77.3%) of these patients. In contrast, only 12.9% (21/163) of the patients who did not have CBDSs had bacterial colonization in their bile samples. In addition, 155 (83.8%) patients had right upper abdominal discomfort. Laparoscopic cholecystectomy is the most common procedure used for removing gallstones, but four patients with calculous cholecystitis underwent open surgery due to severe adhesions. In addition, one patient with CBDSs underwent complete laparoscopic surgery. The median operative time was 80 (59-120) min, and cefotaxime/sulbactam sodium and cefamandole were the main preventive or therapeutic antibiotics used preoperatively. The overall rate of septic complications was 5.4% (10/185), and the incidence of septic complications was similar in the culture-positive and culture-negative




**DOI:** 10.4240/wjgs.v14.i12.1340 

**Figure 1 Flowchart of the patient selection process.**

patients [4.1% (6/147) *vs* 10.5% (4/38)]. The detailed demographic characteristics of both groups are summarized in Table 1, and they show significant differences in age, BMI, presence of CBDSs, previous endoscopic retrograde cholangiopancreatography (ERCP), previous use of antibiotics, presence of multiple stones, open surgery, operation time, and preoperative therapeutic antibiotics. Multivariate logistic regression analysis of these significant variables indicated that the presence of CBDSs (OR = 5.4, 95%CI: 1.8-21.9, $P$ = 0.029) and longer operation time (OR = 4.3, 95%CI: 1.4-13.1, $P$ = 0.01) were independent risk factors for bacterial colonization of bile samples (Table 2).

### *Microbial spectrum of bile specimens*

Of the 38 (20.5%) patients with positive bile culture results, 28 (73.7%) harbored gram-negative bacteria that were predominantly from the family *Enterobacteriaceae*, including *Escherichia coli* (19 cases), *Klebsiella pneumoniae* (5 cases), *Enterobacter cloacae* (2 cases), *Enterobacter aerogenes* (1 case), and *Enterobacter mirabilis* (1 case). Gram-positive bacteria were detected in 10 (26.3%) patient samples and included *Enterococcus faecalis* (6 cases), *Enterococcus faecium* (3 cases), and *Staphylococcus aureus* (1 case) as the predominant species. No fungal species were detected, as shown in Table 3.

### *Antibiotics susceptibility test results*

Based on the antibiotics susceptibility test results, the pathogens were divided into sensitive, intermediate resistant, and resistant groups, and pathogens assigned to the latter two groups were included in the resistance rate analysis. Due to differences in test strips, the results of the susceptibility tests differed across the patients. The resistance rate of *E. coli* against cephalosporins decreased with more advanced generations, and the rates were 68.4%, 57.9%, 52.6%, and 47.3% for cefuroxime, cefotaxime, ceftazidime, and cefepime, respectively. The resistance rate against ciprofloxacin was similar to that against cefoxitin (42.1%). *E. coli* also displayed a high level of resistance against broad-spectrum penicillins, that is, 78.9% and 63.2% against ticarcillin and piperacillin, respectively. Furthermore, *E. coli* exhibited a resistance rate of 83.3% against amoxicillin in 12 of the specimens tested. The combination of piperacillin and the $\beta$-lactamase inhibitor tazobactam was effective against *E. coli*, as it was associated with a low resistance rate of 15.8%. In addition, almost all the isolated bacteria were sensitive to carbapenems, with the exception of one that was resistant to imipenem. *K. pneumoniae* showed a similar resistance spectrum to *E. coli*, except that it had lower resistance against amikacin and ciprofloxacin. *Enterococcus* spp. exhibited a high resistance rate of 88.9% against aminoglycosides (gentamicin and streptomycin), while *E. faecalis* exhibited 100% sensitivity to glycopeptide. In contrast, several strains of *E. faecium* were resistant to glycopeptides (1/3) and penicillins (2/3). The results are summarized in Tables 4 and 5. Finally, 24 of the 38 patients harbored MDR strains, with 10 (52.6%) *E. coli* strains and 1 (20%) *K. pneumoniae* strain producing extended spectrum β-lactamases (ESBLs).

## DISCUSSION

The gallbladder is a sterile organ, but pathological conditions, such as gallstones, polyps, and tumors, create favorable conditions for bacterial colonization by blocking bile circulation, which results in cholestasis[5,13]. Bacterial colonization can lead to inflammation of the biliary tract and even sepsis in severe cases. The main sources of biliary tract infection are the blood and duodenum[10]. In our study, bacteria were detected in the bile specimens of 20.5% cholelithiasis patients, and *Enterobacteriaceae* (73.7%; mainly *E. coli* and *K. pneumoniae*) and *Enterococcus* spp. (23.7%; *E. faecium* and *E. faecalis*) were the dominant species. Consistent with previous studies, most of the bacteria detected here were

**Table 1 Baseline characteristics of the bile culture-positive group and culture-negative group**

| Parameter | Total | Culture-negative | Culture-positive | *P* value |
|---|---|---|---|---|
| Number | 185 | 147 | 38 | - |
| Age (yr; mean ± SD) | 54.3 ± 15.0 | 52.4 ± 14.7 | 61.3 ± 14.2 | 0.001 |
| BMI (kg/m$^2$; mean ± SD) | 23.1 ± 3.4 | 23.4 ± 3.2 | 22.1 ± 3.8 | 0.040 |
| Male (%) | 80 (43.2) | 61 (33.0) | 19 (10.3) | 0.346 |
| Combined with CBDS (%) | 22 (11.9) | 5 (2.7) | 17 (9.2) | < 0.001 |
| Right upper abdominal pain (%) | 155 (83.8) | 120 (64.9) | 35 (18.9) | 0.118 |
| Positive Murphy sign (%) | 27 (14.6) | 24 (13.0) | 3 (1.6) | 0.189 |
| Diabetes mellitus (%) | 11 (5.9) | 8 (4.3) | 3 (1.6) | 0.699 |
| Hypertension (%) | 41 (22.2) | 32 (17.3) | 9 (4.9) | 0.800 |
| History of ERCP (%) | 7 (3.7) | 1 (0.5) | 6 (3.2) | < 0.001 |
| Previous intake of antibiotics (%) | 44 (23.8) | 29 (15.7) | 15 (8.1) | 0.011 |
| WBC count (> 10 × 10$^9$/L) | 16 (8.6) | 11 (5.9) | 5 (2.7) | 0.267 |
| Multiple stones (%) | 132 (71.3) | 99 (53.5) | 33 (17.8) | 0.018 |
| Max diameter of stone (cm; mean ± SD) | 1.2 ± 0.8 | 1.1 ± 0.8 | 1.3 ± 0.7 | 0.177 |
| Non-laparoscopic surgery (%) | 41 (22.2) | 19 (10.3) | 22 (11.9) | < 0.001 |
| Operative time (min), median (IQR) | 80 (59-120) | 70 (56.5-93.8) | 124 (95.0-188.8) | < 0.001 |
| Septic complications (%) | 10 (5.4) | 6 (3.2) | 4 (2.2) | 0.125 |

CBDS: Common bile duct stone; ERCP: Endoscopic retrograde cholangiopancreatography; BMI: Body mass index; WBC: White blood cell.

**Table 2 Multivariate analysis results of risk factors for positive bile culture**

| Variables | OR (95%CI) | *P* |
|---|---|---|
| Operation time > 80 min | 4.3 (1.4-13.1) | 0.01 |
| Combined with CBDS | 5.4 (1.3-21.9) | 0.02 |

95%CI: 95% confidence interval; OR: Odds ratio; CBDS: Common bile duct stone.

endogenous and of intestinal origin[12,14,15]. Unlike other studies, however, we did not detect *Pseudomonas aeruginosa* or any fungal species[15,16]; this could probably be explained by our limited sample size.

The risk of bacterial invasion of the bile is associated with biliary obstruction, older age (> 70 years), acute cholecystitis, CBDSs, cholangitis, ERCP before cholecystectomy, and dysfunctional gallbladder[8,15,17]. In our study, the presence of CBDSs and longer operation time were identified as independent risk factors for positive bile culture. In the case of positive bile culture, postoperative antibiotic use needs to be adjusted in order to minimize the risk of infection after surgery. Studies have shown a higher incidence of postoperative septic complications in patients with positive bile culture than in those without bile infection[6,8,18], with the overall rates varying from 0.9% to 20.0%[6,8,19]. In contrast to these studies, in the present study, the rate of septic complications was 3.2% in the negative culture group and 2.2% in the positive culture group. This indicates that there was no significant correlation between the presence of bacteria and biliary sepsis. The differences in the findings may be associated with the empirical use of cefotaxime/sulbactam sodium and the smaller sample size in our cohort.

According to the definition of MDR proposed by the European Centre for Disease Prevention and Control Advisory Forum in 2010, it is described as resistance to one agent of at least three or more classes of antibiotics, but it does not cover intrinsic resistance or resistance against a key antimicrobial agent[9]. In the present study, although the antibiotic sensitivity tests did not include all the relevant antibiotics, the lowest incidence of MDR was 63.2%, which indicates that the rate of MDR is high in pathogens that infect bile. Cephalosporins and quinolones are commonly used to treat biliary tract infections, and the concentration of these drugs increases in bile after their absorption and metabolism [20,21]. However, as a result of the emergence of drug-resistant bacteria, the efficacy of conventional

**Table 3 Composition of bile isolated bacteria**

| Isolated microbes | Total strains | Frequency |
|---|---|---|
| Gram-negative | 28 | 73.7% |
| *Escherichia coli* | 19 | 50.0% |
| *Klebsiella pneumoniae* | 5 | 13.2% |
| *Enterobacter cloacae* | 2 | 5.3% |
| *Enterobacter aerogenes* | 1 | 2.6% |
| *Enterobacter mirabilis* | 1 | 2.6% |
| Gram-positive | 10 | 26.3% |
| *Enterococcus faecalis* | 6 | 15.8% |
| *Enterococcus faecium* | 3 | 7.9% |
| *Staphylococcus aureus* | 1 | 2.6% |
| Fungus | 0 | 0 |

**Table 4 Antibiotics susceptibility test results for *Enterococcus spp***

| | *Enterococcus faecalis* (6) | | *Enterococcus faecium* (3) | |
|---|---|---|---|---|
| Antimicrobial agents | AST | Resistance (%) | AST | Resistance (%) |
| Gentamicin | 1S + 5I | 5 (83.3) | 3I | 3 (100) |
| Streptomycin | 1S + 4I + 1R | 5 (83.3) | 2I + 1R | 3 (100) |
| Ciprofloxacin | 3S + 3I | 3 (50) | 2S + 1R | 1 (33.3) |
| Levofloxacin | 5S + 1I | 1 (16.7) | 2S + 1R | 1 (33.3) |
| Vancomycin | 6S | 0 | 2S + 1I | 1 (33.3) |
| Teicoplanin | 6S | 0 | 3S | 0 |
| Ampicillin | 6S | 0 | 1S + 1I + 1R | 2 (66.7) |
| Penicillin | 6S | 0 | 1S + 2R | 2 (66.7) |
| Quinupristin-dalfopristin | 1S + 5R | 5 (83.3) | 2S + 1I | 1 (33.3) |
| Tetracycline | 3S + 3R | 3 (50) | 2S + 1R | 1 (33.3) |
| Rifampin | 1S + 1I + 4R | 5 (83.3) | 2S + 1R | 1 (33.3) |
| Erythromycin | 4I + 2R | 6 (100) | 1S + 2R | 2 (66.7) |

AST: Aspartate aminotransferase.

antibacterial drugs has begun to decline[9,10]. In this study, the gram-negative bacteria showed nearly 100% sensitivity to meropenem and imipenem, while 40% of the strains were resistant to cephalosporins and quinolones and over 50% were resistant to second- or third-generation cephalosporins. This high rate of resistance is mainly attributed to the emergence of ESBL-producing bacteria, which accounted for 52.6% of the *E. coli* strains isolated from our cohort. Therefore, the empirical treatment of biliary infections should take into account ESBL-producing bacteria. Treatment with multiple drug combinations, including β-lactamase inhibitors, has been highly effective against gram-negative bacilli[21-23]. This was confirmed by the high sensitivity of *E. coli* to piperacillin and tazobactam in the present study; however, *E. coli* exhibits a fairly high resistance rate against ticarcillin/clavulanic acid or amoxicillin/clavulanic acid. Aminoglycosides are also used to treat biliary infections[20], and the resistance rates of *E. coli* against gentamicin and amikacin were found to be 36.8% and 15.8%, respectively.

MDR *Enterococcus* spp. has been increasingly detected in recent years, and these species exhibit intrinsic resistance to most cephalosporins and carbapenems[9,24]. The overall prevalence of vancomycin-resistant *Enterococcus*, one of the major nosocomial pathogens worldwide[25], is 5%-20% [25,26]. In this study, *Enterococcus* spp., especially *E. faecalis*, were highly sensitive to ampicillin and penicillin. Interestingly, while only 14.7% of *E. faecalis* strains isolated in Japan are resistant to *β*-lactam

**Table 5 Antibiotics susceptibility test results for *Enterobacteriaceae***

| Antimicrobial agents | *Escherichia coli* (*n* = 19) | | *Klebsiella pneumoniae* (5) | | *Enterobacter cloacae* (2) | *Enterobacter aerogenes* (1) | *Enterobacter mirabilis* (1) |
|---|---|---|---|---|---|---|---|
| | AST | Resistance (%) | AST | Resistance (%) | AST | AST | AST |
| Amikacin | 16S + 3R | 3 (15.8) | 5S | 0 | 2S | 1S | 1S |
| Gentamicin | 12S + 7R | 7 (36.8) | 4S + 1R | 1 (20) | 2S | 1S | 1S |
| Amoxicillin | 2S + 10R | - | 5R | 5 (100) | 1R | 1R | - |
| Amoxicillin/clavulanic acid | 11S + 3I + 5R | 8 (42.1) | 3S + 1I + 1R | 2 (40) | 1R | 1I | 1S |
| Ticarcillin | 4S + 15R | 15 (78.9) | 5R | 5 (100) | 2S | 1S | 1S |
| Ticarcillin/clavulanic acid | 4S + 8R | - | 3S + 1R | - | 1S + 1R | 1S | 1S |
| Piperacillin | 7S + 12R | 12 (63.2) | 1S + 3I + 1R | 4 (80) | 2S | 1S | 1S |
| Piperacillin/tazobactam | 16S + 3R | 3 (15.8) | 5S | 0 | 2S | 1S | 1S |
| Cefazolin-1$^{st}$ | 1S + 5R | - | 1R | - | - | - | 1R |
| Cefoxitin | 11S + 8R | 8 (42.1) | 3S + 2R | 2 (40) | 1R | 1R | 1R |
| Cefuroxime-2$^{nd}$ | 6S + 13R | 13 (68.4) | 2S + 3R | 3 (60) | 2S | 1R | 1S |
| Cefotaxime-3$^{rd}$ | 8S + 1I + 10R | 11 (57.9) | 4S + 1I | 1 (25) | 2S | 1S | 1S |
| Ceftazidime-3$^{rd}$ | 9S + 10R | 10 (52.6) | 4S + 1R | 1 (25) | 2S | 1S | 1R |
| Cefepime-4$^{th}$ | 10S + 1I + 8R | 9 (47.3) | 4S + 1R | 1 (25) | 2S | 1S | 1S |
| ESBLs ( + ) | 10 | 10 (52.6) | 1 | - | - | - | - |
| Ciprofloxacin | 11S + 8R | 8 (42.1) | 4S + 1R | 1 (20) | 2S | 1R | 1I |
| Imipenem | 18S + 1R | 1 (5.3) | 5S | 0 | 2S | 1S | 1R |
| Meropenem | 19S | 0 | 5S | 0 | 2S | 1S | 1S |

AST: Aspartate aminotransferase; ESBLs: Extended spectrum β-lactamases.

antibiotics, 85.7% of the *E. faecium* strains are resistant to ampicillin and all strains of both species are resistant to penicillin[26]. In addition, *Enterococcus* spp. were found to be highly resistant to aminoglycosides and sensitive to teicoplanin, and only one vancomycin-resistant *Enterococcus* strain was detected in our study. All these results indicate that the antibiotic regimen against biliary infections should be based on both the antibacterial spectrum of the drugs and the resistance patterns. Therefore, clinicians should routinely test bile samples collected during cholecystectomy in order to monitor the pathogenic species and drug susceptibility. This will not only provide a definite guide for postoperative treatment, but also provide data for future empirical use of antimicrobial agents.

This single-center retrospective study is based on data from hospital medical records, and several limitations should be noted. This study is limited by its retrospective design, that is, a heterogeneous population and the possibility of a type II error. In particular, owing to the small number of patients included, further studies are required to validate our findings.

## CONCLUSION

The risk of biliary infection increases in patients with cholelithiasis, and the risk is higher in patients with CBDSs and longer operation time. The dominant pathogens detected in this study were *E. coli*, *K. pneumoniae*, *E. faecium*, and *E. faecalis*. In addition, the combination of *β*-lactam antibiotics and *β*-lactamase inhibitors was found to be an effective first-line treatment against bile pathogens. However, we must also be aware of the emergence of resistance to certain types of drugs.

## ARTICLE HIGHLIGHTS

### *Research background*

Bacterial infection is an important cause of cholelithiasis or gallstones and interferes with its treatment.

### *Research motivation*

Identified microbial spectrum and drug resistance of pathogens cultured from gallbladder bile specimens is helpful for targeted preventive and therapeutic drugs in the perioperative period.

### *Research objectives*

Investigate the bile microbial spectrum of patients with cholelithiasis and the drug susceptibility patterns in order to establish an empirical antibiotic treatment for cholelithiasis-associated infection.

### *Research methods*

A retrospective single-center study was conducted on patients diagnosed with cholelithiasis between May 2013 and December 2018.

### *Research results*

The presence of common bile duct stones (OR = 5.4, 95%CI: 1.3-21.9, $P$ = 0.03) and longer operation time (> 80 min) (OR = 4.3, 95%CI: 1.4-13.1, $P$ = 0.01) were identified as independent risk factors for positive bile culture. Gram-negative bacteria were detected in 28 positive bile specimens, and *Escherichia coli* (*E. coli*) (19/28) and *Klebsiella pneumoniae* (5/28) were the most frequently identified species. Gram-positive bacteria were present in 10 specimens. All the isolated *E. coli* strains were sensitive to carbapenems, with the exception of one imipenem-resistant strain. *K. pneumoniae* showed a similar resistance spectrum to *E. coli*. *Enterococcus* spp. was largely sensitive to glycopeptides and penicillin, except for a few strains of *E. faecium*.

### *Research conclusions*

The presence of common bile duct stones and longer operation time were identified as independent risk factors for positive bile culture in patients with cholelithiasis. The most commonly detected bacterium was *E. coli*. The combination of β-lactam antibiotics and β-lactamase inhibitors prescribed perioperatively appears to be effective against bile pathogens and is recommended.

### *Research perspectives*

To explore the characteristics of patients infected with drug-resistant bacteria and the prevention and treatment of drug-resistant bacteria.

## FOOTNOTES

**Author contributions:** Huang XM, Zhang ZJ, and Zhang NR contributed equally to this study; Huang XM, Zhang ZJ, and Zhang NR contributed to study design, patient inclusion and exclusion, data collection, data analysis and interpretation, and manuscript writing; Yu JD, Qian XJ, Zhuo XH, and Huang JY contributed to data collection; Pan WD and Wan YL contributed equally to the work; Pan WD and Wan YL contributed to critical revision of the manuscript for important intellectual content and study supervision; all authors read and approved the final manuscript.

**Institutional review board statement:** The study was reviewed and approved by the Institutional Review Board of the Sixth Affiliated Hospital of Sun Yat-sen University (Approval No. 2022ZSLYEC-352).

**Informed consent statement:** The informed consent was waived in these patients.

**Conflict-of-interest statement:** There are no conflicts of interest to report.

**Data sharing statement:** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.



**Country/Territory of origin:** China

**ORCID number:** Nan-Rong Zhang 0000-0002-2998-0722; Yun-Le Wan 0000-0003-2098-218X.

**S-Editor:** Chen YL
**L-Editor:** Webster JR
**P-Editor:** Chen YL

## REFERENCES

1 **Pokharel N**, Rodrigues G, Shenoy G. Evaluation of septic complications in patients undergoing biliary surgery for gall stones in a tertiary care teaching hospital of South India. *Kathmandu Univ Med J (KUMJ)* 2007; **5**: 371-373 [PMID: 18604056]
2 **Abeysuriya V**, Deen KI, Wijesuriya T, Salgado SS. Microbiology of gallbladder bile in uncomplicated symptomatic cholelithiasis. *Hepatobiliary Pancreat Dis Int* 2008; **7**: 633-637 [PMID: 19073410]
3 **Mir MA**, Malik UY, Wani H, Bali BS. Prevalence, pattern, sensitivity and resistance to antibiotics of different bacteria isolated from port site infection in low risk patients after elective laparoscopic cholecystectomy for symptomatic cholelithiasis at tertiary care hospital of Kashmir. *Int Wound J* 2013; **10**: 110-113 [PMID: 22414004 DOI: 10.1111/j.1742-481X.2012.00963.x]
4 **Karpel E**, Madej A, Bułdak Ł, Duława-Bułdak A, Nowakowska-Duława E, Łabuzek K, Haberka M, Stojko R, Okopień B. Bile bacterial flora and its *in vitro* resistance pattern in patients with acute cholangitis resulting from choledocholithiasis. *Scand J Gastroenterol* 2011; **46**: 925-930 [PMID: 21504380 DOI: 10.3109/00365521.2011.560676]
5 **Salvador VB**, Lozada MC, Consunji RJ. Microbiology and antibiotic susceptibility of organisms in bile cultures from patients with and without cholangitis at an Asian academic medical center. *Surg Infect (Larchmt)* 2011; **12**: 105-111 [PMID: 21348769 DOI: 10.1089/sur.2010.005]
6 **Galili O**, Eldar S Jr, Matter I, Madi H, Brodsky A, Galis I, Eldar S Sr. The effect of bactibilia on the course and outcome of laparoscopic cholecystectomy. *Eur J Clin Microbiol Infect Dis* 2008; **27**: 797-803 [PMID: 18369670 DOI: 10.1007/s10096-008-0504-8]
7 **Velázquez-Mendoza JD**, Alvarez-Mora M, Velázquez-Morales CA, Anaya-Prado R. Bactibilia and surgical site infection after open cholecystectomy. *Cir Cir* 2010; **78**: 239-243 [PMID: 20642907]
8 **Morris-Stiff GJ**, O'Donohue P, Ogunbiyi S, Sheridan WG. Microbiological assessment of bile during cholecystectomy: is all bile infected? *HPB (Oxford)* 2007; **9**: 225-228 [PMID: 18333227 DOI: 10.1080/13651820701275105]
9 **Magiorakos AP**, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; **18**: 268-281 [PMID: 21793988 DOI: 10.1111/j.1469-0691.2011.03570.x]
10 **Maseda E**, Maggi G, Gomez-Gil R, Ruiz G, Madero R, Garcia-Perea A, Aguilar L, Gilsanz F, Rodriguez-Baño J. Prevalence of and risk factors for biliary carriage of bacteria showing worrisome and unexpected resistance traits. *J Clin Microbiol* 2013; **51**: 518-521 [PMID: 23196362 DOI: 10.1128/JCM.02469-12]
11 **Kanafani ZA**, Khalifé N, Kanj SS, Araj GF, Khalifeh M, Sharara AI. Antibiotic use in acute cholecystitis: practice patterns in the absence of evidence-based guidelines. *J Infect* 2005; **51**: 128-134 [PMID: 16038763 DOI: 10.1016/j.jinf.2004.11.007]
12 **Suna N**, Yıldız H, Yüksel M, Parlak E, Dişibeyaz S, Odemiş B, Aydınlı O, Bilge Z, Torun S, Tezer Tekçe AY, Taşkıran I, Saşmaz N. The change in microorganisms reproducing in bile and blood culture and antibiotic susceptibility over the years. *Turk J Gastroenterol* 2014; **25**: 284-290 [PMID: 25141317 DOI: 10.5152/tjg.2014.6253]
13 **Kaya M**, Beştaş R, Bacalan F, Bacaksız F, Arslan EG, Kaplan MA. Microbial profile and antibiotic sensitivity pattern in bile cultures from endoscopic retrograde cholangiography patients. *World J Gastroenterol* 2012; **18**: 3585-3589 [PMID: 22826624 DOI: 10.3748/wjg.v18.i27.3585]
14 **Zhao J**, Wang Q, Zhang J. Changes in Microbial Profiles and Antibiotic Resistance Patterns in Patients with Biliary Tract Infection over a Six-Year Period. *Surg Infect (Larchmt)* 2019; **20**: 480-485 [PMID: 31017560 DOI: 10.1089/sur.2019.041]
15 **Yun SP**, Seo HI. Clinical aspects of bile culture in patients undergoing laparoscopic cholecystectomy. *Medicine (Baltimore)* 2018; **97**: e11234 [PMID: 29952986 DOI: 10.1097/MD.0000000000011234]
16 **Darkahi B**, Sandblom G, Liljeholm H, Videhult P, Melhus Å, Rasmussen IC. Biliary microflora in patients undergoing cholecystectomy. *Surg Infect (Larchmt)* 2014; **15**: 262-265 [PMID: 24801654 DOI: 10.1089/sur.2012.125]
17 **Landau O**, Kott I, Deutsch AA, Stelman E, Reiss R. Multifactorial analysis of septic bile and septic complications in biliary surgery. *World J Surg* 1992; **16**: 962-4; discussion 964 [PMID: 1462638 DOI: 10.1007/BF02067003]
18 **Nomura T**, Shirai Y, Hatakeyama K. Impact of bactibilia on the development of postoperative abdominal septic complications in patients with malignant biliary obstruction. *Int Surg* 1999; **84**: 204-208 [PMID: 10533777]
19 **Spaziani E**, Picchio M, Di Filippo A, Greco E, Cerioli A, Maragoni M, Faccì G, Lucarelli P, Marino G, Stagnitti F, Narilli P. Antibiotic prophylaxis in elective laparoscopic cholecystectomy is useless. A prospective multicenter study. *Ann Ital Chir* 2015; **86**: 228-233 [PMID: 25543880]
20 **Westphal JF**, Brogard JM. Biliary tract infections: a guide to drug treatment. *Drugs* 1999; **57**: 81-91 [PMID: 9951953 DOI: 10.2165/00003495-199957010-00007]
21 **Bassotti G**, Chistolini F, Sietchiping-Nzepa F, De-Roberto G, Morelli A. Empirical antibiotic treatment with piperacillin-tazobactam in patients with microbiologically-documented biliary tract infections. *World J Gastroenterol* 2004; **10**: 2281-2283 [PMID: 15259083 DOI: 10.3748/wjg.v10.i15.2281]
22 **Dervisoglou A**, Tsiodras S, Kanellakopoulou K, Pinis S, Galanakis N, Pierakakis S, Giannakakis P, Liveranou S, Ntasiou

P, Karampali E, Iordanou C, Giamarellou H. The value of chemoprophylaxis against Enterococcus species in elective cholecystectomy: a randomized study of cefuroxime *vs* ampicillin-sulbactam. *Arch Surg* 2006; **141**: 1162-1167 [PMID: 17178957 DOI: 10.1001/archsurg.141.12.1162]

23 **Rodríguez-Baño J**, Navarro MD, Romero L, Muniain MA, de Cueto M, Ríos MJ, Hernández JR, Pascual A. Bacteremia due to extended-spectrum beta -lactamase-producing Escherichia coli in the CTX-M era: a new clinical challenge. *Clin Infect Dis* 2006; **43**: 1407-1414 [PMID: 17083012 DOI: 10.1086/508877]

24 **Treitman AN**, Yarnold PR, Warren J, Noskin GA. Emerging incidence of Enterococcus faecium among hospital isolates (1993 to 2002). *J Clin Microbiol* 2005; **43**: 462-463 [PMID: 15635016 DOI: 10.1128/JCM.43.1.462-463.2005]

25 **Amberpet R**, Sistla S, Parija SC, Rameshkumar R. Risk factors for intestinal colonization with vancomycin resistant enterococci' A prospective study in a level III pediatric intensive care unit. *J Lab Physicians* 2018; **10**: 89-94 [PMID: 29403213 DOI: 10.4103/JLP.JLP_32_17]

26 **Abamecha A**, Wondafrash B, Abdissa A. Antimicrobial resistance profile of Enterococcus species isolated from intestinal tracts of hospitalized patients in Jimma, Ethiopia. *BMC Res Notes* 2015; **8**: 213 [PMID: 26036911 DOI: 10.1186/s13104-015-1200-2]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 December 27; 14(12): 1350-1362

DOI: 10.4240/wjgs.v14.i12.1350

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Low preoperative skeletal muscle index increases the risk of mortality among resectable pancreatic cancer patients: A retrospective study

Zhi-Wei Cai, Jia-Lin Li, Meng Liu, Hong-Wei Wang, Chong-Yi Jiang

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Pandey NM, India; Sato H, Japan

**Received:** September 16, 2022
**Peer-review started:** September 16, 2022
**First decision:** October 20, 2022
**Revised:** October 29, 2022
**Accepted:** December 6, 2022
**Article in press:** December 6, 2022
**Published online:** December 27, 2022

**Zhi-Wei Cai, Meng Liu, Hong-Wei Wang, Chong-Yi Jiang,** Department of General Surgery, Hepato-Biliary-Pancreatic Center, Huadong Hospital, Shanghai 200040, China

**Jia-Lin Li,** Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center, Shanghai 200032, China

**Corresponding author:** Chong-Yi Jiang, MD, Chief Doctor, Department of General Surgery, Hepato-Biliary-Pancreatic Center, Huadong Hospital, West No. 221 Yan'an Road, Shanghai 200040, China. jiangzhongyi9@sina.com

## Abstract

***BACKGROUND***

The only potential curative treatment for patients with pancreatic cancer is surgery; however, the prognosis remains poor. Measures of body composition based on computed tomography (CT) have been established as a reliable predictor of the prognosis of cancer patients after surgery.

***AIM***

To elucidate the associations of body composition measures derived from preoperative CT scans with the prognosis of patients with pancreatic cancer.

***METHODS***

One hundred fifteen patients undergoing pancreatic resection with curative intent for pancreatic cancer were retrospectively enrolled. A preoperative CT scan at the third lumbar vertebral level was performed to measure the skeletal muscle index (SMI), mean skeletal muscle radiodensity, subcutaneous adipose tissue index, and visceral to subcutaneous adipose tissue area ratio. The clinical and pathological data were collected. The effects of these factors on long-term survival were evaluated.

***RESULTS***

Among the five body composition measures, only low SMI independently predicted overall survival (OS) [hazard ratio (HR): 2.307; 95% confidence interval (CI): 1.210-4.402] and recurrence-free survival (HR: 1.907; 95%CI: 1.147-3.171). Furthermore, patients with low SMI (*vs* high SMI) were older (68.8 ± 9.3 years *vs* 63.3 ± 8.4 years); low SMI was present in 27 of 56 patients (48.2%) aged 65 years

and older and in 11 of 59 younger patients (18.6%). In addition, subgroup analyses revealed that the correlation between low SMI and OS was observed only in patients aged 65 years and older.

*CONCLUSION*
Low preoperative SMI was more prevalent in elderly patients and was associated with a poor prognosis among pancreatic cancer patients, especially elderly patients.

**Key Words:** Pancreatic cancer; Body composition; Elderly; Skeletal muscle index; Prognosis



**Core Tip:** Measures of body composition have been regarded as a reliable prognostic predictor for cancer patients after surgery, but further research is needed. In this study, we showed that low preoperative skeletal muscle index (SMI) potentially predicts the prognosis of pancreatic cancer patients. We also revealed that low SMI was more prevalent in elderly patients and was associated with a poor prognosis among elderly patients after pancreatic cancer resection.

**Citation:** Cai ZW, Li JL, Liu M, Wang HW, Jiang CY. Low preoperative skeletal muscle index increases the risk of mortality among resectable pancreatic cancer patients: A retrospective study. *World J Gastrointest Surg* 2022; 14(12): 1350-1362
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i12/1350.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i12.1350

## INTRODUCTION

Pancreatic cancer is among the most aggressive malignancies, representing one of the leading causes of cancer-related deaths worldwide[1,2]. The only potential curative treatment modality for patients with pancreatic cancer currently available is surgery. However, approximately 80% of patients are estimated to present with either unresectable or metastatic disease at the time of the first admission[3]. In addition, the prognosis remains poor even for the small subset of patients with a localized, resectable tumor, with only 20% surviving for 5 years following surgery[4]. In this context, multiple factors, such as the tumor status, administration of adjuvant chemotherapy, and surgical radicality, have been recognized as tumor-related prognostic factors. Therefore, the characterization of these prognostic factors may help stratify patients for better individualized treatment and improve long-term survival outcomes.

According to the literature, body mass index (BMI) calculated from height and weight is a valuable indicator of body size. Recently, the relationship between obesity and pancreatic cancer has been extensively studied[5]. Data derived from clinical trials and meta-analyses have consistently shown that obesity (BMI > 25 kg/m$^2$) is associated with poor survival outcomes, but some studies have reported inconsistent associations with overweight or lower levels of obesity[6-8]. This discrepancy may be explained by the fact that BMI measures the relation of weight to height without assessing individual components of the body, such as muscle and adipose tissue, or components of weight with differing associations with survival.

Currently, a paucity of studies have explored measures of body composition mainly in patients with resectable pancreatic cancer[9-11]. Sarcopenia, an age-dependent decrease in skeletal muscle volume, was initially described in 1989[12]. Based on the recent consensus from the European Working Group on Sarcopenia in Older People and the Asian Working Group for Sarcopenia, computed tomography (CT) imaging at the level of the third lumbar vertebra is an effective imaging modality for the clinical detection of sarcopenia[13,14]. Several previous studies have documented that sarcopenia, which is mainly established by the presence of low muscle quantity and quality, is significantly associated with a poor prognosis for advanced pancreatic cancer patients[15-20].

Furthermore, numerous epidemiological and fundamental studies have provided evidence to support a possible link between obesity and pancreatic cancer[8,21,22]. Measures of body composition reflecting obesity, including visceral obesity [namely, a high visceral adipose tissue index (VATI)] and low skeletal muscle radiodensity (SMD) (a measure of muscle quality indicative of adipose tissue deposition in muscle fibers and reduced function), have been established as useful prognostic indicators[9-11,23]. Sarcopenia was recently identified as an independent prognostic factor, especially for elderly patients with esophageal cancer[24]. However, at present, no similar studies have been performed in patients with resectable pancreatic cancer. Therefore, we examined associations between cancer prognosis and the measures of body composition, including muscle mass, muscle radiodensity, and adiposity, in a retrospective cohort. Specifically, we analyzed the effects of measures of body composition on the

prognosis of patients in different age groups.

## MATERIALS AND METHODS

### Patient selection and data collection

A retrospective review was performed on the records from all patients who underwent pancreatectomy for resectable pancreatic ductal adenocarcinoma (PDAC) at a single institution from January 2015 to December 2019. Patients with abdominal CT scans captured within 1 wk before surgery that were available for analysis were included. Patients who had a history of abdominal surgery were excluded from the study. A total of 115 patients were finally enrolled in this study. Preoperative demographics, body weight, height, and laboratory data, including leukocytes, neutrophils, lymphocytes, platelets, albumin, and carbohydrate antigen 19-9 levels, were obtained from the electronic media database. Systemic inflammatory indicators were defined as follows: neutrophil-lymphocyte ratio (absolute neutrophil count divided by absolute lymphocyte count), platelet-to-lymphocyte ratio (absolute platelet count divided by absolute lymphocyte count), and systemic immune-inflammation index (SIII, platelet count × neutrophil-lymphocyte ratio). Tumor size, tumor location, pathological TNM staging (according to AJCC 8$^{th}$ edition), tumor differentiation grade, presence of perineural invasion, status of the resection margin, lymph node metastasis, and adjuvant chemotherapy were also recorded for analysis. This study was approved by the Institutional Review Board of Huadong Hospital Affiliated to Fudan University.

### CT-based body composition assessment

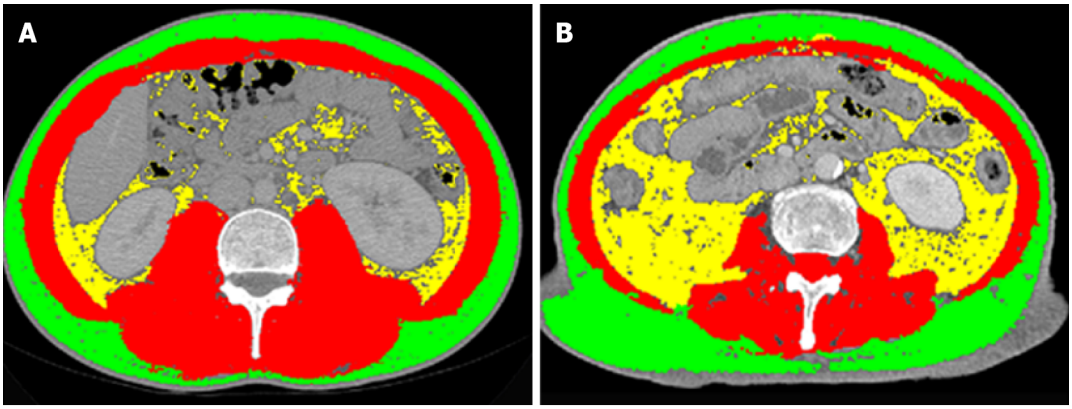
Cross-sectional CT images of the third lumbar vertebra were analyzed using Slice-O-Matic software (v.5. Tomovision, Montreal, Quebec, Canada)[17,25]. In detail, various body composition parameters were measured, including subcutaneous adipose tissue area, visceral adipose tissue area, and skeletal muscle area. The following tissue Hounsfield unit (HU) thresholds were employed: -190 to -30 for subcutaneous adipose tissue, -150 to -50 for visceral adipose tissue, and -29 to 150 for skeletal muscle. As described previously, the body composition evaluation included the subcutaneous adipose tissue index (SATI), VATI, and skeletal muscle index (SMI), which were named and calculated from subcutaneous adipose tissue area, visceral adipose tissue area, and skeletal muscle area divided by height in meters squared ($cm^2/m^2$), respectively[9]. The visceral to subcutaneous adipose tissue area ratio (VSR) was calculated to assess the abdominal adipose tissue distribution, and skeletal muscle radiodensity was measured from the mean CT value (HU) of the whole skeletal muscle area to assess muscle quality. This procedure was performed by two experienced investigators who were blinded to the clinical characteristics of the participants.

### Cutoff values and classification settings

Based on the considerable differences in body composition between sexes, sex-specific cutoff values were established using receiver operating characteristic curves for each body composition parameter[10,26]. The cutoff values were selected based on the best accuracy of 1-year mortality; thus, the cutoff value for SMI ($cm^2/m^2$) in males was 45.16 [area under the curve (AUC) = 0.650] and 34.65 (AUC = 0.698) in females. The cutoff values for mean muscle radiodensity (HU) in males and females were 35.8 (AUC = 0.538) and 30.47 (AUC = 0.793), respectively. The SMI and mean muscle radiodensity cutoff points possessing the maximum absolute value of the log-rank statistic were used to establish the incidence of low SMI and low SMD. In addition, the cutoff values were 0.86 (AUC = 0.574) and 1.06 (AUC = 0.639) for the VSR, 28.70 (AUC = 0.639) and 49.72 (AUC = 0.691) for the VATI ($cm^2/m^2$), and 43.99 (AUC = 0.599) and 48.76 (AUC = 0.635) for the SATI ($cm^2/m^2$) in males and females, respectively. The classifications of underweight, normal weight, and obesity were based on definitions applied to Asian populations[9]. The analyses were performed using the following BMI categories: < 20.0 $kg/m^2$, underweight; 20.0-24.9 $kg/m^2$, normal weight; and ≥ 25.0 $kg/m^2$, obese. According to the World Health Organization, 65 years was the established cutoff to define people as elderly[27].

### Statistical analysis

Patient characteristics were summarized as counts and percentages for categorical variables and means and standard deviations for continuous variables. Differences in variables between groups were analyzed using Pearson's $\chi^2$ test for categorical variables or the independent $t$ test for continuous variables. Overall survival (OS) was defined as the interval from the first diagnosis until death, and recurrence-free survival (RFS) was calculated from the date of surgery to the date of recurrence or metastasis. Cumulative OS and RFS were estimated using the Kaplan-Meier method, and differences between groups were calculated using the log-rank test. The optimal high *vs* low values of inflammatory indicators were defined by examining a grid of cutoff values and choosing the cutoff value with the lowest -2 log-likelihood[28]. The effects of body composition parameters and clinicopathological factors on OS or RFS were evaluated using a Cox proportional hazards model. All variables with $P$ < 0.05 in the univariate analysis were included in the multivariate analysis. The results were presented as




**DOI:** 10.4240/wjgs.v14.i12.1350 

**Figure 1 Selective representative computed tomography images with tag overlay at the third lumbar vertebra level from two individual patients with pancreatic cancer presenting with similar body mass index (21.45 kg/m² in patient A and 21.48 kg/m² in patient B).** The red, yellow and green shadows indicate the skeletal muscle area (SMA), visceral adipose tissue area (VATA), and subcutaneous adipose tissue area (SATA), respectively. Skeletal muscle index, subcutaneous adipose tissue index and visceral adipose tissue index were calculated from SATA, VATA, and SMA divided by height in meters squared, respectively. The visceral to subcutaneous adipose tissue area ratio was calculated by dividing VATA by SATA. Skeletal muscle density indicates the mean computed tomography value (HU) of SMA. A: Body mass index (BMI): 21.45; B: BMI: 21.48. SMI: Skeletal muscle index; SATI: Subcutaneous adipose tissue index; VATI: Visceral adipose tissue index; VSR: Visceral to subcutaneous adipose tissue area ratio; SMD: Skeletal muscle density; HU: Hounsfield unit.

hazard ratios (HRs) with 95% confidence intervals (CIs). All statistical analyses were conducted using SPSS (SPSS 25.0, IBM Inc., Chicago, IL, United States) and GraphPad Prism (GraphPad Software 8.0.1, San Diego, CA, United States). $P$ values < 0.05 were considered statistically significant.

## RESULTS

### *Demographic characteristics of the patients*

The clinicopathological characteristics of the 115 enrolled patients were summarized (Table 1). According to the sex-specific cutoff values, 38 (33.3%) patients were characterized by low SMI, whereas 26 (22.6%) patients were characterized by low SMD. Patients with low SMI were older, more likely to be male, had poorly differentiated carcinoma, and had a tumor located in the pancreatic head compared to those with high SMI. Additionally, patients with low SMI more frequently had lower albumin levels. In addition, an older age and perineural invasion were highly predominant among patients with low SMD. Notably, we observed that neither SMI nor SMD was significantly associated with the TNM stage or indicators of systemic inflammation, such as the neutrophil-lymphocyte ratio, platelet-to-lymphocyte ratio, and SIII.

### *Prognostic value of body composition for patients with resectable pancreatic cancer*

First, the prognostic value of the widely used measurement BMI was assessed. Both obesity and underweight were related to a worse prognosis for pancreatic cancer patients than normal weight; however, a significant difference in survival was not observed between the obese and underweight groups (Supplementary Figure 1). Notably, two normal weight patients with similar BMIs showed rather different body composition parameters from CT-based measurements, including SMI, SMD, VATI, SATI, and VSR (Figure 1). These findings indicated that BMI may not be an appropriate indicator to assess the correlation between body composition and the prognosis. Thus, the correlation between body composition parameters based on CT scans and the survival prognosis was further evaluated. Patients with low preoperative SMI and low SMD experienced a shorter OS than those with high SMI ($P$ < 0.001; Figure 2A) and high SMD ($P$ = 0.006; Figure 2B). Shorter RFS was also observed among patients with low SMI ($P$ = 0.021; Figure 2C) but not among those with low SMD ($P$ = 0.119; Figure 2D). Meanwhile, high VATI, high SATI, and high VSR were not related to either poor OS or RFS outcomes (Supplementary Figure 2).

**Table 1 Patient and tumor characteristics comparing low and high skeletal muscle index or radiodensity**

| Characteristics | Total (*n* = 115) | Low SMI (*n* = 38) | High SMI (*n* = 77) | *P* value | Low SMD (*n* = 26) | High SMD (*n* = 89) | *P* value |
|---|---|---|---|---|---|---|---|
| Age | 65.1 (9.0) | 68.8 (9.3) | 63.3 (8.4) | 0.002[b] | 70.8 (7.0) | 63.5 (8.9) | < 0.001[c] |
| Male sex | 71 (61.7) | 29 (76.3) | 42 (54.5) | 0.024[a] | 13 (50.0) | 58 (65.2) | 0.162 |
| BMI in kg/m$^2$ | 22.7 (3.3) | 20.9 (3.1) | 23.6 (3.0) | < 0.001[c] | 24.0 (4.0) | 22.3 (2.9) | 0.016[a] |
| < 20.0 | 21(18.3) | 14 (36.8) | 7 (9.1) | | 5 (19.2) | 16 (18.0) | |
| 20.0-24.9 | 69 (60.0) | 20 (52.6) | 49 (63.6) | | 10 (38.5) | 59 (66.3) | |
| ≥ 25.0 | 25 (21.7) | 4 (10.5) | 21 (27.3) | 0.001[b] | 11 (42.3) | 14 (15.7) | 0.01[a] |
| Albumin in g/dL | 42.5 (5.6) | 40.6 (4.1) | 43.5 (6.1) | 0.01[a] | 41.7 (7.7) | 42.8 (4.9) | 0.393 |
| Tumor location | | | | | | | |
| Head | 67 (58.3) | 29 (76.3) | 38 (49.4) | | 18 (69.2) | 49 (55.1) | |
| Body + tail | 48 (41.7) | 9 (23.7) | 39 (50.6) | 0.006[b] | 8 (30.8) | 40 (44.9) | 0.197 |
| Tumor size in cm | 3.6 (1.4) | 3.7 (1.7) | 3.3 (1.2) | 0.942 | 3.3 (1.3) | 3.6 (1.4) | 0.602 |
| Differentiation | | | | | | | |
| Well | 5 (4.3) | 1 (2.7) | 4 (5.3) | | 3 (12.0) | 4 (4.6) | |
| Moderate | 100 (87.0) | 31 (83.8) | 69 (92.0) | | 19 (76.0) | 81 (93.1) | |
| Poor | 7 (6.1) | 5 (13.5) | 2 (2.7) | 0.04[a] | 3 (12.0) | 2 (2.3) | 0.774 |
| Nodal metastases | 64 (55.7) | 20 (52.6) | 44 (57.1) | 0.647 | 12 (46.2) | 52 (58.4) | 0.268 |
| Perineural invasion[1] | 81 (86.2) | 27 (87.1) | 54 (85.7) | 0.855 | 25 (100) | 56 (81.2) | 0.046[a] |
| R1 resection | 13 (11.3) | 3 (7.9) | 10 (13.2) | 0.602 | 3 (11.5) | 10 (11.4) | 1.000 |
| Adjuvant therapy | 84 (73.0) | 24 (63.2) | 60 (77.9) | 0.093 | 18 (69.2) | 66 (74.2) | 0.618 |
| TNM stage | | | | | | | |
| I | 43 (37.4) | 14 (36.8) | 29 (37.7) | | 14 (53.8) | 29 (32.6) | |
| II | 57 (49.6) | 19 (50.0) | 38 (49.4) | | 10 (38.5) | 47 (52.8) | |
| III | 15 (13.0) | 5 (13.1) | 10 (13.0) | 0.996 | 2 (7.6) | 13 (14.6) | 0.135 |
| CA19-9 > 200 KU/L | 71 (61.7) | 24 (66.7) | 47 (63.5) | 0.746 | 21 (84.0) | 50 (58.8) | 0.021[a] |
| SMA in cm$^2$ | 123.0 (30.6) | 108.4 (19.9) | 130.2 (32.4) | < 0.001[c] | 113.2 (28.4) | 125.9 (30.7) | 0.056 |
| SMD in HU | 39.4 (8.6) | 38.5 (10.0) | 39.8 (7.8) | 0.462 | 28.5 (5.1) | 42.6 (6.5) | < 0.001[c] |
| SMI in cm$^2$/m$^2$ | 44.6 (9.8) | 38.1 (5.3) | 47.7 (10.0) | < 0.001[c] | 41.1 (9.0) | 45.6 (9.9) | 0.033[a] |
| VAT in cm$^2$ | 113.4 (66.5) | 89 (50.2) | 125.4 (70.5) | < 0.001[c] | 151.0 (60.2) | 102.4 (64.5) | 0.001[b] |
| SAT in cm$^2$ | 121.4 (64.6) | 100.5 (45.4) | 131.7 (70.2) | 0.014[a] | 160.0 (89.3) | 110.1 (50.7) | < 0.001[c] |
| NLR > 2.6 | 44 (38.3) | 16 (42.1) | 28 (36.4) | 0.551 | 13 (50.0) | 31 (34.8) | 0.162 |
| PLR > 108 | 77 (67.0) | 27 (71.1) | 50 (64.9) | 0.512 | 21 (80.8) | 56 (62.9) | 0.089 |
| SIII > 400 | 68 (59.1) | 24 (63.2) | 44 (57.1) | 0.537 | 17 (65.4) | 51 (57.3) | 0.461 |

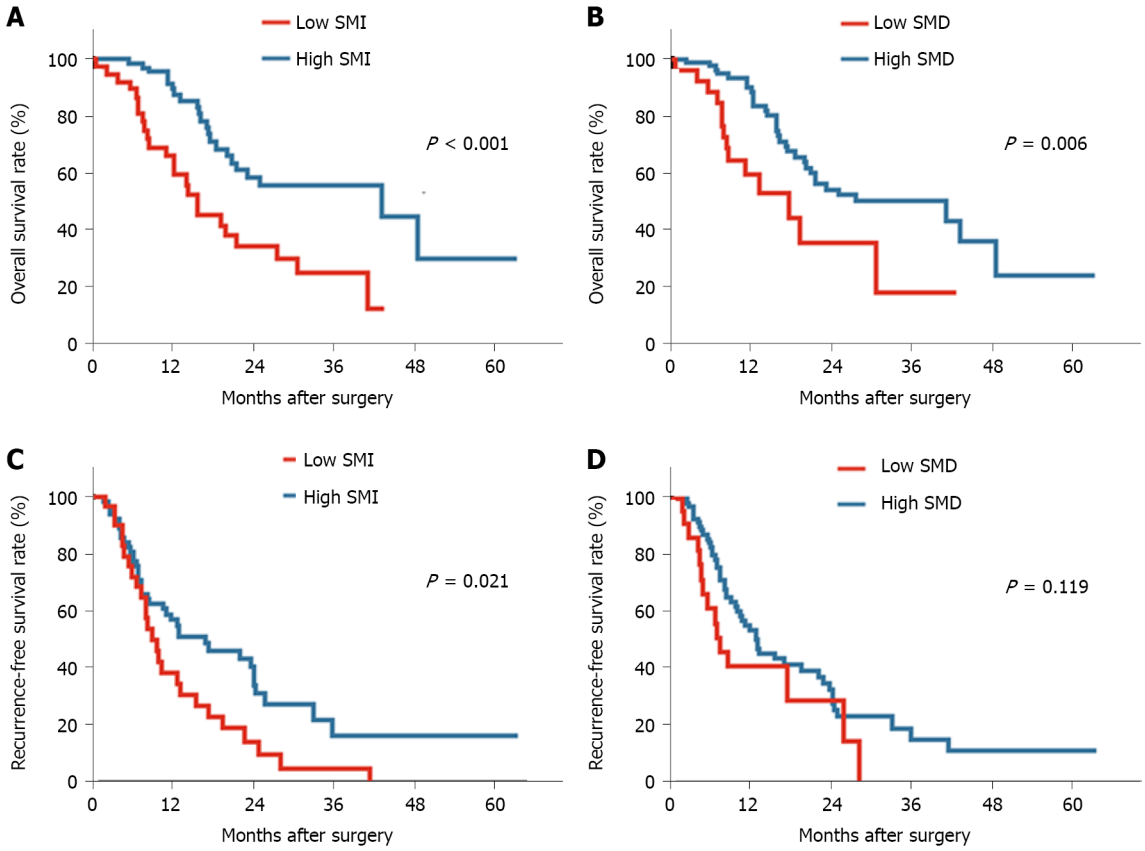
[1]Data were available for 94 patients. Statistics are presented as the means (standard deviations) for age, body mass index, albumin, tumor size, and body composition parameters and *n* (%) for the other parameters.

[a]*P* < 0.05.

[b]*P* < 0.01.

[c]*P* < 0.001.

SMA: Skeletal muscle area; SMD: Skeletal muscle radiodensity; HU: Hounsfield units; SMI: Skeletal muscle index; VAT: Visceral adipose tissue; SAT: Subcutaneous adipose tissue; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SIII: Systemic immune-inflammation index; BMI: Body mass index; CA19-9: Carbohydrate antigen 19-9.




**DOI:** 10.4240/wjgs.v14.i12.1350 

**Figure 2 Kaplan Meier survival curves for overall survival and recurrence-free survival based on skeletal muscle index and skeletal muscle density.** A and C: Overall survival (OS) and recurrence-free survival (RFS) curves for patients with low and high skeletal muscle index; B and D: OS and RFS curves for patients with low and high skeletal muscle density. SMI: Skeletal muscle index; SMD: Skeletal muscle density.

### *Risk factors for mortality and tumor recurrence after resection*

In the univariate risk analysis of factors associated with mortality (Table 2), low SMI, low SMD, high carbohydrate antigen 19-9 levels, high platelet-to-lymphocyte ratio, high SIII, lymph node metastasis, and absence of adjuvant chemotherapy were identified as risk factors for mortality after tumor resection. Remarkably, low SMI remained an independent risk factor for mortality in the multivariate analysis (HR: 2.307; 95%CI: 1.210-4.402; $P$ = 0.011), indicating that a low muscle quantity was a significant risk factor for mortality. We also observed higher mortality among patients with low SMD, although this finding was not significant (HR: 2.093; 95%CI: 1.000-4.379; $P$ = 0.050).

Furthermore, low SMI, lymph node metastasis, and high SIII, but not low SMD, were identified as risk factors based on the univariate analysis of risk factors associated with RFS (Table 3). The multivariate analysis showed that low SMI continued to be independently associated with tumor recurrence (HR: 1.907; 95%CI: 1.147-3.171; $P$ = 0.013).

### *Effects of body composition on mortality and recurrence among elderly patients*

A significant difference in age was observed between the groups with and without low SMI or SMD. We performed subgroup analyses based on age and body composition to further elucidate the potential effect of body composition on the prognosis of elderly patients with PDAC. First, we identified that 48.2% ($n$ = 27) of elderly patients and 18.6% ($n$ = 11) of young patients were characterized by low SMI. In addition, 35.7% ($n$ = 20) of elderly patients and 10.2% ($n$ = 6) of young patients were identified as having low SMD. Compared to young patients, a larger proportion of patients aged 65 years and older had a low SMI or SMD. Moreover, among elderly patients, the presence of low SMI was associated with a significantly decreased OS compared with those with high SMI ($P$ = 0.005; Figure 3A). Furthermore, an almost comparable OS was observed between groups with a high and low SMI among patients younger than 65 years ($P$ = 0.432; Figure 3B). Meanwhile, among the different age groups, the OS and RFS rates in the low SMD group did not differ significantly from those in the high SMD group ($P$ = 0.110 and $P$ = 0.320, respectively; Figure 3C and D). These findings indicated that a low preoperative SMI was more prevalent in elderly patients and was associated with a poor prognosis among pancreatic cancer patients, especially elderly patients.

**Table 2 Univariate and multivariate analyses of risk factors for overall survival following pancreatic cancer resection**

| Factor | Univariate analysis | *P* value | Multivariate analysis | *P* value |
|---|---|---|---|---|
| | HR (95%CI) | | HR (95%CI) | |
| Age ≥ 65 yr | 1.661 (0.905-3.051) | 0.102 | | |
| Male sex | 0.686 (0.371-1.267) | 0.228 | | |
| BMI < 20.0 underweight | 0.534 (0.262-1.085) | 0.083 | | |
| BMI ≥ 25.0 obesity | 0.631 (0.322-1.233) | 0.178 | | |
| Albumin < 3.8 g/dL | 1.146 (0.550-2.388) | 0.716 | | |
| Low SMI | 2.805 (1.559-5.045) | 0.001[b] | 2.307 (1.210-4.402) | 0.011[a] |
| Low SMD | 2.395 (1.261-4.550) | 0.008[b] | 2.093 (1.000-4.379) | 0.05 |
| Tumor location, head | 1.620 (0.870-3.019) | 0.128 | | |
| Tumor size > 2 cm | 1.107 (0.494-2.480) | 0.805 | | |
| Differentiation poor | 3.102 (0.947-10.158) | 0.061 | | |
| Nodal metastases | 1.853 (1.022-3.358) | 0.042[a] | 2.308 (1.200-4.442) | 0.012[a] |
| Perineural invasion | 2.303 (0.701-7.564) | 0.169 | | |
| R1 Resection | 1.165 (0.415-3.267) | 0.772 | | |
| TNM stage III | 1.515 (0.673-3.414) | 0.316 | | |
| Adjuvant therapy | 0.528 (0.284-0.980) | 0.043[a] | 0.480 (0.242-0.952) | 0.036[a] |
| CA19-9 > 200 KU/L | 1.891 (1.021-3.504) | 0.043[a] | 0.851 (0.428-1.689) | 0.644 |
| NLR > 2.6 | 1.630 (0.911-2.916) | 0.099 | | |
| PLR > 108 | 2.208 (1.150-4.238) | 0.017[a] | 1.296 (0.517-3.250) | 0.58 |
| SIII > 400 | 1.911 (1.044-3.500) | 0.036[a] | 1.338 (0.586-3.057) | 0.489 |

[a]$P < 0.05$.
[b]$P < 0.01$.
HR: Hazard ratio; BMI: Body mass index; CA19-9: Carbohydrate antigen 19-9; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SIII: Systemic immune-inflammation index; SMI: Skeletal muscle index; SMD: Skeletal muscle radiodensity; CI: Confidence interval.

## DISCUSSION

In this retrospective study, we assessed preoperative body composition measures from clinically acquired CT scans and comprehensively analyzed the effects of these measures on mortality and cancer recurrence in our single cohort of patients undergoing surgical resection for PDAC. Our findings revealed that low SMI was highly prevalent and associated with a significantly increased risk of death and cancer recurrence among pancreatic cancer patients. We also identified that elderly patients exhibited a higher risk of low SMI than younger patients. Based on the results of the subgroup analysis of mortality and recurrence stratified by age, we noted that low SMI was a valuable predictor of mortality, specifically in the elderly patient subgroup. Thus, prognostic measures may be easily integrated into routine clinical care using new software to generate a highly accurate measure of SMI from clinically collected CT scans.

Results from our cohort and some other cohorts of patients with resectable pancreatic cancer indicated that elderly patients are more vulnerable to sarcopenia (usually defined by a low SMI) than young patients[15,23,29]. Most experts believe that age-related sarcopenia is an inevitable part of aging [30]. The aging-related denervation process exerts a strong effect on quantitative changes in muscle, such as loss of muscle fibers and atrophy, and qualitative changes in muscle affecting protein function, the repair process, and coordinated contractility and resilience to stress, leading to a loss of muscle volume and function in older age[31]. However, our results were inconsistent with some findings from previous studies that no significant difference in age was observed between the subgroups with and without sarcopenia[10,32]. This difference may be attributed to the cutoff values used for low SMI. In addition, the cutoff value for sarcopenia in previous studies that showed between-cohort age-related differences were considerably lower than the corresponding value in studies that did not show any significant difference in age between sarcopenia and non-sarcopenia cohorts. Currently, no established consensus value is available for CT-based sarcopenia (namely, low SMI) in Asian populations.

**Table 3 Univariate and multivariate analysis of risk factors for recurrence-free survival following pancreatic cancer resection**

| Factor | Univariate analysis | *P* value | Multivariate analysis | *P* value |
|---|---|---|---|---|
| | HR (95%CI) | | HR (95%CI) | |
| Age > 65 yr | 1.661 (0.905-3.051) | 0.102 | | |
| Male sex | 0.631 (0.382-1.041) | 0.071 | | |
| BMI < 20.0 underweight | 1.216 (0.660-2.240) | 0.530 | | |
| BMI ≥ 25.0 obesity | 1.823 (0.969-3.430) | 0.062 | | |
| Albumin < 3.8 g/dL | 0.871 (0455-1.668) | 0.677 | | |
| Low SMI | 1.784 (1.083-2.939) | 0.023[a] | 1.907 (1.147-3.171) | 0.013[a] |
| Low SMD | 1.567 (0.885-2.773) | 0.123 | | |
| Tumor location, head | 1.327 (0.795-2.215) | 0.278 | | |
| Tumor size > 2 cm | 1.611 (0.767-3.382) | 0.208 | | |
| Differentiation poor | 0.978 (0.238-4.022) | 0.976 | | |
| Nodal metastases | 1.897 (1.134-3.174) | 0.015[a] | 1.922 (1.129-3.272) | 0.016[a] |
| Perineural invasion | 1.886 (0.841-4.231) | 0.124 | | |
| R1 Resection | 1.593 (0.754-3.365) | 0.222 | | |
| TNM stage III | 1.703 (0.833-3.483) | 0.144 | | |
| Adjuvant therapy | 0.866 (0.479-1.567) | 0.635 | | |
| CA19-9 in Ku/L > 200 | 1.439 (0.855-2.421) | 0.170 | | |
| NLR > 2.6 | 1.071 (0.648-1.769) | 0.789 | | |
| PLR > 108 | 1.612 (0.955-2.722) | 0.074 | | |
| SIII > 400 | 1.827 (1.097-3.043) | 0.021[a] | 1.655 (0.984-2.785) | 0.058 |
| Platelets > 310 × $10^9$ | 1.245 (0.533-2.910) | 0.613 | | |

[a]$P < 0.05$.

HR: Hazard ratio; BMI: Body mass index; CA19-9: Carbohydrate antigen 19-9; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SIII: Systemic immune-inflammation index; SMI: Skeletal muscle index; SMD: Skeletal muscle radiodensity; CI: Confidence interval.

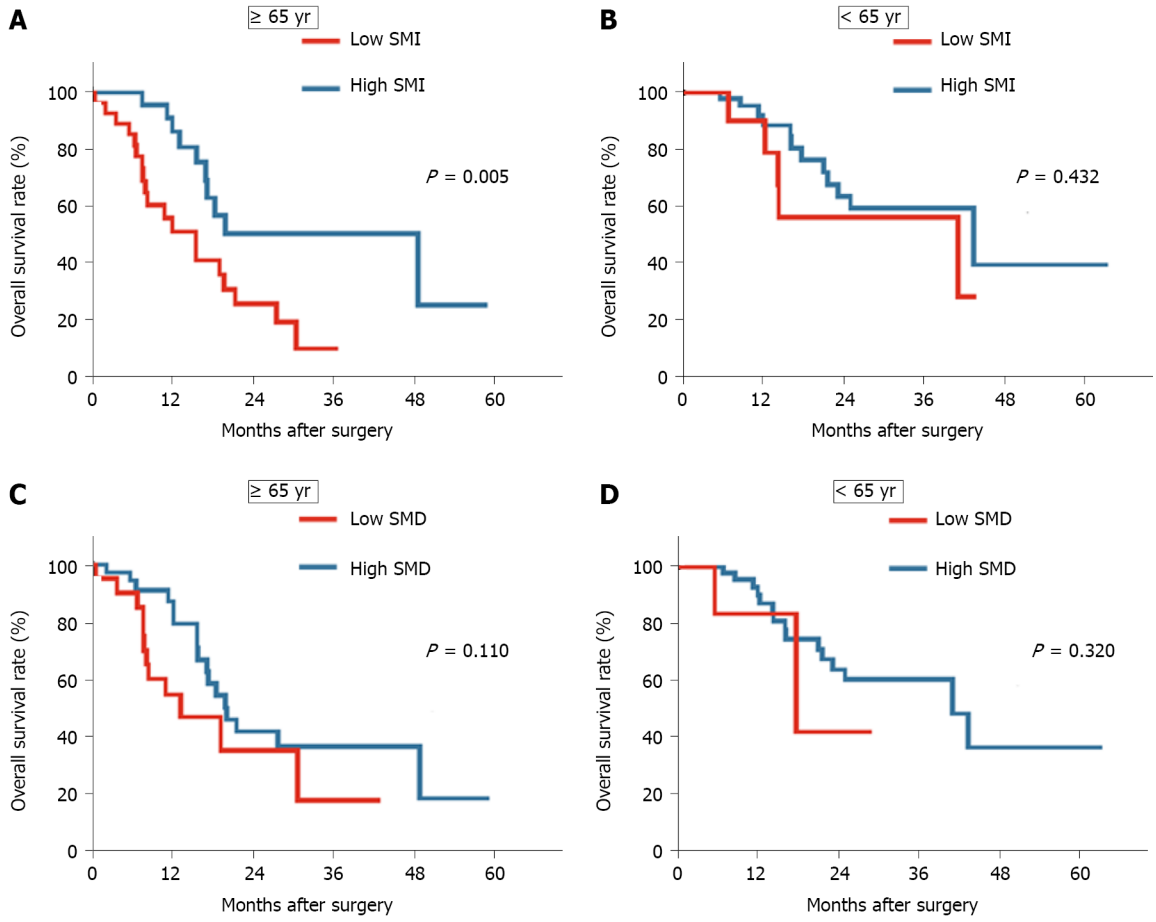
Therefore, more large-scale studies are needed in the future to establish a consensus cutoff value for sarcopenia in Asian populations and confirm these observations.

We further identified that low preoperative SMI was an independent prognostic factor for mortality and cancer recurrence for PDAC patients after pancreatectomy. These findings are consistent with previous reports describing the effect of low SMI on PDAC patients[10,15,32,33]. More importantly, we found that low SMI exerted a greater adverse effect on the prognosis among elderly patients. In contrast, no remarkable association between low SMI and mortality was identified among nonelderly patients. Likewise, Nakashima *et al*[24] revealed that low SMI was significantly associated with patients with esophageal cancer aged 65 years and older but not with those younger than 65 years[24].

Furthermore, comparable OS and RFS rates were observed among both elderly and young patients with low SMI. Additionally, low SMI contributes to a long-term prognosis that is similar to that of lymph node metastasis in elderly patients. Several studies have reported that sarcopenia is associated with insulin resistance, vitamin D deficiency, increased inflammatory cytokine levels, such as tumor necrosis factor-α and interleukin-6, and decreased concentrations of myokines, such as interleukin-15 [34-37]. Notably, all of the aforementioned inflammatory cytokines are related to the progression of pancreatic cancer[38-42]. Thus, the quantity of skeletal muscle may be linked to the prognosis of patients with PDAC through various mechanisms.

Recently, with the gradual increase in the incidence of PDAC among elderly patients and the aging population, the number of pancreatic cancer patients with sarcopenia is estimated to increase steadily [43]. Therefore, an early preoperative diagnosis of low SMI/sarcopenia coupled with early intervention is essential for elderly patients to extend their OS and simultaneously promote a good quality of life, which would also conserve large amounts of medical resources.

In this study, we did not observe a relationship between survival and SMD (a surrogate of muscle quality) in patients with pancreatic cancer. To our knowledge, only one previous study of patients with unresectable pancreatic cancer and distal cholangiocarcinoma reported a significant relationship




**DOI:** 10.4240/wjgs.v14.i12.1350 

**Figure 3 Kaplan Meier overall survival curves of the cohort stratified by age.** A and C: Overall survival (OS) curves for patients aged 65 and older stratified according to skeletal muscle index (SMI) (A) and skeletal muscle density (SMD) (C); B and D: OS curves for patients aged younger than 65 yr stratified by SMI (B) and SMD (D). SMI: Skeletal muscle index; SMD: Skeletal muscle density.

between SMD and the tumor prognosis[11]. In that study, low SMD was defined operationally as a mean skeletal muscle radiodensity of < 33 HU in patients with a BMI ≥ 25 kg/m² and < 41 HU in patients with a BMI < 25 kg/m² across the orthogonal view. Moreover, the prevalence of low SMD (55.3%) was much higher among patients in the previous study than among patients in the present study (22.6%). These results imply that fatty infiltration into muscle may be a hallmark of more advanced cancer but is not as predominant in cancer at an earlier stage.

However, despite these promising results, we acknowledge several limitations of the present study. First, this study was performed retrospectively at a single center with a relatively small sample size; hence, the potential for selection bias exists. Therefore, larger prospective cohort studies are needed to confirm these findings. Second, we must consider whether our cutoff values are adequate to define low SMI or sarcopenia. Although the cutoff value must be determined from a normal population of people of different ages, a unified standard is unavailable for the general Asian populations. Moreover, no specific cutoff values for pancreatic cancer were available to identify patients with sarcopenia. Here, we determined the cutoff values in this population using receiver operating characteristic curves, which is considered a more accurate method than the use of standard deviations to set cutoff values. However, more studies are still needed to explore more specific indicators that may reflect muscle function and are not limited by race or region.

## CONCLUSION

In summary, low preoperative SMI, which is simply diagnosed through routine staging CT scans, was associated with a poor prognosis, especially among elderly patients with pancreatic cancer. Thus, the early identification of aging-specific factors, such as SMI, enables early interventions to ameliorate clinical outcomes in elderly patients with pancreatic cancer.

## ARTICLE HIGHLIGHTS

### *Research background*

The only potential curative treatment for patients with pancreatic cancer is surgery; however, the prognosis remains poor.

### *Research motivation*

Measures of body composition based on computed tomography (CT) scans have been established as reliable predictors of the prognosis of cancer patients after surgery, but further research focusing on pancreatic cancer is needed.

### *Research objectives*

To elucidate the associations of body composition measures derived from preoperative CT scans with the prognosis of patients with pancreatic cancer.

### *Research methods*

One hundred fifteen patients undergoing pancreatic resection with curative intent for pancreatic cancer were retrospectively enrolled. The preoperative CT scan at the third lumbar vertebral level was measured for skeletal muscle index (SMI), mean skeletal muscle radiodensity, subcutaneous adipose tissue index, visceral adipose tissue index, and subcutaneous adipose tissue area ratio. The clinical and pathological data were collected. The effects of these factors on long-term survival were evaluated.

### *Research results*

Among the five body composition measures, only low SMI independently predicted overall survival (OS) [hazard ratio (HR): 2.307; 95% confidence interval (CI): 1.210-4.402] and recurrence-free survival (HR: 1.907; 95%CI: 1.147-3.171). Furthermore, patients with low SMI (*vs* high SMI) were older (68.8 ± 9.3 years *vs* 63.3 ± 8.4 years); low SMI was present in 27 of 56 patients (48.2%) aged 65 years and older and in 11 of 59 younger patients (18.6%). In addition, subgroup analyses revealed that the correlation between low SMI and OS was observed only in patients aged 65 years and older.

### *Research conclusions*

Low preoperative SMI was more prevalent in elderly patients and was associated with a poor prognosis among pancreatic cancer patients, especially elderly patients.

### *Research perspectives*

The early identification of aging-specific factors, such as low SMI, allows for the possibility to facilitate early interventions to ameliorate clinical outcomes in elderly patients with pancreatic cancer.

## ACKNOWLEDGEMENTS

We sincerely thank Xin-Xin Xu and Dr. He Li for their guidance on this manuscript.

## FOOTNOTES

**Author contributions:** Cai ZW, Li JL, and Liu M contributed equally to this manuscript; Jiang CY participated in the conception and design of this study; Cai ZW participated in the data collection, analysis, and drafting of the article; Li JL and Liu M participated in the design of the study and data analyses; Wang HW participated in the data collection; All authors have read and approved the final manuscript.

**Supported by** Shanghai Science and Technology Commission of Shanghai Municipality, No. 20Y11908600; Shanghai Shenkang Hospital Development Center, No. SHDC2020CR5008; and Shanghai Municipal Health Commission, No. 20194Y0195.

**Institutional review board statement:** The study was reviewed and approved by the Ethics Review Committee of Huadong Hospital (Shanghai).

**Informed consent statement:** All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Data sharing statement:** No additional data are available.

**Country/Territory of origin:** China

**ORCID number:** Zhi-Wei Cai 0000-0002-5121-0687; Jia-Lin Li 0000-0002-1696-9890; Meng Liu 0000- 0002-0481-2968; Hong-Wei Wang 0000-0003-2432-3608; Chong-Yi Jiang 0000-0002-9691-4055.

**S-Editor:** Fan JR
**L-Editor:** Filipodia
**P-Editor:** Fan JR

## REFERENCES

1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
2 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**: 7-30 [PMID: 31912902 DOI: 10.3322/caac.21590]
3 **Hidalgo M**. Pancreatic cancer. *N Engl J Med* 2010; **362**: 1605-1617 [PMID: 20427809 DOI: 10.1056/NEJMra0901557]
4 **Mizrahi JD**, Surana R, Valle JW, Shroff RT. Pancreatic cancer. *Lancet* 2020; **395**: 2008-2020 [PMID: 32593337 DOI: 10.1016/S0140-6736(20)30974-0]
5 **Brown JC**, Meyerhardt JA. Obesity and Energy Balance in GI Cancer. *J Clin Oncol* 2016; **34**: 4217-4224 [PMID: 27903148]
6 **Greenlee H**, Unger JM, LeBlanc M, Ramsey S, Hershman DL. Association between Body Mass Index and Cancer Survival in a Pooled Analysis of 22 Clinical Trials. *Cancer Epidemiol Biomarkers Prev* 2017; **26**: 21-29 [PMID: 27986655 DOI: 10.1158/1055-9965.EPI-15-1336]
7 **Mintziras I**, Miligkos M, Wächter S, Manoharan J, Maurer E, Bartsch DK. Sarcopenia and sarcopenic obesity are significantly associated with poorer overall survival in patients with pancreatic cancer: Systematic review and meta-analysis. *Int J Surg* 2018; **59**: 19-26 [PMID: 30266663 DOI: 10.1016/j.ijsu.2018.09.014]
8 **Majumder K**, Gupta A, Arora N, Singh PP, Singh S. Premorbid Obesity and Mortality in Patients With Pancreatic Cancer: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2016; **14**: 355-368.e; quiz e32 [PMID: 26460214 DOI: 10.1016/j.cgh.2015.09.036]
9 **Fujiwara N**, Nakagawa H, Kudo Y, Tateishi R, Taguri M, Watadani T, Nakagomi R, Kondo M, Nakatsuka T, Minami T, Sato M, Uchino K, Enooku K, Kondo Y, Asaoka Y, Tanaka Y, Ohtomo K, Shiina S, Koike K. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. *J Hepatol* 2015; **63**: 131-140 [PMID: 25724366 DOI: 10.1016/j.jhep.2015.02.031]
10 **Okumura S**, Kaido T, Hamaguchi Y, Kobayashi A, Shirai H, Yao S, Yagi S, Kamo N, Hatano E, Okajima H, Takaori K, Uemoto S. Visceral Adiposity and Sarcopenic Visceral Obesity are Associated with Poor Prognosis After Resection of Pancreatic Cancer. *Ann Surg Oncol* 2017; **24**: 3732-3740 [PMID: 28871520 DOI: 10.1245/s10434-017-6077-y]
11 **Rollins KE**, Tewari N, Ackner A, Awwad A, Madhusudan S, Macdonald IA, Fearon KC, Lobo DN. The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma. *Clin Nutr* 2016; **35**: 1103-1109 [PMID: 26411749 DOI: 10.1016/j.clnu.2015.08.005]
12 **Rosenberg IH**. Sarcopenia: origins and clinical relevance. *J Nutr* 1997; **127**: 990S-991S [PMID: 9164280 DOI: 10.1093/jn/127.5.990S]
13 **Cruz-Jentoft AJ**, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019; **48**: 16-31 [PMID: 30312372 DOI: 10.1093/ageing/afy169]
14 **Chen LK**, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, Chou MY, Chen LY, Hsu PS, Krairit O, Lee JS, Lee WJ, Lee Y, Liang CK, Limpawattana P, Lin CS, Peng LN, Satake S, Suzuki T, Won CW, Wu CH, Wu SN, Zhang T, Zeng P, Akishita M, Arai H. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc* 2014; **15**: 95-101 [PMID: 24461239 DOI: 10.1016/j.jamda.2013.11.025]
15 **Ninomiya G**, Fujii T, Yamada S, Yabusaki N, Suzuki K, Iwata N, Kanda M, Hayashi M, Tanaka C, Nakayama G, Sugimoto H, Koike M, Fujiwara M, Kodera Y. Clinical impact of sarcopenia on prognosis in pancreatic ductal adenocarcinoma: A retrospective cohort study. *Int J Surg* 2017; **39**: 45-51 [PMID: 28110029 DOI: 10.1016/j.ijsu.2017.01.075]
16 **van Dijk DP**, Bakens MJ, Coolsen MM, Rensen SS, van Dam RM, Bours MJ, Weijenberg MP, Dejong CH, Olde Damink SW. Low skeletal muscle radiation attenuation and visceral adiposity are associated with overall survival and surgical site infections in patients with pancreatic cancer. *J Cachexia Sarcopenia Muscle* 2017; **8**: 317-326 [PMID: 27897432 DOI: 10.1002/jcsm.12155]
17 **Sato H**, Goto T, Hayashi A, Kawabata H, Okada T, Takauji S, Sasajima J, Enomoto K, Fujiya M, Oyama K, Ono Y,

Sugitani A, Mizukami Y, Okumura T. Prognostic significance of skeletal muscle decrease in unresectable pancreatic cancer: Survival analysis using the Weibull exponential distribution model. *Pancreatology* 2021; **21**: 892-902 [PMID: 33722506 DOI: 10.1016/j.pan.2021.03.002]

18 **Emori T**, Itonaga M, Ashida R, Tamura T, Kawaji Y, Hatamaru K, Yamashita Y, Shimokawa T, Koike M, Sonomura T, Kawai M, Kitano M. Impact of sarcopenia on prediction of progression-free survival and overall survival of patients with pancreatic ductal adenocarcinoma receiving first-line gemcitabine and nab-paclitaxel chemotherapy. *Pancreatology* 2022; **22**: 277-285 [PMID: 35033425 DOI: 10.1016/j.pan.2021.12.013]

19 **Uemura S**, Iwashita T, Ichikawa H, Iwasa Y, Mita N, Shiraki M, Shimizu M. The impact of sarcopenia and decrease in skeletal muscle mass in patients with advanced pancreatic cancer during FOLFIRINOX therapy. *Br J Nutr* 2021; **125**: 1140-1147 [PMID: 32883372 DOI: 10.1017/S0007114520003463]

20 **Asama H**, Ueno M, Kobayashi S, Fukushima T, Kawano K, Sano Y, Tanaka S, Nagashima S, Morimoto M, Ohira H, Maeda S. Sarcopenia: Prognostic Value for Unresectable Pancreatic Ductal Adenocarcinoma Patients Treated With Gemcitabine Plus Nab-Paclitaxel. *Pancreas* 2022; **51**: 148-152 [PMID: 35404889 DOI: 10.1097/MPA.0000000000001985]

21 **Incio J**, Liu H, Suboj P, Chin SM, Chen IX, Pinter M, Ng MR, Nia HT, Grahovac J, Kao S, Babykutty S, Huang Y, Jung K, Rahbari NN, Han X, Chauhan VP, Martin JD, Kahn J, Huang P, Desphande V, Michaelson J, Michelakos TP, Ferrone CR, Soares R, Boucher Y, Fukumura D, Jain RK. Obesity-Induced Inflammation and Desmoplasia Promote Pancreatic Cancer Progression and Resistance to Chemotherapy. *Cancer Discov* 2016; **6**: 852-869 [PMID: 27246539 DOI: 10.1158/2159-8290.CD-15-1177]

22 **Cai Z**, Liang Y, Xing C, Wang H, Hu P, Li J, Huang H, Wang W, Jiang C. Cancerassociated adipocytes exhibit distinct phenotypes and facilitate tumor progression in pancreatic cancer. *Oncol Rep* 2019; **42**: 2537-2549 [PMID: 31638193 DOI: 10.3892/or.2019.7365]

23 **Okumura S**, Kaido T, Hamaguchi Y, Fujimoto Y, Masui T, Mizumoto M, Hammad A, Mori A, Takaori K, Uemoto S. Impact of preoperative quality as well as quantity of skeletal muscle on survival after resection of pancreatic cancer. *Surgery* 2015; **157**: 1088-1098 [PMID: 25799468 DOI: 10.1016/j.surg.2015.02.002]

24 **Nakashima Y**, Saeki H, Nakanishi R, Sugiyama M, Kurashige J, Oki E, Maehara Y. Assessment of Sarcopenia as a Predictor of Poor Outcomes After Esophagectomy in Elderly Patients With Esophageal Cancer. *Ann Surg* 2018; **267**: 1100-1104 [PMID: 28437312 DOI: 10.1097/SLA.0000000000002252]

25 **Kays JK**, Shahda S, Stanley M, Bell TM, O'Neill BH, Kohli MD, Couch ME, Koniaris LG, Zimmers TA. Three cachexia phenotypes and the impact of fat-only loss on survival in FOLFIRINOX therapy for pancreatic cancer. *J Cachexia Sarcopenia Muscle* 2018; **9**: 673-684 [PMID: 29978562 DOI: 10.1002/jcsm.12307]

26 **Zore T**, Palafox M, Reue K. Sex differences in obesity, lipid metabolism, and inflammation-A role for the sex chromosomes? *Mol Metab* 2018; **15**: 35-44 [PMID: 29706320 DOI: 10.1016/j.molmet.2018.04.003]

27 **Macchini M**, Chiaravalli M, Zanon S, Peretti U, Mazza E, Gianni L, Reni M. Chemotherapy in elderly patients with pancreatic cancer: Efficacy, feasibility and future perspectives. *Cancer Treat Rev* 2019; **72**: 1-6 [PMID: 30414985 DOI: 10.1016/j.ctrv.2018.10.013]

28 **Aziz MH**, Sideras K, Aziz NA, Mauff K, Haen R, Roos D, Saida L, Suker M, van der Harst E, Mieog JS, Bonsing BA, Klaver Y, Koerkamp BG, van Eijck CH. The Systemic-immune-inflammation Index Independently Predicts Survival and Recurrence in Resectable Pancreatic Cancer and its Prognostic Value Depends on Bilirubin Levels: A Retrospective Multicenter Cohort Study. *Ann Surg* 2019; **270**: 139-146 [PMID: 29334554 DOI: 10.1097/SLA.0000000000002660]

29 **Peng YC**, Wu CH, Tien YW, Lu TP, Wang YH, Chen BB. Preoperative sarcopenia is associated with poor overall survival in pancreatic cancer patients following pancreaticoduodenectomy. *Eur Radiol* 2021; **31**: 2472-2481 [PMID: 32974690 DOI: 10.1007/s00330-020-07294-7]

30 **Dhillon RJ**, Hasni S. Pathogenesis and Management of Sarcopenia. *Clin Geriatr Med* 2017; **33**: 17-26 [PMID: 27886695 DOI: 10.1016/j.cger.2016.08.002]

31 **Larsson L**, Degens H, Li M, Salviati L, Lee YI, Thompson W, Kirkland JL, Sandri M. Sarcopenia: Aging-Related Loss of Muscle Mass and Function. *Physiol Rev* 2019; **99**: 427-511 [PMID: 30427277 DOI: 10.1152/physrev.00061.2017]

32 **Gruber ES**, Jomrich G, Tamandl D, Gnant M, Schindl M, Sahora K. Sarcopenia and sarcopenic obesity are independent adverse prognostic factors in resectable pancreatic ductal adenocarcinoma. *PLoS One* 2019; **14**: e0215915 [PMID: 31059520 DOI: 10.1371/journal.pone.0215915]

33 **Choi MH**, Yoon SB, Lee K, Song M, Lee IS, Lee MA, Hong TH, Choi MG. Preoperative sarcopenia and post-operative accelerated muscle loss negatively impact survival after resection of pancreatic cancer. *J Cachexia Sarcopenia Muscle* 2018; **9**: 326-334 [PMID: 29399990 DOI: 10.1002/jcsm.12274]

34 **Lutz CT**, Quinn LS. Sarcopenia, obesity, and natural killer cell immune senescence in aging: altered cytokine levels as a common mechanism. *Aging (Albany NY)* 2012; **4**: 535-546 [PMID: 22935594]

35 **Kelley DE**, Goodpaster BH, Storlien L. Muscle triglyceride and insulin resistance. *Annu Rev Nutr* 2002; **22**: 325-346 [PMID: 12055349]

36 **Gilsanz V**, Kremer A, Mo AO, Wren TA, Kremer R. Vitamin D status and its relation to muscle mass and muscle fat in young women. *J Clin Endocrinol Metab* 2010; **95**: 1595-1601 [PMID: 20164290 DOI: 10.1210/jc.2009-2309]

37 **Zoico E**, Rossi A, Di Francesco V, Sepe A, Olioso D, Pizzini F, Fantin F, Bosello O, Cominacini L, Harris TB, Zamboni M. Adipose tissue infiltration in skeletal muscle of healthy elderly men: relationships with body composition, insulin resistance, and inflammation at the systemic and tissue level. *J Gerontol A Biol Sci Med Sci* 2010; **65**: 295-299 [PMID: 19864639 DOI: 10.1093/gerona/glp155]

38 **Robinson DW Jr**, Eisenberg DF, Cella D, Zhao N, de Boer C, DeWitte M. The prognostic significance of patient-reported outcomes in pancreatic cancer cachexia. *J Support Oncol* 2008; **6**: 283-290 [PMID: 18724539]

39 **Friess H**, Guo XZ, Nan BC, Kleeff J, Büchler MW. Growth factors and cytokines in pancreatic carcinogenesis. *Ann N Y Acad Sci* 1999; **880**: 110-121 [PMID: 10415856]

40 **Hamada S**, Masamune A, Yoshida N, Takikawa T, Shimosegawa T. IL-6/STAT3 Plays a Regulatory Role in the Interaction Between Pancreatic Stellate Cells and Cancer Cells. *Dig Dis Sci* 2016; **61**: 1561-1571 [PMID: 26738736 DOI: 10.1007/s10620-015-4001-5]

41 **Barreto SG**, Neale RE. Vitamin D and pancreatic cancer. *Cancer Lett* 2015; **368**: 1-6 [PMID: 26276715 DOI: 10.1016/j.canlet.2015.06.030]
42 **Mutgan AC**, Besikcioglu HE, Wang S, Friess H, Ceyhan GO, Demir IE. Insulin/IGF-driven cancer cell-stroma crosstalk as a novel therapeutic target in pancreatic cancer. *Mol Cancer* 2018; **17**: 66 [PMID: 29475434 DOI: 10.1186/s12943-018-0806-0]
43 **DeSantis CE**, Miller KD, Dale W, Mohile SG, Cohen HJ, Leach CR, Goding Sauer A, Jemal A, Siegel RL. Cancer statistics for adults aged 85 years and older, 2019. *CA Cancer J Clin* 2019; **69**: 452-467 [PMID: 31390062 DOI: 10.3322/caac.21577]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 December 27; 14(12): 1363-1374

DOI: 10.4240/wjgs.v14.i12.1363

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Observational Study

# Development of a prediction model for enteral feeding intolerance in intensive care unit patients: A prospective cohort study

Xue-Mei Lu, Deng-Shuai Jia, Rui Wang, Qing Yang, Shan-Shan Jin, Lan Chen

**Specialty type:** Nursing

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Ait Addi R, Morocco; Juneja D, India; Soares RLS, Brazil

**Received:** August 27, 2022
**Peer-review started:** August 27, 2022
**First decision:** September 25, 2022
**Revised:** October 15, 2022
**Accepted:** November 16, 2022
**Article in press:** November 16, 2022
**Published online:** December 27, 2022

**Xue-Mei Lu, Deng-Shuai Jia,** School of Nursing, Shanghai Jiao Tong University, Shanghai 200025, China

**Xue-Mei Lu, Lan Chen,** Department of Nursing, Shanghai General Hospital, Shanghai Jiao Tong University, Shanghai 200080, China

**Rui Wang, Qing Yang, Shan-Shan Jin,** Department of Critical Care Medicine, Shanghai General Hospital, Shanghai Jiao Tong University, Shanghai 200080, China

**Corresponding author:** Lan Chen, PhD, Chief Nurse, Department of Nursing, Shanghai General Hospital, Shanghai Jiao Tong University, No. 86 Wu Jin Road, Shanghai 200080, China. 13636317690@126.com

## Abstract

*BACKGROUND*

Enteral nutrition (EN) is essential for critically ill patients. However, some patients will have enteral feeding intolerance (EFI) in the process of EN.

*AIM*

To develop a clinical prediction model to predict the risk of EFI in patients receiving EN in the intensive care unit.

*METHODS*

A prospective cohort study was performed. The enrolled patients' basic information, medical status, nutritional support, and gastrointestinal (GI) symptoms were recorded. The baseline data and influencing factors were compared. Logistic regression analysis was used to establish the model, and the bootstrap resampling method was used to conduct internal validation.

*RESULTS*

The sample cohort included 203 patients, and 37.93% of the patients were diagnosed with EFI. After the final regression analysis, age, GI disease, early feeding, mechanical ventilation before EN started, and abnormal serum sodium were identified. In the internal validation, 500 bootstrap resample samples were performed, and the area under the curve was 0.70 (95%CI: 0.63-0.77).

*CONCLUSION*

This clinical prediction model can be applied to predict the risk of EFI.

**Key Words:** Enteral feeding intolerance; Critical care medicine; Clinical prediction model; Nutrition assessment; Nutritional support; Critical care nursing



**Core Tip:** Enteral nutrition (EN) is an essential piece of providing care to critically ill patients. However, some patients will experience complications related to EN and become intolerant to this nutritional support. In this study, we developed a model to predict patients who are at high risk of enteral feeding intolerance. In the future when an intensive care unit patient requires EN, nurses can distinguish whether the patient is a high-risk patient. Then, they can allocate their time to more observation of the high-risk patient to discover the patient's complications and administer effective measures in advance. In the long-term, this strategy will reduce the workload of the nursing staff and will achieve more accurate care.

**Citation:** Lu XM, Jia DS, Wang R, Yang Q, Jin SS, Chen L. Development of a prediction model for enteral feeding intolerance in intensive care unit patients: A prospective cohort study. *World J Gastrointest Surg* 2022; 14(12): 1363-1374
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i12/1363.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i12.1363

## INTRODUCTION

Enteral nutrition (EN) is a preferred and cost-effective approach to nutritional support[1,2]. When EN is provided, nutrients in the gastrointestinal (GI) tract activate intestinal endocrine cells and lymphoid tissues, which positively contributes to GI function (*e.g.*, movement, digestion, and immunity)[3,4]. However, during the provision of EN, many complications can develop that have an adverse impact on nutritional support[5]. Enteral feeding intolerance (EFI) is a common and primary manifestation among many GI complications.

EFI is the inability to deliver adequate energy or nutrients to patients due to GI symptoms in the absence of mechanical obstruction[6]. EFI develops in 2%-75% of enteral feeding patients in intensive care units (ICUs)[7]. When EFI occurs, prokinetic agents and post-pyloric feeding are recommended[8]. If EFI cannot be attenuated by medications or other feeding access, then EN is reduced or suspended[9, 10]. This may result in an inability to attain nutritional goals or in malnutrition.

Therefore, distinguishing high-risk patients before EFI occurs is very important and has a guiding role in clinical practice. Many studies have explored the mechanics and causes for the development of EFI in clinical practice. A review summarized some of the main reasons: (1) Admission diagnosis of burns, head injuries, sepsis, and multi-trauma; (2) Premorbid conditions of disordered glucose metabolism, age, and sex; (3) Electrolyte disorders; and (4) Use of drugs such as sedatives, analgesics, and catecholamines[9]. A recent review of a multicenter and multiyear database indicated that EFI was more likely to occur in burn, cardiovascular/vascular disease, GI disease, and sepsis patients in the ICU [11]. However, in recent years, assessment of EFI at the bedside was driven by clinician opinion, which is still subjective to some extent. This may result in misjudgment of EFI occurrence and have an adverse effect on nutrition delivery and clinical recovery.

A clinical prediction model (CPM) is built upon the use of mathematical formulas to estimate the probability that a particular individual will have a disease or an outcome in the future[12,13]. CPM can assist clinicians in decision-making and developing therapy programs in complex clinical situations and may help patients have better outcomes. Many studies have identified variables associated with EFI, such as diabetes, abdominal surgery, and head injury. This study aimed to analyze different risk factors for EFI occurrence in the ICU and to construct a CPM that would screen high-risk ICU patients to implement early prevention and intervention methods.

## MATERIALS AND METHODS

### *Study design, setting, and participants*

A prospective cohort study was conducted with patients in the ICU at a college hospital, which is a general teaching hospital with 116 ICU beds at the northern and southern campuses. This study was performed in three of the five ICU departments, which included comprehensive ICU, emergency ICU, and neurosurgery ICU. This study was performed between November 2020 and May 2021.

Patients in the ICU were included in the study when EN was started. Patients who received EN for less than 24 h were not included in the model-construction dataset. Eligible patients received the standard nutrition protocol on medical advice (continuous infusion *via* nutrition pump at rates between 20 mL/h to 150 mL/h). Depending on the patient's condition, different feeding tubes and formulas were chosen. Exclusion criteria included the following: (1) Age < 18 years; (2) Oral intake; (3) Pregnancy or breastfeeding; (4) Occlusive ileus; and (5) Informed consent not obtained from the patient or their next of kin.

### Variables

**Outcome measure:** According to the results of the literature review and discussion with experts, the primary outcome was patients diagnosed with EFI, including GI symptoms and reduction or suspension of EN. A patient was diagnosed with EFI if one or more listed GI symptoms occurred and resulted in the reduction or suspension of EN within 2 wk of starting EN[7,14]. When patients had several symptoms, one symptom was determined to be the main symptom rather than recording several duplicate symptoms.

GI symptoms included the following: (1) Moderate gastric residual volume (defined as GRV, reaching 200 mL)[7,15,16]. Ultrasonography was adopted once a day 4 h after completion of EN using the following formula: GRV = 27.0 + 14.6 × gastric antral cross-sectional area - 1.28 × age, where gastric antral cross-sectional area = (anteroposterior diameter × craniocaudal diameter × II)/4[17]; (2) Diarrhea, which was defined as having three or more loose or liquid stools within 24 h with a stool weight greater than 200–250 g/day (estimated by assistant nurses)[18]; (3) Vomiting, which was defined as the expulsion of gastric contents from the oropharynx or nasopharynx one or more times a day[19]; (4) Aspiration, which referred to the entry of oropharyngeal food, secretions, or gastroesophageal reflux into the subglottic airway[20]; (5) Regurgitation, which referred to the reflux of gastric contents into the oropharynx without nausea, retching, or straining[21]; (6) Constipation, which was considered a reduction in the frequency of defecation to less than three times a week and difficulty defecating or dry stools[22]; and (7) Abdominal distention, which was considered an uncomfortable feeling of fullness and distension of the abdomen, and abdominal ultrasound showed gas or dilation of the bowel[21].

**Predictor selection:** We searched databases and consulted with medical experts in GI surgery and critical care medicine (see Supplementary Tables 1 and 2, which demonstrates the literature screening and factor coding results). Eligible studies had a primary endpoint of EFI occurring when diagnosed with GI symptoms. After expert group discussion, the predictor of proton-pump inhibitor use was excluded. The following 14 predictors were selected: age[23-29]; trauma (including blunt trauma, penetrating trauma, and burns)[30-32]; head injury (including postoperative neurosurgery and brain trauma)[33]; sepsis[34]; abdominal surgery[23,31,32]; GI disease (including GI surgery, GI inflammation, *etc.*)[11,23,28]; blood glucose[35,36]; serum albumin (hypoproteinemia or abnormal content level of albumin)[37]; electrolyte disorders (abnormal content level of K, Na, Cl, Mg, Ca, and P)[38]; mechanical ventilation (had or having mechanical ventilation)[5,23,26]; sedative and analgesic medicine (fentanyl, dexmedetomidine, propofol, and so on)[39]; catecholamine medicine (epinephrine, norepinephrine, and dopamine)[40,41]; early feeding (feeding initiated within 48 h after admission to the ICU)[40]; and tube feeding protocol (feeding formulas, largest feeding speeds, and largest total volume).

### Data sources/measurement

A structured form was prospectively used to obtain baseline data for the enrolled patients. When a patient began to receive EN, the nurses responsible for that patient recorded EN and GI symptoms daily. Doctors measured ultrasonographic results daily using a Doppler ultrasound diagnostic apparatus (GE Venue; GE Healthcare, Chicago, IL, United States). The follow-up endpoint was: (1) A diagnosis of EFI; (2) EN for more than 2 wk; (3) Transfer out of the ICU (including to home, to another hospital, and to another department in the hospital); (4) Gastric tube removal; or (5) Death.

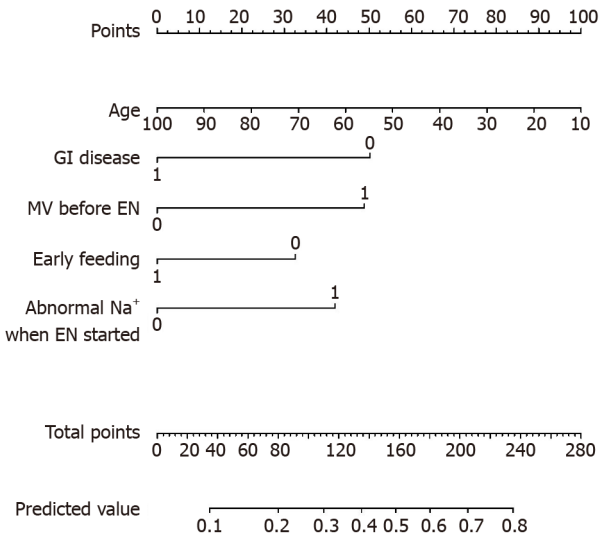
### Study size

Fourteen predictors were identified based on a literature analysis and expert consultation. The sample size of the case group was calculated to be 10 times greater than the predictors. Considering a 10% drop-off rate, we planned to include at least 155 patients.

### Statistical analyses

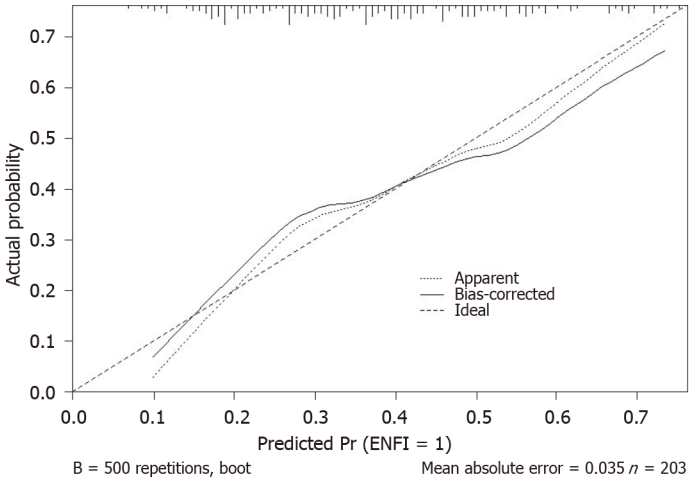
We searched for predictors of EFI that were repeatedly reported in studies or systematic reviews and could be easily ascertained in different settings by those with various clinical experience. These data were recorded by researchers for many days in the cohort and checked by 2 people.

Data analyses were conducted using IBM SPSS Statistics (version 25.0. Armonk, NY: IBM Corp) and R software (version 4.0.3; R Core Team). Descriptive data, including mean and standard deviation, frequency, percentage, median, and quartile, were used for the univariate analysis. When univariate analysis showed that independent variables were associated with intolerance ($P < 0.15$), they were included in the multiple logistic regression model. Variables were entered into the logistic regression




**DOI:** 10.4240/wjgs.v14.i12.1363 **Copyright** ©The Author(s) 2022.

**Figure 1 Nomogram for predicting enteral feeding intolerance in intensive care unit patients.** 0: No; 1: Yes. EN: Enteral nutrition; GI: Gastrointestinal; MV: Mechanical ventilation.




**DOI:** 10.4240/wjgs.v14.i12.1363 **Copyright** ©The Author(s) 2022.

**Figure 2 Calibration curve of the prediction model performance during internal validation.**

analysis, and we used the stepwise approach to perform the multivariable selection. Finally, we displayed the model using a nomogram because this format is more convenient.

Internal validation was performed using bootstrap validation. We assessed the predictive accuracy of the prognostic instrument with discrimination and calibration. Discrimination was calculated using the area under the curve, ranging from 0.5 (no discrimination) to 1.0 (perfect discrimination). Calibration was assessed using a calibration plot.

## RESULTS

### *Participants*

The three ICUs had 74 beds, and 684 patients were treated in the three ICUs during the study period. The cohort included 203 EN participants for the final analysis, including 153 patients from the comprehensive ICU, 34 patients from the neurosurgery ICU, and 16 patients from the emergency ICU. Overall, EFI occurred in 37.93% of ICU patients. The baseline characteristics of the enrolled patients are shown in Table 1.

**Table 1 Baseline characteristics of the participants included in the analysis**

| Variables | EFI group, *n* = 77 | Non-EFI group, *n* = 126 | Statistics | *P* value |
|---|---|---|---|---|
| Age in yr | 64.55 ± 15.86 | 69.06 ± 14.31 | $t$ = 2.091 | 0.038 |
| Sex, *n* (%) | | | $\chi^2$ = 1.919 | 0.166 |
| Male | 55 (71.4) | 78 (61.9) | | |
| Female | 22 (28.6) | 48 (38.1) | | |
| BMI in kg/m$^2$ | 23.64 ± 3.41 | 23.91 ± 4.70 | $t$ = 0.030 | 0.672 |
| APACHE II | 15.0 (9.0, 23.0) | 15.0 (9.5, 21.0) | $Z$ = -0.117 | 0.907 |
| SOFA | 6.0 (3.0, 10.0) | 5.0 (1.0, 8.0) | $Z$ = -1.533 | 0.125 |
| Diagnosis, *n* (%) | | | $\chi^2$ = 1.574 | 0.986 |
| Respiratory disease | 15 (19.5) | 26 (20.6) | | |
| Circulatory disease | 6 (7.8) | 9 (7.1) | | |
| Neurological disease | 12 (15.6) | 25 (19.8) | | |
| Digestive disease | 11 (14.3) | 18 (14.3) | | |
| Post-surgery | 22 (28.6) | 30 (23.8) | | |
| Sepsis | 5 (6.5) | 7 (5.6) | | |
| Multiple trauma | 3 (3.9) | 4 (3.2) | | |
| Other | 3 (3.9) | 7 (5.6) | | |
| Endpoint event, *n* (%) | | | | |
| Diagnosis of EFI | 77 (100) | | | |
| EN for more than 2 wk | | 35 (27.8) | | |
| Transfer out of the ICU | | 65 (51.6) | | |
| Gastric tube removal | | 18 (14.3) | | |
| Death | | 8 (6.3) | | |

APACHE II: Acute physiology and chronic health evaluation II; BMI: Body mass index; EFI: Enteral feeding intolerance; EN: Enteral nutrition; ICU: Intensive care unit; SOFA: Sepsis-related organ failure assessment.

### *EFI occurrence*

A total of 77 patients were included in the case group. EFI occurred more often in the first 7 d after EN started, and more than 90% of EFI cases lasted less than 3 d. Diarrhea, distention, and regurgitation were the most common GI symptoms among patients with EFI. The EFI occurrence in the case group is shown in Table 2.

### *Selected factors for the model*

Univariate analysis of the cohort (Table 3) identified an association between EFI and seven predictors that have been consistently reported in the literature; these include age, GI disease, medical history of mechanical ventilation, mechanical ventilation occupied, sedatives, early feeding, and feeding formula. Four novel potential predictors were also identified, including abnormal serum sodium and serum phosphorus before EN was started and abnormal serum sodium and serum chlorine when EN was started. These variables were entered into a multivariate model. Sepsis was also included in the model because clinical experts strongly recommended it.

### *Model fitting*

We applied the stepwise approach to perform multivariable selection, and five variables were included for the final analysis. Age, GI disease, and early feeding decreased the risk of EFI in the ICU. Mechanical ventilation started before EN and abnormal serum sodium when EN was started increased the risk of EFI in the ICU. We fitted the model using the final variables to obtain the final CPM (Table 4).

### *Predictive nomogram for the probability of EFI*

The nomogram illustrated the strength of the association of the predictors with the outcome (Figure 1).

**Table 2 Enteral feeding intolerance occurrence in the case group, *n* (%)**

| Variables | Case group, *n* = 77 |
|---|---|
| EN tube | |
| Nasogastric | 72 (93.5) |
| Nasal jejunal | 3 (3.9) |
| Jejunostomy | 2 (2.6) |
| When EFI occurred after EN started | |
| 1-3 d | 20 (26.0) |
| 4-7 d | 32 (41.6) |
| 8-14 d | 25 (32.5) |
| Number of days EFI lasted | |
| 1 d | 46 (59.7) |
| 2-3 d | 28 (36.4) |
| ≥ 4 d | 3 (3.9) |
| GI symptoms | |
| Diarrhea | 31 (40.3) |
| Abdominal distention | 22 (28.6) |
| Regurgitation | 14 (18.2) |
| Vomiting | 5 (6.5) |
| Aspiration | 2 (2.6) |
| Large GRV | 2 (2.6) |
| Constipation | 1 (1.3) |

EFI: Enteral feeding intolerance; EN: Enteral nutrition; GI: Gastrointestinal; GRV: Gastric residual volume.

The "0" indicated "NO" (*i.e.* the patient had no history of GI disease, did not receive mechanical ventilation before EN, did not receive early feeding, and/or had no abnormal serum sodium when EN was started), and the "1" indicated "YES" (*i.e.* the patient had a history of GI disease, received mechanical ventilation before EN, received early feeding, and/or had abnormal serum sodium when EN was started). The variable of "age" was a continuous variable. On the point scale axis, each variable was given a point based on the value. A total score could be easily calculated by adding every single point. By projecting the total points to the lower total point scale, we were able to estimate the probability of EFI. According to statistical standards, if 1 patient's predictive probability was more than 0.5, then there was a higher possibility that EFI will occur.

### *Performance of the nomogram*

We did the bootstrap validation, and model performance showed an area under the curve of 0.70. The calibration curve of the model's performance is demonstrated in Figure 2.

## DISCUSSION

We developed a novel practical prognostic instrument for predicting the risk of EFI in the ICU that may support clinicians when making treatment recommendations for patients receiving EN. Development of the model followed established recommendations. We identified three protective predictors, namely age, GI disease, and early feeding. Moreover, two risk factors were determined, namely mechanical ventilation before EN started and abnormal serum sodium. The internally validated area under the curve was 0.70 for the model to predict EFI outcomes.

We developed the CPM using an assembled population from three different ICU departments at one center. We made every effort to enroll patients with different diseases. Therefore, our model could apply to most situations in the ICU. To control for potential bias, the data of every patient were divided into three parts. The basic information was recorded by a researcher, the daily EN data were recorded

**Table 3 Univariate analysis of predictors associated with enteral feeding intolerance**

| Variables | EFI group, *n* = 77 | Non-EFI group, *n* = 126 | Statistics | *P* value |
|---|---|---|---|---|
| Age in yr, mean ± SD | 64.55 ± 15.86 | 69.06 ± 14.31 | $t$ = 2.091 | 0.038 |
| Sex, *n* (%) | | | $\chi^2$ = 1.919 | 0.166 |
| Male | 55 (71.4) | 78 (61.9) | | |
| Female | 22 (28.6) | 48 (38.1) | | |
| Diabetes, *n* (%) | 20 (26.0) | 33 (26.2) | $\chi^2$ = 0.001 | 0.973 |
| Abdominal surgery, *n* (%) | 9 (11.7) | 21 (16.7) | $\chi^2$ = 0.941 | 0.332 |
| GI disease, *n* (%) | 15 (19.5) | 37 (29.4) | $\chi^2$ = 2.451 | 0.117 |
| Head injury, *n* (%) | 14 (18.2) | 18 (14.3) | $\chi^2$ = 0.546 | 0.460 |
| Sepsis, *n* (%) | 5 (6.5) | 12 (9.5) | $\chi^2$ = 0.572 | 0.449 |
| Trauma, *n* (%) | 3 (3.9) | 8 (6.3) | | 0.539 |
| Analgesic, *n* (%) | 33 (42.9) | 49 (38.9) | $\chi^2$ = 0.313 | 0.576 |
| Sedative, *n* (%) | 49 (63.6) | 58 (46.0) | $\chi^2$ = 5.942 | 0.015 |
| Catecholamines, *n* (%) | 22 (28.6) | 26 (20.6) | $\chi^2$ = 1.667 | 0.197 |
| Early feeding, *n* (%) | 42 (54.5) | 88 (69.8) | $\chi^2$ = 4.856 | 0.028 |
| Feeding volume in mL | 1000 (500, 1500) | 1000 (500, 1400) | $Z$ = -0.495 | 0.620 |
| Feeding speed in mL/h | 80 (50, 100) | 80 (50, 100) | $Z$ = -0.220 | 0.826 |
| Mechanical ventilation, *n* (%) | | | | |
| Before EN started | 54 (70.1) | 60 (47.6) | $\chi^2$ = 9.837 | 0.002 |
| When EN started | 54 (70.1) | 64 (50.8) | $\chi^2$ = 7.342 | 0.007 |
| Abnormal level of albumin, *n* (%) | | | | |
| Diagnosis with hypoproteinemia | 1 (1.3) | 4 (3.2) | | 0.652 |
| Albumin before EN | 14 (18.2) | 21 (16.7) | $\chi^2$ = 0.077 | 0.782 |
| Albumin when EN started | 1 (1.3) | 6 (4.8) | | 0.257 |
| Abnormal level of electrolytes, *n* (%) | | | | |
| Diagnosis with electrolyte disorders | 5 (6.5) | 12 (9.5) | $\chi^2$ = 0.572 | 0.449 |
| Before EN started, *n* (%) | | | | |
| Potassium | 32 (41.6) | 45 (35.7) | $\chi^2$ = 0.693 | 0.405 |
| Sodium | 38 (49.4) | 49 (38.9) | $\chi^2$ = 2.136 | 0.144 |
| Chlorine | 54 (70.1) | 88 (69.8) | $\chi^2$ = 0.002 | 0.965 |
| Magnesium | 53 (68.8) | 81 (64.3) | $\chi^2$ = 0.440 | 0.507 |
| Calcium | 69 (89.6) | 118 (93.7) | $\chi^2$ = 1.075 | 0.300 |
| Phosphorus | 55 (71.4) | 77 (61.1) | $\chi^2$ = 2.237 | 0.135 |
| When EN started, *n* (%) | | | | |
| Potassium | 14 (18.2) | 22 (17.5) | $\chi^2$ = 0.017 | 0.896 |
| Sodium | 32 (41.6) | 33 (26.2) | $\chi^2$ = 5.186 | 0.023 |
| Chlorine | 55 (71.4) | 76 (60.3) | $\chi^2$ = 2.578 | 0.108 |
| Magnesium | 38 (49.4) | 59 (46.8) | $\chi^2$ = 0.122 | 0.727 |
| Calcium | 69 (89.6) | 113 (89.7) | $\chi^2$ = 0.000 | 0.987 |
| Phosphorus | 43 (55.8) | 63 (50.0) | $\chi^2$ = 0.654 | 0.419 |
| Feeding formula, *n* (%) | | | $\chi^2$ = 10.861 | 0.048 |
| Rice soup | 10 (13.0) | 5 (4.0) | | |

| | | |
|---|---|---|
| Peptisorb | 14 (18.2) | 39 (31.0) |
| Nutrison Fibre | 15 (19.5) | 33 (26.2) |
| TPF-D[1] | 24 (31.2) | 32 (25.4) |
| TPF-T[2] | 3 (3.9) | 2 (1.6) |
| Water | 11 (14.3) | 15 (11.9) |

[1]TPF-D: Enteral Nutritional Emulsion "RuiDai," suitable for diabetics.
[2]TPF-T: Enteral Nutritional Emulsion "RuiNeng", rich in fat and calorie.
EN: Enteral nutrition; EFI: Enteral feeding intolerance; GI: Gastrointestinal.

**Table 4 Final clinical prediction model of enteral feeding intolerance in the intensive care unit**

| Variable | OR (95%CI) | *Z* statistic | *P* value |
|---|---|---|---|
| Age in yr | 0.98 (0.96, 1.00) | -1.881 | 0.060 |
| GI disease | 0.41 (0.18, 0.86) | -2.254 | 0.024 |
| Early feeding | 0.56 (0.28, 1.11) | -1.652 | 0.099 |
| MV before EN | 2.39 (1.27, 4.58) | 2.682 | 0.007 |
| Abnormal $Na^+$ when EN started | 2.11 (1.11, 4.07) | 2.262 | 0.024 |

EN: Enteral nutrition; GI: Gastrointestinal; MV: Mechanical ventilation; OR: Odds ratio.

by clinical nurses, and the ultrasonographic data were recorded by ICU doctors trained in performing ultrasonography. The researcher was unable to obtain the other data before the follow-up ended. In addition, we utilized the quantitative method of content analysis to guarantee the scientific rationality of our study.

Alternative predictors were found from the literature and clinical experts. When we performed univariate analysis, we included predictors with *P* values smaller than 0.15 with the aim that no possible significant factors were omitted. We determined the potential effective predictors based on the *P* value and by considering those predictors recommended by experts or that were highly suspected. These predictors were well-defined, easily measured, and routinely available. In internal validation, we used the bootstrap validation to assess discrimination and calibration and repeated the validation 500 times for accuracy.

In our study, we found that older patients were less likely to develop EFI. This result is similar to the results of existing studies[28,29] but contrary to conventional wisdom. After a literature review, expert consultation, and clinical observation, we identified some reasons that explain this counterintuitive result. Older patients are given less EN because of their energy requirements and physical condition. In our study, patients aged 60 years or older received on average less EN per day than younger patients [900 (500, 1200) *vs* 1000 (500, 1500), respectively]. Critically ill elderly patients have many chronic diseases, such as diabetes, chronic gastroenteritis, and hepatic dysfunction. To promote GI motility and regulate water balance, nutrition teams often use water or rice soup as the initial nutrition for the elderly. Water or rice soup is used for a period of time to facilitate a later transition to an EN emulsion, which may reduce stimulation of the GI tract in elderly patients[42]. The direct relationship between age and EFI requires further experimental analysis to completely understand the relationship.

Similarly, we found that ICU patients with GI disease (*e.g.*, pancreatitis, post-gastrectomy, or upper GI hemorrhage) were less likely to experience EFI. In our study, patients with GI disease were likely given less feed to avoid worsening their health issues [patients with GI disease: 575 (275, 975) *vs* patients without GI disease: 1000 (725, 1500), $P < 0.000$]. In clinical practice, the intention of a small volume of EN is not to meet energy requirements but to maintain the structural and functional integrity of the GI tract [43]. Therefore, GI symptoms may be slight and difficult to observe in this circumstance. In addition, medical interventions (*e.g.*, metoclopramide, probiotics, acupuncture, and enema) are administered to patients diagnosed with GI disease[44-46]. This advance treatment may lead to a decreased occurrence of EFI.

A previous attempt to develop a prediction model yielded promising results but had limited applicability because its target population was patients with gastrectomy for gastric cancer rather than ICU patients[47]. Some preventive measures have been implemented to reduce EFI occurrence in ICU patients, such as fat-modified enteral formula and bolus enteral feeding methods[48-50]. However, there is a gap in the knowledge of distinguishing patients at high risk of EFI. Medical workers can apply our model when it is recommended that a patient receives EN. By analyzing the conditions between the

period of being admitted to the ICU and receiving EN, patients at high risk are determined and are given a set of preventive measures, which is an effective measure for reducing the occurrence of EFI. Notably, experienced clinical workers already have some knowledge of which patients will be high risk for EFI and have put protective measures into clinical practice. Based on the current nutritional management practices in our center, the predictive model should be used knowing that high-risk patients may have already received preventive measures.

There are potential limitations to our study. Because of time and manpower, we developed the model using a small sample size in a single center. The effect of sepsis, trauma, electrolytes could not be properly addressed because of the small sample size. The differences between these factors between the two groups may be overlooked. Due to the actual situation, the effect of various formula feeds could not be ascertained because of use of several feeding formulas. In addition, the representativeness and predictive performance of our model may have limitations. However, this limit may be slight because the final model includes only five variables. Moreover, the delivery strategy of intermittent or continuous feeding and the temperature of the nutrient solution contribute to EFI occurrence[51]. Our study did not consider these effects because all included patients received room temperature continuous feeding in our medical center. During the study, there may have been some confounding factors that we did not consider, including etiology, medications, and fluids. For future research, these factors should be considered, and we suggest external validation in different centers over additional time periods. In the future, we hope to be able to analyze the effect of individual factors on EFI on the basis of expanding the sample size. In addition, applying our prediction model to additional interventional studies as a tool to optimize clinical management is a long-term goal.

## CONCLUSION

We have developed and internally validated a CPM for predicting the risk of EFI in patients receiving EN in the ICU. The developed nomogram is easy to use and might help clinicians make individualized predictions of each patient's probability of experiencing EFI. Early identification of patients at high risk of EFI can greatly help doctors and nurses better manage clinical care. Clinical nurses can implement different nursing measures according to each patient's risk. These measures will ultimately help ICU patients achieve better nutritional support and a quicker recovery.

## ARTICLE HIGHLIGHTS

### *Research background*

Enteral nutrition (EN) is essential for critically ill patients, but some patients develop enteral feeding intolerance (EFI). Intolerance can hinder a patient's energy intake and recovery. Therefore, predicting EFI is of vital importance in clinical practice.

### *Research motivation*

Determining which patients are at high risk of developing EFI based on their current physical condition and medical treatment will allow physicians and nurses to individualize medical care and begin EFI preventative measures for the high-risk patients.

### *Research objectives*

To develop a clinical prediction model (CPM) to predict the risk of EFI in patients receiving EN in the intensive care unit (ICU). We currently know that many factors can influence the development of EFI.

### *Research methods*

A prospective cohort study was performed, and we prospectively recorded enrolled patients' data. Prospective cohort studies can more realistically document patient data and clinical responses, reducing human intervention. We used ultrasound measurement of the antrum cross-sectional area to measure gastric residual volume, which can effectively reduce the occurrence of complications and increase the efficiency of feeding.

### *Research results*

We developed and internally validated a CPM for predicting the risk of EFI in patients receiving EN in the ICU. After univariate and multivariate analyses, five factors were used for the CPM, including age, gastrointestinal disease, early feeding, mechanical ventilation before EN started, and abnormal serum sodium when EN started.

### *Research conclusions*

This model can help clinical workers to identify patients at high risk for EFI earlier, which will allow these patients to receive preventative measures in advance.

### *Research perspectives*

In the future, an increased sample size and analyzing more variables will develop a more accurate clinical predictive model. Prospective cohort studies and randomized control studies are the best methods for the future research.

## ACKNOWLEDGEMENTS

We thank the patients whose anonymized data were used for this research. We acknowledge all collaborators in this study and all clinical workers in the intensive care units. We thank the nurses responsible for helping us collect data every day. We thank Professor Lu and Professor Fang for their guidance on the research project. We thank Mrs. Kang, the statistician, for her help in the data analysis stage.

## FOOTNOTES

**Author contributions:** Lu XM contributed to conceptualization, methodology, formal analysis, investigation, data curation, writing the original draft, and project administration; Jia DS contributed to conceptualization, methodology, investigation, and writing the original draft; Wang R and Yang Q contributed to methodology, investigation, and resources; Jin SS contributed to investigation and resources; Chen L contributed to conceptualization, methodology, resources, review and editing of the manuscript, supervision, and project administration; All authors read and approved the final manuscript.

**Institutional review board statement:** The study protocol was approved (numbered 2020KY230) by the appropriate ethics committee (Medical Ethics Committee of Shanghai General Hospital) on December 23, 2020.

**Informed consent statement:** Before we enrolled patients, informed consent was obtained from the patient or next of kin. Since we needed to complete daily ultrasonography of patients, we needed to obtain their informed consent.

**Conflict-of-interest statement:** The authors declare having no conflicts of interest.

**Data sharing statement:** If there is a need to get the dataset, please contact Xue-Mei Lu (lu_xm1118@163.com). The information of the patients in the dataset is anonymized.

**STROBE statement:** The authors have read the STROBE Statement–checklist of items, and the manuscript was prepared and revised according to the STROBE Statement–checklist of items.



**Country/Territory of origin:** China

**ORCID number:** Lan Chen 0000-0002-4309-0240.

**S-Editor:** Zhang H
**L-Editor:** A
**P-Editor:** Zhang H

## REFERENCES

1 **Baiu I**, Spain DA. Enteral Nutrition. *JAMA* 2019; **321**: 2040 [PMID: 31135851 DOI: 10.1001/jama.2019.4407]
2 **Singer P**, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, Hiesmayr M, Mayer K, Montejo JC, Pichard C, Preiser JC, van Zanten ARH, Oczkowski S, Szczeklik W, Bischoff SC. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr* 2019; **38**: 48-79 [PMID: 30348463 DOI: 10.1016/j.clnu.2018.08.037]
3 **Barnes JL**. Enteral Nutrients and Gastrointestinal Physiology. *J Infus Nurs* 2018; **41**: 35-42 [PMID: 29293196 DOI: 10.1097/NAN.0000000000000260]
4 **McClave SA**, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, McCarthy MS, Davanos E, Rice

TW, Cresci GA, Gervasio JM, Sacks GS, Roberts PR, Compher C; Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2016; **40**: 159-211 [PMID: 26773077 DOI: 10.1177/0148607115621863]

5 **Blumenstein I**, Shastri YM, Stein J. Gastroenteric tube feeding: techniques, problems and solutions. *World J Gastroenterol* 2014; **20**: 8505-8524 [PMID: 25024606 DOI: 10.3748/wjg.v20.i26.8505]

6 **Heyland DK**, van Zanten ARH, Grau-Carmona T, Evans D, Beishuizen A, Schouten J, Hoiting O, Bordejé ML, Krell K, Klein DJ, Gonzalez J, Perez A, Brown R, James J, Harris MS; Investigators of the PROMOTE LP101-CL-201 Trial. A multicenter, randomized, double-blind study of ulimorelin and metoclopramide in the treatment of critically ill patients with enteral feeding intolerance: PROMOTE trial. *Intensive Care Med* 2019; **45**: 647-656 [PMID: 31062046 DOI: 10.1007/s00134-019-05593-2]

7 **Reintam Blaser A**, Deane AM, Preiser JC, Arabi YM, Jakob SM. Enteral Feeding Intolerance: Updates in Definitions and Pathophysiology. *Nutr Clin Pract* 2021; **36**: 40-49 [PMID: 33242218 DOI: 10.1002/ncp.10599]

8 **Volkert D**, Beck AM, Cederholm T, Cruz-Jentoft A, Goisser S, Hooper L, Kiesswetter E, Maggio M, Raynaud-Simon A, Sieber CC, Sobotka L, van Asselt D, Wirth R, Bischoff SC. ESPEN guideline on clinical nutrition and hydration in geriatrics. *Clin Nutr* 2019; **38**: 10-47 [PMID: 30005900 DOI: 10.1016/j.clnu.2018.05.024]

9 **Deane A**, Chapman MJ, Fraser RJ, Bryant LK, Burgstad C, Nguyen NQ. Mechanisms underlying feed intolerance in the critically ill: implications for treatment. *World J Gastroenterol* 2007; **13**: 3909-3917 [PMID: 17663503 DOI: 10.3748/wjg.v13.i29.3909]

10 **Preiser JC**, Arabi YM, Berger MM, Casaer M, McClave S, Montejo-González JC, Peake S, Reintam Blaser A, Van den Berghe G, van Zanten A, Wernerman J, Wischmeyer P. A guide to enteral nutrition in intensive care units: 10 expert tips for the daily practice. *Crit Care* 2021; **25**: 424 [PMID: 34906215 DOI: 10.1186/s13054-021-03847-4]

11 **Heyland DK**, Ortiz A, Stoppe C, Patel JJ, Yeh DD, Dukes G, Chen YJ, Almansa C, Day AG. Incidence, Risk Factors, and Clinical Consequence of Enteral Feeding Intolerance in the Mechanically Ventilated Critically Ill: An Analysis of a Multicenter, Multiyear Database. *Crit Care Med* 2021; **49**: 49-59 [PMID: 33148950 DOI: 10.1097/CCM.0000000000004712]

12 **Collins GS**, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ* 2015; **350**: g7594 [PMID: 25569120 DOI: 10.1136/bmj.g7594]

13 **Dankers FJWM**, Traverso A, Wee L, van Kuijk SMJ. Prediction Modeling Methodology. 2018 Dec 22. In: Kubben P, Dumontier M, Dekker A. Fundamentals of Clinical Data Science [Internet]. Cham (CH): Springer; 2019 [PMID: 31314250]

14 **National Heart**, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. , Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, Morris A, Dong N, Rock P. Initial trophic *vs* full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA* 2012; **307**: 795-803 [PMID: 22307571 DOI: 10.1001/jama.2012.137]

15 **Sharma V**, Gudivada D, Gueret R, Bailitz J. Ultrasound-Assessed Gastric Antral Area Correlates With Aspirated Tube Feed Volume in Enterally Fed Critically Ill Patients. *Nutr Clin Pract* 2017; **32**: 206-211 [PMID: 28362573 DOI: 10.1177/0884533616681530]

16 **Arabi YM**, Aldawood AS, Haddad SH, Al-Dorzi HM, Tamim HM, Jones G, Mehta S, McIntyre L, Solaiman O, Sakkijha MH, Sadat M, Afesh L; PermiT Trial Group. Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults. *N Engl J Med* 2015; **372**: 2398-2408 [PMID: 25992505 DOI: 10.1056/NEJMoa1502826]

17 **Sharma S**, Deo AS, Raman P. Effectiveness of standard fasting guidelines as assessed by gastric ultrasound examination: A clinical audit. *Indian J Anaesth* 2018; **62**: 747-752 [PMID: 30443056 DOI: 10.4103/ija.IJA_54_18]

18 **Nemeth V**, Pfleghaar N. Diarrhea. 2021 Nov 29. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [PMID: 28846339]

19 **Reintam Blaser A**, Jakob SM, Starkopf J. Gastrointestinal failure in the ICU. *Curr Opin Crit Care* 2016; **22**: 128-141 [PMID: 26835609 DOI: 10.1097/MCC.0000000000000286]

20 **Kollmeier BR**, Keenaghan M. Aspiration Risk. 2022 Jun 30. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [PMID: 29262188]

21 **Reintam Blaser A**, Malbrain ML, Starkopf J, Fruhwald S, Jakob SM, De Waele J, Braun JP, Poeze M, Spies C. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. *Intensive Care Med* 2012; **38**: 384-394 [PMID: 22310869 DOI: 10.1007/s00134-011-2459-y]

22 **Diaz S**, Bittar K, Mendez MD. Constipation. 2022 Jul 25. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [PMID: 30020663]

23 **Xu L**, Wang T, Chen T, Yang WQ, Liang ZP, Zhu JC. Identification of risk factors for enteral feeding intolerance screening in critically ill patients. *Saudi Med J* 2017; **38**: 816-825 [PMID: 28762434 DOI: 10.15537/smj.2017.8.20393]

24 **Sierp EL**, Kurmis R, Lange K, Yandell R, Chapman M, Greenwood J, Chapple LS. Nutrition and Gastrointestinal Dysmotility in Critically Ill Burn Patients: A Retrospective Observational Study. *JPEN J Parenter Enteral Nutr* 2021; **45**: 1052-1060 [PMID: 32767430 DOI: 10.1002/jpen.1979]

25 **Nguyen NQ**, Ng MP, Chapman M, Fraser RJ, Holloway RH. The impact of admission diagnosis on gastric emptying in critically ill patients. *Crit Care* 2007; **11**: R16 [PMID: 17288616 DOI: 10.1186/cc5685]

26 **Adike A**, Quigley EM. Gastrointestinal motility problems in critical care: a clinical perspective. *J Dig Dis* 2014; **15**: 335-344 [PMID: 24673805 DOI: 10.1111/1751-2980.12147]

27 **Mao Z**, Liu G, Yu Q, Qi S, Lou Y, Liu C, Li Q, Xue C, Kang H, Hong Q, Zhou F. Association between serum lactate levels and enteral feeding intolerance in septic patients treated with vasopressors: a retrospective cohort study. *Ann Transl Med* 2020; **8**: 1240 [PMID: 33178772 DOI: 10.21037/atm-20-6317]

28 **Gungabissoon U**, Hacquoil K, Bains C, Irizarry M, Dukes G, Williamson R, Deane AM, Heyland DK. Prevalence, risk factors, clinical consequences, and treatment of enteral feed intolerance during critical illness. *JPEN J Parenter Enteral*

*Nutr* 2015; **39**: 441-448 [PMID: 24637246 DOI: 10.1177/0148607114526450]
29 **Wang K**, McIlroy K, Plank LD, Petrov MS, Windsor JA. Prevalence, Outcomes, and Management of Enteral Tube Feeding Intolerance: A Retrospective Cohort Study in a Tertiary Center. *JPEN J Parenter Enteral Nutr* 2017; **41**: 959-967 [PMID: 26850741 DOI: 10.1177/0148607115627142]
30 **Fraser RJ**, Bryant L. Current and future therapeutic prokinetic therapy to improve enteral feed intolerance in the ICU patient. *Nutr Clin Pract* 2010; **25**: 26-31 [PMID: 20130155 DOI: 10.1177/0884533609357570]
31 **Virani FR**, Peery T, Rivas O, Tomasek J, Huerta R, Wade CE, Lee J, Holcomb JB, Uray K. Incidence and Effects of Feeding Intolerance in Trauma Patients. *JPEN J Parenter Enteral Nutr* 2019; **43**: 742-749 [PMID: 30508254 DOI: 10.1002/jpen.1469]
32 **Vazquez-Sandoval A**, Ghamande S, Surani S. Critically ill patients and gut motility: Are we addressing it? *World J Gastrointest Pharmacol Ther* 2017; **8**: 174-179 [PMID: 28828195 DOI: 10.4292/wjgpt.v8.i3.174]
33 **Tan M**, Zhu JC, Yin HH. Enteral nutrition in patients with severe traumatic brain injury: reasons for intolerance and medical management. *Br J Neurosurg* 2011; **25**: 2-8 [PMID: 21323401 DOI: 10.3109/02688697.2010.522745]
34 **Hu B**, Sun R, Wu A, Ni Y, Liu J, Guo F, Ying L, Ge G, Ding A, Shi Y, Liu C, Xu L, Jiang R, Lu J, Lin R, Zhu Y, Wu W, Xie B. Prognostic Value of Prolonged Feeding Intolerance in Predicting All-Cause Mortality in Critically Ill Patients: A Multicenter, Prospective, Observational Study. *JPEN J Parenter Enteral Nutr* 2020; **44**: 855-865 [PMID: 31429970 DOI: 10.1002/jpen.1693]
35 **Nguyen N**, Ching K, Fraser R, Chapman M, Holloway R. The relationship between blood glucose control and intolerance to enteral feeding during critical illness. *Intensive Care Med* 2007; **33**: 2085-2092 [PMID: 17909745 DOI: 10.1007/s00134-007-0869-7]
36 **Camilleri M**, Parkman HP, Shafi MA, Abell TL, Gerson L; American College of Gastroenterology. Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 2013; **108**: 18-37; quiz 38 [PMID: 23147521 DOI: 10.1038/ajg.2012.373]
37 **Atasever AG**, Ozcan PE, Kasali K, Abdullah T, Orhun G, Senturk E. The frequency, risk factors, and complications of gastrointestinal dysfunction during enteral nutrition in critically ill patients. *Ther Clin Risk Manag* 2018; **14**: 385-391 [PMID: 29503558 DOI: 10.2147/TCRM.S158492]
38 **Btaiche IF**, Chan LN, Pleva M, Kraft MD. Critical illness, gastrointestinal complications, and medication therapy during enteral feeding in critically ill adult patients. *Nutr Clin Pract* 2010; **25**: 32-49 [PMID: 20130156 DOI: 10.1177/0884533609357565]
39 **Heinonen T**, Ferrie S, Ferguson C. Gut function in the intensive care unit - What is 'normal'? *Aust Crit Care* 2020; **33**: 151-154 [PMID: 30745063 DOI: 10.1016/j.aucc.2018.12.007]
40 **Merchan C**, Altshuler D, Aberle C, Papadopoulos J, Schwartz D. Tolerability of Enteral Nutrition in Mechanically Ventilated Patients With Septic Shock Who Require Vasopressors. *J Intensive Care Med* 2017; **32**: 540-546 [PMID: 27377392 DOI: 10.1177/0885066616656799]
41 **Reintam A**, Parm P, Redlich U, Tooding LM, Starkopf J, Köhler F, Spies C, Kern H. Gastrointestinal failure in intensive care: a retrospective clinical study in three different intensive care units in Germany and Estonia. *BMC Gastroenterol* 2006; **6**: 19 [PMID: 16792799 DOI: 10.1186/1471-230X-6-19]
42 **Boirie Y**, Morio B, Caumon E, Cano NJ. Nutrition and protein energy homeostasis in elderly. *Mech Ageing Dev* 2014; **136-137**: 76-84 [PMID: 24486557 DOI: 10.1016/j.mad.2014.01.008]
43 **Zhang D**, Li H, Li Y, Qu L. Gut rest strategy and trophic feeding in the acute phase of critical illness with acute gastrointestinal injury. *Nutr Res Rev* 2019; **32**: 176-182 [PMID: 30919797 DOI: 10.1017/S0954422419000027]
44 **Dossett ML**, Cohen EM, Cohen J. Integrative Medicine for Gastrointestinal Disease. *Prim Care* 2017; **44**: 265-280 [PMID: 28501229 DOI: 10.1016/j.pop.2017.02.002]
45 **Floch MH**. The Role of Prebiotics and Probiotics in Gastrointestinal Disease. *Gastroenterol Clin North Am* 2018; **47**: 179-191 [PMID: 29413011 DOI: 10.1016/j.gtc.2017.09.011]
46 **Deane AM**, Chapman MJ, Abdelhamid YA. Any news from the prokinetic front? *Curr Opin Crit Care* 2019; **25**: 349-355 [PMID: 31247631 DOI: 10.1097/MCC.0000000000000634]
47 **Xiaoyong W**, Xuzhao L, Deliang Y, Pengfei Y, Zhenning H, Bin B, Zhengyan L, Fangning P, Shiqi W, Qingchuan Z. Construction of a model predicting the risk of tube feeding intolerance after gastrectomy for gastric cancer based on 225 cases from a single Chinese center. *Oncotarget* 2017; **8**: 99940-99949 [PMID: 29245951 DOI: 10.18632/oncotarget.21966]
48 **Reddy S**, Bailey M, Beasley R, Bellomo R, Mackle D, Psirides A, Young P. Effect of saline 0.9% or Plasma-Lyte 148 therapy on feeding intolerance in patients receiving nasogastric enteral nutrition. *Crit Care Resusc* 2016; **18**: 198-204 [PMID: 27604334]
49 **Qiu C**, Chen C, Zhang W, Kou Q, Wu S, Zhou L, Liu J, Ma G, Chen J, Chen M, Luo H, Zhang X, Lai J, Yu Z, Yu X, Liao W, Guan X, Ouyang B. Fat-Modified Enteral Formula Improves Feeding Tolerance in Critically Ill Patients: A Multicenter, Single-Blind, Randomized Controlled Trial. *JPEN J Parenter Enteral Nutr* 2017; **41**: 785-795 [PMID: 26350918 DOI: 10.1177/0148607115601858]
50 **Nasiri M**, Farsi Z, Ahangari M, Dadgari F. Comparison of Intermittent and Bolus Enteral Feeding Methods on Enteral Feeding Intolerance of Patients with Sepsis: A Triple-blind Controlled Trial in Intensive Care Units. *Middle East J Dig Dis* 2017; **9**: 218-227 [PMID: 29255580 DOI: 10.15171/mejdd.2017.77]
51 **Ma Y**, Cheng J, Liu L, Chen K, Fang Y, Wang G, Zhu J, Chen L. Intermittent *vs* continuous enteral nutrition on feeding intolerance in critically ill adults: A meta-analysis of randomized controlled trials. *Int J Nurs Stud* 2021; **113**: 103783 [PMID: 33161333 DOI: 10.1016/j.ijnurstu.2020.103783]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 December 27; 14(12): 1375-1386

DOI: 10.4240/wjgs.v14.i12.1375

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Prospective Study

# Real-time *in vivo* distal margin selection using confocal laser endomicroscopy in transanal total mesorectal excision for rectal cancer

Jie Tan, Hong-Li Ji, Yao-Wen Hu, Zhi-Ming Li, Bao-Xiong Zhuang, Hai-Jun Deng, Ya-Nan Wang, Ji-Xiang Zheng, Wei Jiang, Jun Yan

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Enomoto H, Japan; Krishnan A, United States

**Received:** July 16, 2022
**Peer-review started:** July 16, 2022
**First decision:** October 30, 2022
**Revised:** November 13, 2022
**Accepted:** December 6, 2022
**Article in press:** December 6, 2022
**Published online:** December 27, 2022

**Jie Tan, Hong-Li Ji, Yao-Wen Hu, Zhi-Ming Li, Bao-Xiong Zhuang, Hai-Jun Deng, Ya-Nan Wang, Ji-Xiang Zheng, Wei Jiang, Jun Yan,** Department of General Surgery, Nanfang Hospital, Guangzhou 510515, Guangdong Province, China

**Jun Yan,** Department of General Surgery, Southern Medical University, Guangzhou 510515, Guangdong Province, China

**Jun Yan,** Guangdong Provincial Key Laboratory of Precision Medicine for Gastrointestinal Tumor, Nanfang Hospital, Guangzhou 510515, Guangdong Province, China

**Corresponding author:** Jun Yan, MD, PhD, Chief Doctor, Professor, Surgeon, Department of General Surgery, Nanfang Hospital, No. 1838 North Guangzhou Road, Guangzhou 510515, Guangdong Province, China. yanjunfudan@163.com

## Abstract

### *BACKGROUND*

Transanal total mesorectal excision (TaTME) allows patients with ultralow rectal cancer to be treated with sphincter-saving surgery. However, accurate delineation of the distal resection margin (DRM), which is essential to achieve R0 resection for low rectal cancer in TaTME, is technically demanding.

### *AIM*

To assess the feasibility of optical biopsy using probe-based confocal laser endomicroscopy (pCLE) to select the DRM during TaTME for low rectal cancer.

### *METHODS*

A total of 43 consecutive patients who were diagnosed with low rectal cancer and scheduled for TaTME were prospectively enrolled from January 2019 to January 2021. pCLE was used to determine the distal edge of the tumor as well as the DRM during surgery. The final pathological report was used as the gold standard. The diagnostic accuracy of pCLE examination was calculated.

### *RESULTS*

A total of 86 pCLE videos of 43 patients were included in the analyses. The sensitivity, specificity and accuracy of real-time pCLE examination were 90.00%

[95% confidence interval (CI): 76.34%-97.21%], 86.96% (95%CI: 73.74%-95.06%) and 88.37% (95%CI: 79.65%-94.28%), respectively. The accuracy of blinded pCLE reinterpretation was 86.05% (95%CI: 76.89%-92.58%). Furthermore, our results show satisfactory interobserver agreement (κ = 0.767, standard error = 0.069) for the detection of cancer tissue by pCLE. There were no positive DRMs (≤ 1 mm) in this study. The median DRM was 7 mm [interquartile range (IQR) = 5-10 mm]. The median Wexner score was 5 (IQR = 3-6) at 6 mo after stoma closure.

*CONCLUSION*

Real-time *in vivo* pCLE examination is feasible and safe for selecting the DRM during TaTME for low rectal cancer (clinical trial registration number: NCT04016948).

**Key Words:** Transanal total mesorectal excision; Probe-based confocal laser endomicroscopy; Optical biopsy; Distal resection margin; Low rectal cancer



**Core Tip:** Transanal total mesorectal excision (TaTME) allows patients even with ultra-low rectal cancer to be treated with sphincter-saving surgery. However, low rectal cancer resection with sphincter preservation may lead to a positive distal resection margin (DRM), with a high risk for local recurrence. Confocal laser endomicroscopy (CLE) enables the real-time, *in vivo* optical biopsy of living tissue. Real-time *in vivo* probe-based CLE examination can provide optical biopsy and is feasible and safe for selecting the DRM during TaTME for low rectal cancer.

**Citation:** Tan J, Ji HL, Hu YW, Li ZM, Zhuang BX, Deng HJ, Wang YN, Zheng JX, Jiang W, Yan J. Real-time *in vivo* distal margin selection using confocal laser endomicroscopy in transanal total mesorectal excision for rectal cancer. *World J Gastrointest Surg* 2022; 14(12): 1375-1386
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i12/1375.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i12.1375

## INTRODUCTION

Colorectal cancer is the third most prevalent type of cancer and the second primary cause of cancer-related mortality worldwide[1]. Low rectal carcinoma often requires abdominoperineal resection and permanent abdominal colostomy, and it places major economic and psychological burdens on patients [2]. Transanal total mesorectal excision (TaTME) is increasingly adopted by colorectal surgeons in the treatment of patients with low rectal cancer[3,4]. This technique gives patients, even those with ultralow rectal cancer, the opportunity to undergo sphincter-saving surgery. However, low rectal cancer resection with sphincter preservation may lead to a positive distal resection margin (DRM), with a high risk for local recurrence[5-7]. To date, no devices have been used in the surgical field to guide resection margin selection. Frozen biopsy is recommended during surgery for low rectal cancer to confirm a negative DRM. However, it cannot be used to guide selection of the resection margin in real time, and it is a time-consuming, irreversible, and traumatic process. Accordingly, accurate delineation of the DRM is essential to achieve R0 resection for low rectal cancer.

Recently, several studies have reported that confocal laser endomicroscopy (CLE) enables the real-time, *in vivo* optical biopsy of living tissue[8-12]. It has the potential to fundamentally change the role of biopsy in the gastrointestinal field, and a state-of-the-art classification system (Miami classification) has been proposed for normal and pathological states in gastrointestinal diseases based on probe-based CLE (pCLE)[13]. However, no studies have investigated the feasibility of optical biopsy using pCLE in the real-time *in vivo* selection of the DRM during TaTME for low rectal cancer. We hypothesize that real-time *in vivo* pCLE examination can help surgeons select the DRM accurately and might contribute to improving the oncological and functional prognosis of low rectal cancer after treatment with TaTME. The aim of this study was to evaluate the feasibility of optical biopsy using pCLE for selecting the DRM during TaTME in the treatment of low rectal cancer.

## MATERIALS AND METHODS

### Study design

This was a prospective, single-center study that was approved by the Institutional Review Board of Nanfang Hospital of Southern Medical University. The study protocol was registered at ClinicalTrials.gov (No. NCT04016948).

### Patients

Patients who were diagnosed with low rectal cancer by preoperative endoscopic biopsy and scheduled for TaTME were prospectively enrolled in this study. Written informed consent was obtained from each patient prior to participation. Inclusion criteria were as follows: Diagnosis of low rectal cancer (tumor lying within 5 cm from the anal verge) and planned treatment with TaTME; age of at least 18 years; and American Society of Anesthesiologists class 1-3. The exclusion criteria were as follows: (1) T4b cancer as determined by computed tomography, magnetic resonance imaging or endoscopic examination; (2) Emergent case with obstruction or perforation; (3) Coagulopathy (international normalized ratio > 1.5 or prothrombin time < 50%); (4) Impaired renal function (creatinine level > 1.2 mg/dL); (5) Pregnancy; (6) Breastfeeding; and (7) Past history of allergies.

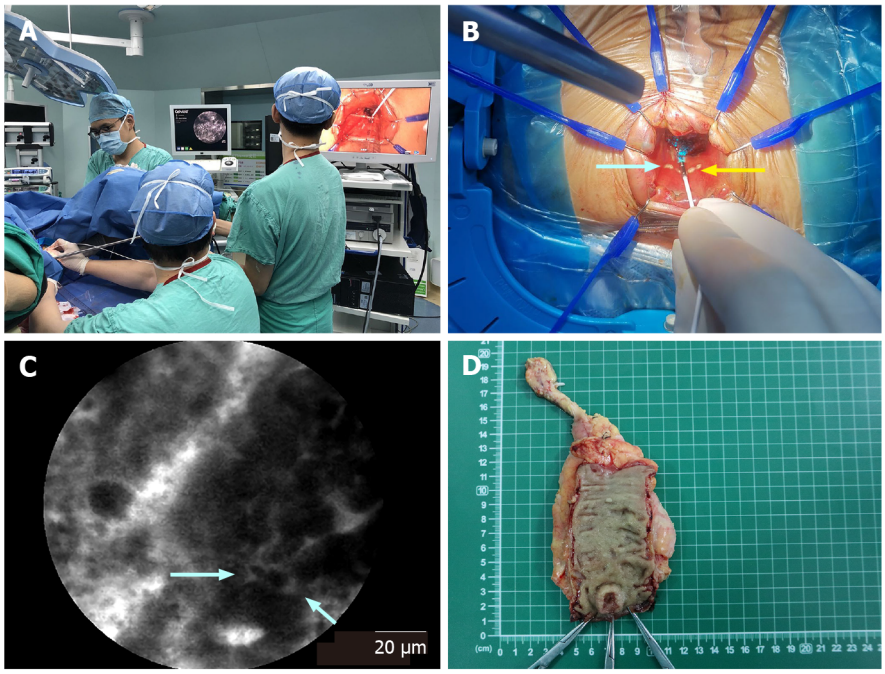
### Equipment and procedure

During surgery, pCLE was used to determine the distal edge of the tumor as well as to examine the preselected DRM. pCLE was performed using the Cellvizio Endomicroscopy System [Mauna Kea Technologies (MKT), Paris, France]. The ColoFlex UHD probe, a flexible mini-probe with a lateral resolution of 1 μm, was used in our study. The pCLE imaging data were collected at a scan rate of 12 frames/s. The probe has a field of view of 240 μm and can image at a depth of 60 μm below the mucosal surface, and it allows optical biopsies with 1000 times magnification.

Before image acquisition, fluorescein sodium was injected intravenously. The fluorescent agent used was 10% fluorescein sodium (Baiyunshan Mingxing Pharmaceutical Company, Guangzhou, China). The fluorescein sodium (0.5 mL) hypersensitivity test was implemented 20 min before pCLE examination. Then, 2.5 mL of fluorescein sodium diluted with 2.5 mL of 0.9% sodium chloride was injected intravenously 5 min prior to pCLE imaging. After strict sterilization, one end of the probe was connected to the laser outlet of Cellvizio, and the other end was placed on the surgical table. Adequate exposure of the tumor lesion was achieved using a colorectal retractor (CooperSurgical Lone Star colorectal retractor, Beijing Xinya S&T Co., Ltd., Beijing, China), and pCLE imaging was performed by the surgeon under direct vision by using the probe in direct contact with the tissues (Figure 1). The pCLE video recording was initiated when the probe contacted the lesion, and it terminated when the probe moved away from the lesion. The pathologist analyzed the pCLE videos and evaluated the margin between the abnormal tissue of the lesion and the surrounding normal mucosa in real time. A dot was marked with an electric scalpel at the distal edge of the tumor as determined by pCLE (Figure 1B and 1C). If the pathologist could not determine the distal edge of the tumor, then the dot was marked at a nontumor site identified by pCLE imaging as the closest healthy tissue below the macroscopic lesion. Then, the DRM was located 5-10 mm below the marked dot (Figure 1B). Finally, pCLE examination was performed preceding the surgical resection to ensure a negative DRM. Conventional samples were collected for histology at the marked dot and the DRM (Figure 1D). Histopathological analysis of the samples and the final resection specimen was performed as the gold standard, and the diagnosis made by pCLE was compared with that of the final pathological reports. All pCLE videos were stored on a personal computer in the form of MKT files (proprietary format, MKT Software, Paris, France).

### pCLE optical biopsy diagnostic criteria

The pCLE optical biopsy diagnostic criteria were according to the "Miami criteria"[13] and Kuiper *et al* [14]'s diagnostic classification. Briefly, the diagnostic criteria include the crypt architecture and vessel architecture classification. The crypt architecture was divided into three types. Normal mucosa was scored as crypt type 1 and presented normal regular luminal openings, size, and distribution of crypts covered by a homogeneous layer of epithelial cells, including goblet cells. Hyperplastic polyps and inflammatory lesions were scored as crypt type 2 and presented regular-shaped or star-shaped luminal crypt openings with normal or reduced goblet cells. Neoplastic lesions were scored as crypt type 3, which included variable width of epithelial lining with tubular-shaped crypts and loss of goblet cells (striped dark epithelium) and irregular and decreased volume of lamina propria. For vessel architecture, normal mucosa was scored as vessel type 1 and presented a hexagonal, honeycomb appearance that presented a network of capillaries outlining the luminal openings of the crypts. Hyperplastic polyps and inflammatory lesions were scored as vessel type 2, presented hexagonal, honeycomb appearance with mild (or no) increase in the number of capillaries or increased amounts of normal vessels without leakage. Neoplasia was scored as vessel type 3, presenting dilated and distorted vessels with elevated leakage and irregular architecture with little or no orientation to adjunct tissue. We analyzed the pCLE imaging features and made relative diagnoses according to the above categories.




**DOI:** 10.4240/wjgs.v14.i12.1375 **Copyright** ©The Author(s) 2022.

**Figure 1 Selection of the distal resection margin guided by probe-based confocal laser endomicroscopy.** A: During transanal total mesorectal excision, the surgeon used the tip of the probe in direct contact with the tissues. In the meantime, the pathologist analyzed the real-time probe-based confocal laser endomicroscopy (pCLE) videos; B: A dot (white arrow) was marked by an electric scalpel at the distal edge of the tumor, which was determined by pCLE optical biopsy. Then, the distal resection margin (DRM) (yellow arrow) was marked 5-10 mm below the marked dot; C: In pCLE videos, the distal edge of the tumor (white arrow) was determined at the end of the distorted structures (dark, irregularly thickened epithelium); D: Conventional samples were collected for histology at the marked dot and DRM after surgery.

For the patients who received neoadjuvant chemoradiotherapy, we adopted a pCLE scoring classification system created by Safatle-Ribeiro *et al*[15], assigning one point to the presence of each feature as follows: Vascular features including fluorescein leakage and an increased vessel/crypt ratio; and epithelial features including dark irregular crypts, intratumoral budding, back-to-back glands, and a cribriform pattern. Hence, in our study, patients with 0-1 points were diagnosed with complete response (no residual neoplasia), and those with 2-6 points were diagnosed with partial response (residual neoplasia). Consequently, we analyzed the diagnostic accuracy of pCLE in patients with neoadjuvant chemoradiotherapy according to the above classification.

### *Evaluation of pCLE videos*

During the surgery, one pathologist (observer A) made a real-time interpretation of the findings of the pCLE examination. Then, reinterpretation of the same pCLE videos was performed by another pathologist (observer B) who was blinded to the real-time diagnosis and final histopathology report. Finally, the real-time and blinded interpretations of the pCLE videos were compared with the final pathological report. Both observers had been trained in the pCLE system and image interpretation and had read more than 100 pCLE images of the colorectum. The quality of all videos was evaluated, and the diagnosis was made according to the "Miami criteria"[13]. We also adopted the colonic crypt architecture and vessel architecture classification for pCLE established by Kuiper *et al*[14]. The sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV) and interobserver agreement of pCLE optical biopsy in distinguishing between normal and cancerous tissue were calculated.

### *Specimen quality assessment*

The TME specimen quality should be assessed based on the following features. Grade 1 represents low quality: Incomplete mesorectum; mesorectum fascia defects deeper than 5 mm; conical gross specimen. Grade 2 represents moderate quality: Relatively intact mesorectum; mesorectum fascia defects deeper than 5 mm; no visible muscularis propria with adequate resection margin; approximately conical gross specimen. Grade 3 represents high quality: Intact mesorectum; no mesorectum fascia defects deeper than 5 mm; no visible muscularis propria; cylindrical specimen. A circumferential resection margin (CRM) was defined as positive when it was less than 1 mm, and a positive CRM or positive DRM was considered R1 resection. All TME specimens were evaluated by pathologists after surgery.

### Sample size calculation

From January 2019 to June 2019, the average time for intraoperative diagnosis by frozen section was 25 ± 10 min in our hospital. We hypothesized that the average time of intraoperative diagnosis by pCLE would be 20 min, and 43 cases were determined. With this number of cases, the study would have 90% power to detect a difference between the two techniques to prove the superiority of pCLE (two-sided type I error = 0.05).

### Statistical analysis

Patient demographic and clinical data and pCLE image characteristics were evaluated by descriptive statistics. The data of continuous variables are represented as the mean ± SD or median [interquartile range (IQR)], and the data of categorical variables are presented as numbers and frequencies. The intraobserver agreement was calculated by means of intraclass correlation coefficients (ICCs). Based on the 95% confidence interval (CI) of the ICC estimate, values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively. Cohen's kappa (κ) was calculated to assess the interobserver agreement of the two observers. The $\kappa$ value was graded as follows: Poor (0.01-0.20); fair (0.21-0.40); moderate (0.41-0.60); substantial (0.61-0.80); and excellent (0.81-1.00). Statistical Package for the Social Sciences software (Release 22.0, SPSS, Inc., 2012) was applied for statistical analyses.

## RESULTS

### Patient demographics and tumor characteristics

From January 2019 to January 2021, a total of 43 consecutive patients were enrolled according to the predefined inclusion and exclusion criteria. Patient demographics and tumor characteristics are shown in Table 1. There were 29 males (67.4%) and 14 females (32.6%), with a median age of 57 (IQR = 47-65) years. The median tumor height (the height from the anal verge to the distal edge of the tumor) was 4 cm (IQR = 3.6-4.6 cm). Preoperative neoadjuvant chemoradiotherapy was administered to 21 patients (48.8%), three of whom showed a complete response (no viable cancer cells). Finally, 43 marked dots and 43 DRMs were analyzed by comparing the pCLE diagnosis with the pathological reports. All pCLE procedures were performed successfully and safely, and no adverse reactions were observed following fluorescein injection.

### pCLE optical biopsy

In total, 43 patients underwent pCLE examination, including 21 patients who underwent neoadjuvant chemoradiotherapy. Representative pCLE images and matched images of hematoxylin and eosin-stained rectal tissues are shown in Figure 2. In normal rectal tissues, pCLE images presented normal round crypt structures with regular luminal openings, covered by a homogeneous single-cell-layered epithelium with dark goblet cells, and regular narrow vessels with hexagonal, honeycomb appearance surrounding crypts (Figure 2A). In rectal neoplastic tissues, pCLE images presented dark and irregularly thickened epithelium with decreased volume of lamina propria and dilated, distorted vessels with elevated leakage (Figure 2C). We analyzed the tissue features in 86 pCLE videos and made relative diagnoses. The intraoperative real-time pCLE imaging correctly diagnosed 36 tumor lesions and 40 normal lesions in 40 pathological tumor lesions and 46 pathological normal lesions.

In 21 patients who underwent neoadjuvant chemoradiotherapy, 3 patients had a complete response, while 18 had a partial response after neoadjuvant chemoradiotherapy according to the pathological reports after surgery. Representative endoscopic images and corresponding pCLE images are shown Figure 3. All patients received endoscopic examination before surgery to evaluate the residual lesions. Seven patients' endoscopic reports showed a complete response, presenting a residual scar (Figure 3A). Fourteen patients' endoscopic reports showed a partial response, presenting a residual tumor lesion (Figure 3C). In complete response rectal tissues (no neoplastic features), the typical pCLE images showed regular crypts with thickening epithelium and enlarged vessels with fibrotic stroma (Figure 3B). The pCLE images of residual neoplasia showed atypical glands with dark and irregular crypts and enlarged twisty vessels (Figure 3D). The pCLE imaging correctly diagnosed 15 cases of residual neoplasia (scored in range 2-6 points) in 18 cases of pathological partial response.

### pCLE diagnostic accuracy

A total of 86 pCLE videos from 43 patients were included in the analyses. The sensitivity, specificity, PPV, and NPV of real-time pCLE examination (observer A) in distinguishing between cancerous and normal tissue were 90.00% (95%CI: 76.34%-97.21%), 86.96% (95%CI: 73.74%-95.06%), 85.71% (95%CI: 71.46%-94.57%), and 90.91% (95%CI: 78.33%-97.47%), respectively (Table 2). The overall rate of accuracy was 88.37% (95%CI: 79.65%-94.28%). In the blinded pCLE reinterpretation after surgery (observer B), the sensitivity, specificity, PPV, NPV and accuracy of the pCLE examination were 87.50% (95%CI: 73.20%-95.81%), 84.78% (95%CI: 71.13%-93.66%), 83.33% (95%CI: 68.64%-93.03%), 88.64% (95%CI: 75.44%-

**Table 1 Patient demographics and tumor characteristics**

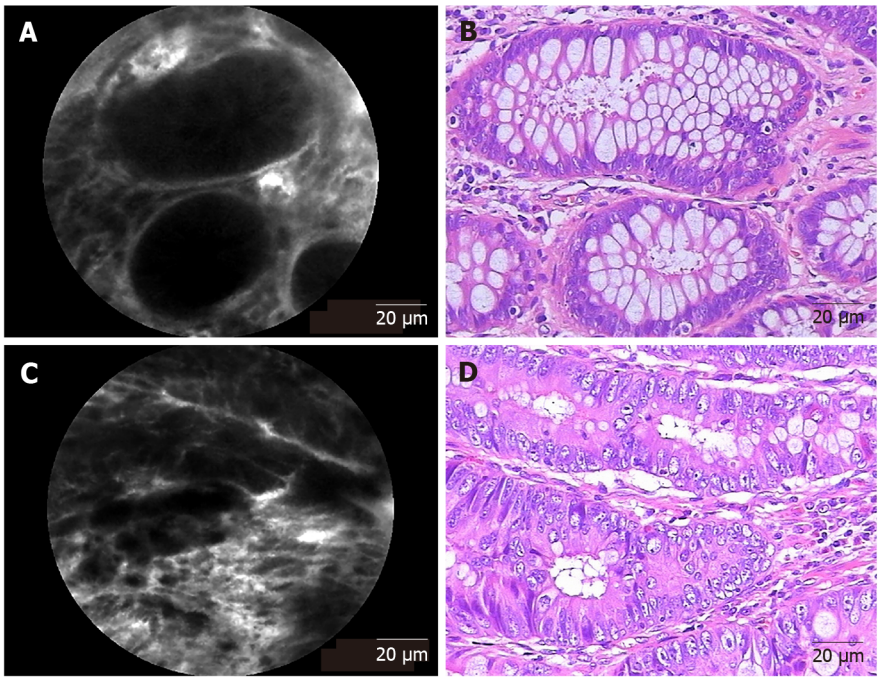
| Variable | *n* = 43 |
|---|---|
| Age: Median (IQR), yr | 57 (47-65) |
| Sex: Male/female, *n* | 29/14 |
| BMI: Median (IQR), kg/m$^2$ | 22.40 (19.50-23.95) |
| ASA class, *n* (%) | |
| 1 | 8 (18.6) |
| 2 | 30 (69.8) |
| 3 | 5 (11.6) |
| 4 | 0 |
| Tumor size: Median (IQR), cm | 2.5 (2.0-3.8) |
| Tumor height[1]: Median (IQR), cm | 4.0 (3.6-4.6) |
| Histological subtype, *n* (%) | |
| Adenocarcinoma | 39 (90.7) |
| Mucinous adenocarcinoma/signet ring cell carcinoma | 4 (9.3) |
| Differentiation grade, *n* (%) | |
| Well | 7 (16.3) |
| Moderate | 32 (74.4) |
| Poor | 4 (9.3) |
| Neoadjuvant chemoradiotherapy, *n* (%) | 21 (48.8) |
| TRG[2], *n* (%) | |
| Grade 0 | 3 (7.0) |
| Grade 1 | 10 (23.3) |
| Grade 2 | 7 (14.0) |
| Grade 3 | 1 (2.3) |
| T stage, *n* (%) | |
| T0 | 5 (11.6) |
| T1 | 4 (9.3) |
| T2 | 17 (39.5) |
| T3 | 13 (30.2) |
| T4 | 4 (9.3) |
| N stage, *n* (%) | |
| N0 | 30 (69.8) |
| N1 | 10 (23.3) |
| N2 | 3 (7.0) |
| M stage, *n* (%) | |
| M0 | 43 (100) |
| M1 | 0 |

[1]Height of the distal edge of the tumor from the anal verge.
[2]Tumor regression grade.
BMI: Body mass index; ASA: American Society of Anesthesiologists; TRG: Tumor Regression Grade; IQR: Interquartile range.

**Table 2 Probe-based confocal laser endomicroscopy diagnostic accuracy considering pathology as the standard reference**

| | Observer A (real-time interpretation) | | Observer B (blinded interpretation) | |
|---|---|---|---|---|
| | % | 95%CI | % | 95%CI |
| Sensitivity | 90.00 | 76.34-97.21 | 87.50 | 73.20-95.81 |
| Specificity | 86.96 | 73.74-95.06 | 84.78 | 71.13-93.66 |
| Accuracy | 88.37 | 79.65-94.28 | 86.05 | 76.89-92.58 |
| PPV | 85.71 | 71.46-94.57 | 83.33 | 68.64-93.03 |
| NPV | 90.91 | 78.33-97.47 | 88.64 | 75.44-96.21 |
| Interobserver agreement | $\kappa$ = 0.767, standard error = 0.069 | | | |

CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value.




**DOI:** 10.4240/wjgs.v14.i12.1375 

**Figure 2 Representative probe-based confocal laser endomicroscopy images and corresponding hematoxylin and eosin-stained images of rectal tissues.** A: Probe-based confocal laser endomicroscopy (pCLE) image of normal tissue presenting normal round crypt structures with regular luminal openings covered by a homogeneous single-cell-layered epithelium with dark goblet cells and regular narrow vessels with hexagonal, honeycomb appearance surrounding crypts; B: Corresponding image of normal rectal tissue stained by hematoxylin and eosin (H&E); C: pCLE image of rectal neoplastic tissues manifesting as dark and irregularly thickened epithelium with decreased volume of lamina propria and dilated, distorted vessels with elevated leakage. The epithelium was dark and irregularly thickened, and the vessels were dilated; D: Corresponding image of H&E-stained rectal adenocarcinoma tissue.

96.21%), and 86.05% (95%CI: 76.89%-92.58%), respectively (Table 2).

The neoadjuvant chemoradiotherapy group showed a lower sensitivity (83.33% *vs* 95.45%, $P$ = 0.485), specificity (77.27% *vs* 95.83%, $P$ = 0.153), accuracy (80.00% *vs* 95.65%, $P$ = 0.055), and PPV (75.00% *vs* 95.45%, $P$ = 0.147) than the nonneoadjuvant treatment group (Table 3). In our study, the mean ICC was 0.839 (95%CI: 0.763-0.892), which means that the intraobserver agreement was good. The interobserver agreement was substantial for the detection of rectal cancer, with a mean $\kappa$ of 0.767 (standard error = 0.069).

### *Surgical and functional outcomes*

The surgical and functional outcomes are shown in Table 4. No positive DRMs were detected in our study. All TME specimens were evaluated by pathologists after surgery. There were 40 specimens defined as grade 3 and 3 specimens defined as grade 2. The median distance from the lowest edge of the tumor to the DRM was 7 mm (IQR = 5-10 mm). The median operative duration was 240 min (IQR = 202-265 min), while the median intraoperative pCLE examination duration was 17 min (IQR = 15-18 min).

**Table 3 Comparison of real-time probe-based confocal laser endomicroscopy diagnostic accuracy between the neoadjuvant group and the nonneoadjuvant group**

| | Neoadjuvant group (*n* = 42) | | Nonneoadjuvant group (*n* = 44) | | *P* value |
|---|---|---|---|---|---|
| | % | 95%CI | % | 95%CI | |
| Sensitivity | 83.33 | 58.58-96.42 | 95.45 | 77.16-99.88 | 0.458 |
| Specificity | 77.27 | 54.63-92.18 | 95.83 | 78.88-99.89 | 0.153 |
| Accuracy | 80.00 | 64.35-90.95 | 95.65 | 85.16-99.47 | 0.055 |
| PPV | 75.00 | 50.90-91.34 | 95.45 | 77.16-99.88 | 0.147 |
| NPV | 85.00 | 62.11-96.79 | 95.83 | 78.88-99.89 | 0.473 |

CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value.

**Table 4 Surgical and functional outcomes**

| Variable | |
|---|---|
| Operative duration: Median (IQR), min | 240 (202-265) |
| pCLE examination duration: Median (IQR), min | 17 (15-18) |
| Estimated blood loss: Median (IQR), mL | 27 (20-50) |
| DRM distance: Median (IQR), mm | 7.0 (5.0-10.0) |
| Anastomotic leakage, *n* (%) | 2 (4.7) |
| Positive DRM, *n* (%) | 0 (0) |
| Wexner score[1], median (IQR) | 5 (3-6) |
| Anastomotic stenosis, *n* (%) | 1 (2.3) |
| Recurrence, *n* (%) | 1 (2.3) |
| Metastasis, *n* (%) | 2 (4.7) |

[1]An incontinence score designed by Wexner, determined at 6 mo after stoma closure.
pCLE: Probe-based confocal laser endomicroscopy; DRM: Distal resection margin; IQR: Interquartile range.

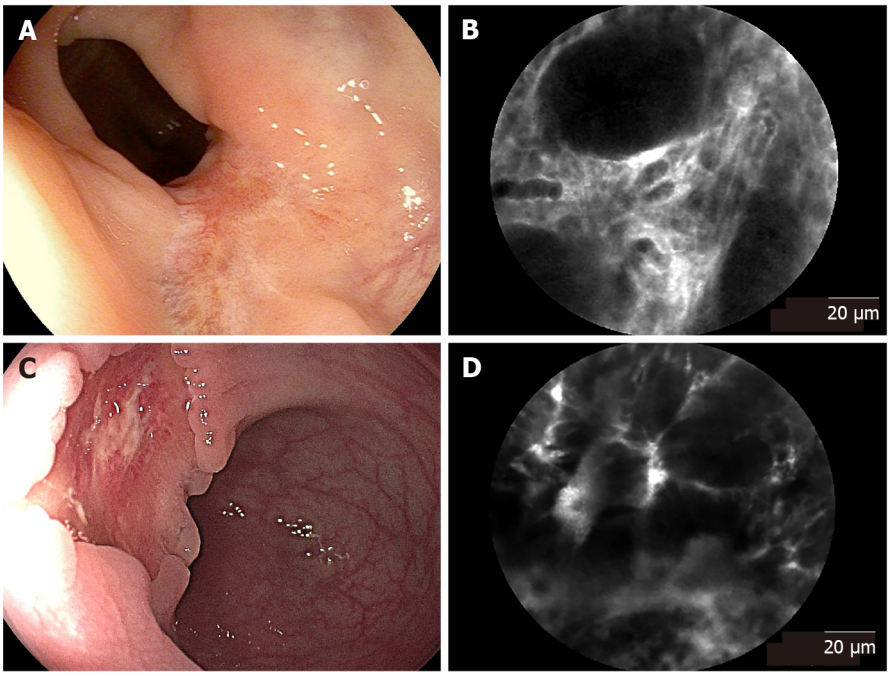
The time required to select the DRM decreased over time.

The median Wexner score was 5 (IQR = 3-6), as evaluated at six months after stoma closure. The median follow-up period was 24 (range, 22-46) mo. One patient had anastomotic stenosis. Two patients had liver metastasis at 6 mo and 13 mo after surgery. One patient died one year after metastasis, and another died 18 mo after metastasis. Notably, one patient had cancer recurrence 18 mo after surgery.

## DISCUSSION

Sphincter-saving low rectal cancer resection is technically challenging, especially in obese patients with large tumors. The narrow pelvis and the forward angle of the distal rectum restrict the laparoscopic view, making it difficult to perform laparoscopic procedures. TaTME provides an open approach from the anus to cancerous lesions and provides an excellent view of the surgical field, allowing the tumor to be seen directly from the bottom to the top. In our study, the transanal approach allowed the pCLE probe to directly contact the tissues without endoscopy. Therefore, pCLE can provide continuous and stable imaging of the tissue architecture and cellular morphology in the mucosal layer during TaTME. The pCLE analysis evaluated both epithelial and vascular patterns of malignancy, including the Cannizzaro-Spessotto scale, vessel/crypt ratio, stroma, dark crypts, budding, back-to-back glands and cribriform pattern[15]. To our knowledge, this is the first study of optical biopsy using pCLE to select the DRM in TaTME for low rectal cancer.

To date, surgeons only "experientially" determine the DRM using surgical instruments or macroscopic examination of the tumor margin, which may lead to an insufficient or excessive DRM. de Lacy *et al*[6] reported that patients with low rectal cancer treated with TaTME had a positive DRM rate of 7.8%. pCLE can provide *in vivo* microscopic imaging of the colorectal mucosa and submucosa,




**DOI:** 10.4240/wjgs.v14.i12.1375 **Copyright** ©The Author(s) 2022.

**Figure 3 Endoscopic images and corresponding probe-based confocal laser endomicroscopy images of rectal tissues after neoadjuvant chemoradiotherapy.** A: Endoscopic image of rectal tissue with complete response, presenting a residual scar; B: Corresponding probe-based confocal laser endomicroscopy (pCLE) image showed regular crypts with thickening epithelium and enlarged vessels with fibrotic stroma; C: Endoscopic image of rectal tissue with partial response, presenting a residual tumor lesion; D: Corresponding pCLE image showed atypical glands with dark and irregular crypts and enlarged twisty vessels.

enabling the real-time histological diagnosis of superficial and submucosal cancer infiltration[8,10]. In some studies, pCLE showed high agreement with true histopathology, reaching an accuracy of 88%-94.44%[8,10,16]. In our study, the accuracy of real-time pCLE examination was 88.37% (95%CI: 79.65%-94.28%). A direct and stable plane can be provided in TaTME for pCLE examination without the use of endoscopy.

Our study demonstrates that pCLE examination can be useful for detecting cancer infiltration and selecting the DRM. In our study, the diagnosis made by pCLE showed a good correlation with that made by histopathology as the gold standard. Real-time pCLE examination could differentiate between cancerous and normal tissue with a favorable accuracy of 88.37%. In particular, the sensitivity (90.00%) and NPV (90.91%) were high, resulting in high accuracy in not selecting a positive DRM. Wijsmuller *et al*[17] reported that neoadjuvant chemoradiotherapy could significantly alter pCLE rendering due to subsequent inflammation, edema, fibrosis and crypt distortion. Our results show a lower sensitivity (83.33% *vs* 95.45%, $P = 0.458$), specificity (77.27% *vs* 95.83%, $P = 0.153$), accuracy (80.00% *vs* 95.65%, $P = 0.055$), and PPV (75.00% *vs* 95.45%, $P = 0.147$) in the neoadjuvant chemoradiotherapy group than in the nonneoadjuvant treatment group. However, these differences between the two groups were not statistically significant. Therefore, pCLE examination is suitable for patients with or without neoadjuvant chemoradiotherapy. It is undeniable that the response to neoadjuvant chemoradiotherapy may lead to crypt distortion with epithelial irregularities due to inflammation, edema and fibrosis (Figure 2C), and these may increase the incidence of diagnostic errors. Therefore, awareness of neoadjuvant chemoradiotherapy before pCLE examination may be helpful to improve the diagnostic accuracy.

Several studies have reported that a DRM of 1 cm or less did not compromise oncological safety[18,19]. Therefore, we were relatively liberal with the selection of the DRM as long as it was confirmed to be negative intraoperatively by pCLE. There were no positive DRMs in our study, confirming the feasibility of optical biopsy using pCLE as an accurate method to select a tumor-free DRM in TaTME. As reported in a recent study[20], the mean DRM distance of patients who underwent TaTME for the treatment of low rectal cancer was 17.7 mm, which was much longer than our result of 7 mm. Previous studies investigating anorectal function after anterior resection for rectal cancer have suggested that a shorter remaining rectum might contribute to more disordered postoperative anorectal function because the rectal anal inhibitory reflex is generally preserved with higher levels of anastomosis and a longer residual rectum[21,22]. In this study, the median Wexner score was 5 (range, 3-6) at 6 mo after stoma closure, which means that patients in our study had satisfactory anorectal function after surgery. In summary, real-time pCLE examination may help reduce the tumor-free DRM and potentially contribute to the postoperative restoration of anorectal function in patients with low rectal cancer.

In this study, we first used pCLE to evaluate the tumor margin and select the DRM with satisfactory accuracy. We recommend pCLE examination as a routine test to help surgeons select the DRM in TaTME and perform "tailored surgery" for low rectal cancer patients. The limitation of this study was based on a single center, and the sample size was relatively small, which might limit the power of the study. Therefore, a large-scale multicenter, prospective, randomized controlled trial needs to be performed. The cancer cells sometimes crawl mainly submucosa rather than the mucosal layer, such as poorly differentiated adenocarcinomas. Due to the limitation of current technology, the pCLE imaging depth is restricted to 60 μm. Therefore, in our experience, patients who have been diagnosed with poorly differentiated adenocarcinoma preoperatively should receive submucosal intraoperative frozen biopsy to ensure distal margin safety.

## CONCLUSION

In conclusion, real-time *in vivo* pCLE examination is feasible and safe for selecting the DRM during TaTME for low rectal cancer, with high accuracy and a particularly high NPV. The pCLE examination is convenient, timesaving and easy for surgeons to perform and could thus be promoted as a regular examination for selecting the DRM during TaTME for low rectal cancer.

## ARTICLE HIGHLIGHTS

### *Research background*

Transanal total mesorectal excision (TaTME) allows patients even with ultra-low rectal cancer to be treated with sphincter-saving surgery. However, accurate delineation of the distal resection margin (DRM), which is essential to achieve R0 resection for low rectal cancer in TaTME, is technically demanding. Probe-based confocal laser endomicroscopy (pCLE) enables the real-time, *in vivo* optical biopsy of living tissue, which means it might help making intraoperative real-time diagnosis for suspicious tumor lesions. Therefore, we investigated whether pCLE can provide optical biopsy for DRM selection and help tailored surgery in low rectal cancer.

### *Research motivation*

No studies have investigated the feasibility of optical biopsy using pCLE in the real-time *in vivo* selection of the DRM during TaTME for low rectal cancer. This study aimed to explore whether real-time *in vivo* pCLE examination can help surgeons select the DRM accurately and contribute to improving the surgical outcome and oncological and functional prognosis of low rectal cancer after treatment with TaTME. To our knowledge, this is the first study of optical biopsy using pCLE to select the DRM in TaTME for low rectal cancer.

### *Research objectives*

This study investigated whether real-time *in vivo* pCLE examination is feasible and safe for selecting the DRM during TaTME for low rectal cancer.

### *Research methods*

The pCLE exaination was used to determine the distal magin during surgery. The final pathological report was used as the gold standard. The diagnostic accuracy of pCLE examination was calculated.

### *Research results*

Real-time *in vivo* pCLE examination is feasible and safe for selecting the DRM during TaTME for low rectal cancer, with high accuracy and a particularly high negative predictive value. The pCLE examination is convenient, timesaving and easy for surgeons to perform and could thus be promoted as a regular examination for selecting the DRM during TaTME for low rectal cancer.

### *Research conclusions*

Real-time *in vivo* pCLE examination can provide optical biopsy for distal margin selecting in TaTME for low rectal cancer.

### *Research perspectives*

Real-time *in vivo* pCLE can be used to determine the distal margin in TaTME surgical procedure for low rectal cancer.

## FOOTNOTES

**Author contributions:** J Yan and Tan J designed the research study; Tan J, Ji HL, Hu YW, Li ZM, Zhuang BX, Deng HJ, Wang YN, Zheng JX, Wang T, Jiang W, Han ZL, and Yan J performed the research; Tan J, Ji HL, Hu YW, Li ZM, Zhuang BX, Deng HJ, Wang YN, Zheng JX, Wang T, Jiang W, Han ZL, and Yan J analyzed the data and wrote the manuscript; and all authors have read and approve the final manuscript.

**Supported by** the National Natural Science Foundation of China, No. 82273360; the Science and Technology Planning Project of Guangzhou City, No. 202206010085; the Clinical Research Project of Southern Medical University, No. LC2016PY010; and the Clinical Research Project of Nanfang Hospital, No. 2018CR034.

**Institutional review board statement:** The study was reviewed and approved by the Southern Medical University Nanfang Hospital Institutional Review Board (Approval No. NFEC-2017-091).

**Clinical trial registration statement:** This study is registered at Clinical Trial. The registration identification number is NCT04016948.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Data sharing statement:** Technical appendix, statistical code, and dataset available from the corresponding author at yanjunfudan@163.com.

**CONSORT 2010 statement:** The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.



**Country/Territory of origin:** China

**ORCID number:** Jie Tan 0000-0001-6344-6737; Jun Yan 0000-0003-1373-4380.

**S-Editor:** Wang JJ
**L-Editor:** A
**P-Editor:** Wang JJ

## REFERENCES

1 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; **69**: 7-34 [PMID: 30620402 DOI: 10.3322/caac.21551]
2 **Renehan AG**, Malcomson L, Emsley R, Gollins S, Maw A, Myint AS, Rooney PS, Susnerwala S, Blower A, Saunders MP, Wilson MS, Scott N, O'Dwyer ST. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. *Lancet Oncol* 2016; **17**: 174-183 [PMID: 26705854 DOI: 10.1016/S1470-2045(15)00467-2]
3 **Penna M**, Hompes R, Arnold S, Wynn G, Austin R, Warusavitarne J, Moran B, Hanna GB, Mortensen NJ, Tekkis PP; TaTME Registry Collaborative. Transanal Total Mesorectal Excision: International Registry Results of the First 720 Cases. *Ann Surg* 2017; **266**: 111-117 [PMID: 27735827 DOI: 10.1097/SLA.0000000000001948]
4 **Francis N**, Penna M, Mackenzie H, Carter F, Hompes R; International TaTME Educational Collaborative Group. Consensus on structured training curriculum for transanal total mesorectal excision (TaTME). *Surg Endosc* 2017; **31**: 2711-2719 [PMID: 28462478 DOI: 10.1007/s00464-017-5562-5]
5 **Deijen CL**, Velthuis S, Tsai A, Mavroveli S, de Lange-de Klerk ES, Sietses C, Tuynman JB, Lacy AM, Hanna GB, Bonjer HJ. COLOR III: a multicentre randomised clinical trial comparing transanal TME versus laparoscopic TME for mid and low rectal cancer. *Surg Endosc* 2016; **30**: 3210-3215 [PMID: 26537907 DOI: 10.1007/s00464-015-4615-x]
6 **de Lacy FB**, van Laarhoven JJEM, Pena R, Arroyave MC, Bravo R, Cuatrecasas M, Lacy AM. Transanal total mesorectal excision: pathological results of 186 patients with mid and low rectal cancer. *Surg Endosc* 2018; **32**: 2442-2447 [PMID: 29101570 DOI: 10.1007/s00464-017-5944-8]
7 **Zeng WG**, Liu MJ, Zhou ZX, Wang ZJ. A Distal Resection Margin of ≤1 mm and Rectal Cancer Recurrence After Sphincter-Preserving Surgery: The Role of a Positive Distal Margin in Rectal Cancer Surgery. *Dis Colon Rectum* 2017; **60**: 1175-1183 [PMID: 28991082 DOI: 10.1097/DCR.0000000000000900]
8 **Kim B**, Kim YH, Park SJ, Cheon JH, Kim TI, Kim WH, Kim H, Hong SP. Probe-based confocal laser endomicroscopy for

evaluating the submucosal invasion of colorectal neoplasms. *Surg Endosc* 2017; **31**: 594-601 [PMID: 27324335 DOI: 10.1007/s00464-016-5003-x]

9 **Buchner AM**, Gomez V, Heckman MG, Shahid MW, Achem S, Gill KR, Jamil LH, Kahaleh M, Lo SK, Picco M, Riegert-Johnson D, Raimondo M, Sciemeca D, Wolfsen H, Woodward T, Wallace MB. The learning curve of in vivo probe-based confocal laser endomicroscopy for prediction of colorectal neoplasia. *Gastrointest Endosc* 2011; **73**: 556-560 [PMID: 21353852 DOI: 10.1016/j.gie.2011.01.002]

10 **De Palma GD**, Staibano S, Siciliano S, Persico M, Masone S, Maione F, Siano M, Mascolo M, Esposito D, Salvatori F, Persico G. In vivo characterisation of superficial colorectal neoplastic lesions with high-resolution probe-based confocal laser endomicroscopy in combination with video-mosaicing: a feasibility study to enhance routine endoscopy. *Dig Liver Dis* 2010; **42**: 791-797 [PMID: 20409761 DOI: 10.1016/j.dld.2010.03.009]

11 **Shahid MW**, Buchner AM, Raimondo M, Woodward TA, Krishna M, Wallace MB. Accuracy of real-time vs. blinded offline diagnosis of neoplastic colorectal polyps using probe-based confocal laser endomicroscopy: a pilot study. *Endoscopy* 2012; **44**: 343-348 [PMID: 22382851 DOI: 10.1055/s-0031-1291589]

12 **Gómez V**, Buchner AM, Dekker E, van den Broek FJ, Meining A, Shahid MW, Ghabril MS, Fockens P, Heckman MG, Wallace MB. Interobserver agreement and accuracy among international experts with probe-based confocal laser endomicroscopy in predicting colorectal neoplasia. *Endoscopy* 2010; **42**: 286-291 [PMID: 20354938 DOI: 10.1055/s-0029-1243951]

13 **Wallace M**, Lauwers GY, Chen Y, Dekker E, Fockens P, Sharma P, Meining A. Miami classification for probe-based confocal laser endomicroscopy. *Endoscopy* 2011; **43**: 882-891 [PMID: 21818734 DOI: 10.1055/s-0030-1256632]

14 **Kuiper T**, van den Broek FJ, van Eeden S, Wallace MB, Buchner AM, Meining A, van Hee K, Fockens P, Dekker E. New classification for probe-based confocal laser endomicroscopy in the colon. *Endoscopy* 2011; **43**: 1076-1081 [PMID: 21971922 DOI: 10.1055/s-0030-1256767]

15 **Safatle-Ribeiro AV**, Marques CFS, Pires C, Arraes L, Baba ER, Meirelles L, Kawaguti FS, da Costa Martins B, Lenz LT, de Lima MS, Gusmon-Oliveira CC, Ribeiro U Jr, Maluf-Filho F, Nahas SC. Diagnosis of Clinical Complete Response by Probe-Based Confocal Laser Endomicroscopy (pCLE) After Chemoradiation for Advanced Rectal Cancer. *J Gastrointest Surg* 2021; **25**: 357-368 [PMID: 33443686 DOI: 10.1007/s11605-020-04878-y]

16 **Liu Z**, Luo X, Jiang W, Chen D, Chen W, Li K, Liu X, Cui Z, Li Z, Han Z, Liu S, Li G, Xu C, Yan J. Real-time in vivo optical biopsy using confocal laser endomicroscopy to evaluate distal margin in situ and determine surgical procedure in low rectal cancer. *Surg Endosc* 2019; **33**: 2332-2338 [PMID: 30386986 DOI: 10.1007/s00464-018-6519-z]

17 **Wijsmuller AR**, Ghnassia JP, Varatharajah S, Schaeffer M, Leroy J, Marescaux J, Ignat M, Mutter D. Prospective Trial on Probe-Based Confocal Laser Endomicroscopy for the Identification of the Distal Limit in Rectal Adenocarcinoma. *Surg Innov* 2018; **25**: 313-322 [PMID: 29732957 DOI: 10.1177/1553350618773011]

18 **Kiran RP**, Lian L, Lavery IC. Does a subcentimeter distal resection margin adversely influence oncologic outcomes in patients with rectal cancer undergoing restorative proctectomy? *Dis Colon Rectum* 2011; **54**: 157-163 [PMID: 21228662 DOI: 10.1007/DCR.0b013e3181fc9378]

19 **Bujko K**, Rutkowski A, Chang GJ, Michalski W, Chmielik E, Kusnierz J. Is the 1-cm rule of distal bowel resection margin in rectal cancer based on clinical evidence? *Ann Surg Oncol* 2012; **19**: 801-808 [PMID: 21879269 DOI: 10.1245/s10434-011-2035-2]

20 **Ren J**, Liu S, Luo H, Wang B, Wu F. Comparison of short-term efficacy of transanal total mesorectal excision and laparoscopic total mesorectal excision in low rectal cancer. *Asian J Surg* 2021; **44**: 181-185 [PMID: 32461015 DOI: 10.1016/j.asjsur.2020.05.007]

21 **Rasmussen OO**, Petersen IK, Christiansen J. Anorectal function following low anterior resection. *Colorectal Dis* 2003; **5**: 258-261 [PMID: 12780889 DOI: 10.1046/j.1463-1318.2003.00439.x]

22 **Kakodkar R**, Gupta S, Nundy S. Low anterior resection with total mesorectal excision for rectal cancer: functional assessment and factors affecting outcome. *Colorectal Dis* 2006; **8**: 650-656 [PMID: 16970574 DOI: 10.1111/j.1463-1318.2006.00992.x]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 December 27; 14(12): 1387-1396

DOI: 10.4240/wjgs.v14.i12.1387

ISSN 1948-9366 (online)

META-ANALYSIS

# Short- and long-term outcomes of laparoscopic *vs* open surgery for T2 gallbladder cancer: A systematic review and meta-analysis

Wei Zhang, De-Liang Ouyang, Xu Che

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Rahmati M, Iran; AF Liu, China

**Received:** September 25, 2022
**Peer-review started:** September 25, 2022
**First decision:** October 20, 2022
**Revised:** October 28, 2022
**Accepted:** December 6, 2022
**Article in press:** December 6, 2022
**Published online:** December 27, 2022

**Wei Zhang, Xu Che,** Department of Hepatobiliary and Pancreatic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen 518116, Guangdong Province, China

**De-Liang Ouyang,** Department of General Surgery, The Third Affiliated Hospital, Hengyang Medical School, University of South China, Hengyang 421900, Hunan Province, China

**Corresponding author:** Xu Che, MD, Associate Professor, Chief Doctor, Department of Hepatobiliary and Pancreatic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 113 Baohe Avenue, Longgang District, Shenzhen 518116, Guangdong Province, China. yixuetg@foxmail.com

## Abstract

### *BACKGROUND*

With the development of laparoscopic techniques, gallbladder cancer (GBC) is no longer a contraindication to laparoscopic surgery (LS). Although LS is recommended for stage T1 GBC, the value of LS for stage T2 GBC is still controversial.

### *AIM*

To evaluate the short- and long-term outcomes of LS in comparison to those of open surgery (OS) for stage T2 GBC.

### *METHODS*

We searched the PubMed, Embase, Cochrane Library, Ovid, Google Scholar, and Web of Science databases for published studies comparing the efficacy of LS and OS in the treatment of stage T2 GBC, with a cutoff date of September 2022. The Stata 15 statistical software was used for analysis. Relative risk (RR) and weighted mean difference (WMD) were calculated to assess binary and continuous outcome indicators, respectively. Begg's test and Egger's test were used for detecting publication bias.

### *RESULTS*

A total of five studies were included, with a total of 297 patients, 153 in the LS group and 144 in the OS group. Meta-analysis results showed that the LS group was better than the OS group in terms of operative time [WMD = -41.29, 95% confidence interval (CI): -75.66 to -6.92, $P$ = 0.02], estimated blood loss (WMD = -261.96, 95%CI: -472.60 to -51.31, $P$ = 0.01), and hospital stay (WMD = -5.67, 95%CI:

-8.53 to -2.81, $P$ = 0.0001), whereas there was no significant difference between the two groups in terms of blood transfusion (RR = 0.60, 95%CI: 0.31-1.15, $P$ = 0.13), complications (RR = 0.72, 95%CI: 0.39-1.33, $P$ = 0.29), number of lymph nodes retrieved (WMD = –1.71, 95%CI: -4.27 to -0.84, $P$ = 0.19), recurrence (RR = 0.41, 95%CI: 0.06-2.84, $P$ = 0.36), 3-year and 5-year overall survival (RR = 0.99, 95%CI: 0.82-1.18, $P$ = 0.89 and RR = 1.02, 95%CI: 0.68-1.53, $P$ = 0.92; respectively), and 3-year and 5-year disease-free survival (RR = 1.01, 95%CI: 0.84-1.21, $P$ = 0.93 and RR = 1.15, 95%CI: 0.90-1.46, $P$ = 0.26; respectively).

***CONCLUSION***

The long-term outcomes of LS for T2 GBC are similar to those of OS, but LS is superior to OS in terms of operative time, intraoperative bleeding, and postoperative hospital stay. Nevertheless, these findings should be validated *via* high-quality randomized controlled trials and longer follow-ups.

**Key Words:** Gallbladder cancer; T2 stage; Laparoscopic cholecystectomy; Oncological outcome; Meta-analysis



**Core Tip:** This study evaluated the safety and efficacy of laparoscopic surgery in comparison to those of open surgery for stage T2 gallbladder cancer. A total of five studies were included after retrieving various literature databases, with a cutoff date of September 2022. Meta-analysis results showed that the laparoscopic surgery group was better than the open surgery group in terms of operative time, estimated blood loss, and hospital stay, whereas there was no significant difference between the two groups in terms of blood transfusion, complications, number of lymph nodes retrieved, recurrence, and 3-year and 5-year overall and disease-free survival rates.

**Citation:** Zhang W, Ouyang DL, Che X. Short- and long-term outcomes of laparoscopic *vs* open surgery for T2 gallbladder cancer: A systematic review and meta-analysis. *World J Gastrointest Surg* 2022; 14(12): 1387-1396
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i12/1387.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i12.1387

## INTRODUCTION

Gallbladder cancer (GBC) is one of the most common malignancies of the biliary system and has the sixth highest incidence among gastrointestinal tumors[1]. Radical resection is the only potentially curative treatment for GBC[2-4]. Traditional open extended cholecystectomy, including regional lymph node dissection and wedge resection of the gallbladder bed, is the standard radical surgery for stage T2 GBC[5,6]. Since the late 1980s, laparoscopic surgery (LS) has been widely used to treat benign gallbladder disease, and GBC has been considered a contraindication to LS[7,8]. With the continuous improvement of devices and techniques in recent years, curative resection of gastrocolic cancer and liver cancer in difficult sites and even pancreaticoduodenectomy can be conducted laparoscopically. Additionally, LS is increasingly employed in radical resection of stage T1a GBC, and thus GBC is no longer a contraindication to LS[9]. However, the short- and long-term outcomes of LS for stage T2 GBC are still controversial.

Although there are still concerns about the efficacy of laparoscopic radical surgery of stage T2 GBC, LS has already been exploratively applied to treat patients with T2 GBC, and even T3 GBC, at several large medical institutes. There has been a rapid increase in incidental GBC with the widespread use of laparoscopic techniques in benign gallbladder disease, especially in patients with T2 GBC[10,11]. It has become a point of debate whether LS is safe for the treatment of T2 GBC and whether open surgery (OS) is required.

Previous studies on T2 GBC have been limited to case reports or small sample retrospective single arm case series on the technical feasibility, safety, and oncological outcomes. Several recent studies have reported long-term outcomes of laparoscopic treatment of stage T2 GBC[12-16]. As there is still a lack of evidence from high-quality multicenter randomized controlled trials (RCTs), we believe that it is necessary to conduct a meta-analysis to provide an evidence-based reference for laparoscopic radical surgery of T2 GBC.

## MATERIALS AND METHODS

This meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[17]. The data used in this study were derived from published studies and are anonymous. This study did not need informed consent from patients or a review by an institutional ethics committee. This meta-analysis was registered under the registration number CRD42022367334 on the systematic review registration platform PROSPERO (https://www.crd.york.ac.uk/PROSPERO/). We also cited high-quality articles in *Reference Citation Analysis* (https://www.referencecitation-analysis.com).

### Search strategy

The PubMed, Medline, Cochrane Library, Ovid, Google Scholar, and Web of Science databases were searched with a cutoff date of September 2022. The search topics were "laparosco*", "open", "extended cholecystectomy", "open surgery" and "T2 gallbladder cancer". The search strategy for each database is described in the Supplementary material. We also conducted an expanded search based on the references of the retrieved publications. Table 1 lists the basic characteristics of the included studies.

### Inclusion criteria

(1) Population: Stage T2 GBC; (2) Intervention: LS; (3) Comparison: OS; (4) Study sample size: Unlimited; (5) Type of studies: RCTs and prospective or retrospective cohort studies; (6) Follow-up time: Unlimited; (7) Language type of the publications: Unlimited; (8) Study type: Human studies; and (9) Primary outcomes: Overall survival, disease-free survival, recurrence, and the number of lymph nodes removed. Secondary outcomes: Operative time, intraoperative blood loss, hospital stay, and postoperative complications.

### Exclusion criteria

(1) Studies with unknown follow-up times or incomplete data and no response from the contact author and those not peer-reviewed; (2) Single arm studies with LS or OS; and (3) Robots, reviews, case reports, and animal studies.

### Quality assessment

The quality of the cohort studies (retrospective or prospective) was assessed using the Newcastle-Ottawa Scale, which specifically included study population selection, comparability, and exposure evaluation or outcome evaluation. The RCTs were conducted for the risk assessment according to the "risk assessment tool" recommended by the Cochrane Collaboration Network[18-20].

### Statistical analysis

The meta-analysis was performed using the STATA SE 13 software. Relative risk (RR) and weighted mean difference (WMD) were used to calculate the pooled statistics for binary and continuous data, respectively, and the 95% confidence interval (CI) was reported for each. Heterogeneity was assessed using the $\chi^2$ test, with the significance level set at $P = 0.05$. This meta-analysis was carried out using a random effects model. $P < 0.05$ was considered to indicate statistical significance[21]. Begg's test and Egger's test were performed using the Stata 15 software to quantitatively assess each outcome for publication bias. Funnel plots were drawn to qualitatively and visually assess the outcomes for publication bias.

## RESULTS

### Search results and study selection

After searching the publication databases and excluding duplications, 47 articles remained. We then excluded the reviews (including systematic reviews), case reports, and meta-analyses as well as the studies that were not relevant based on their titles or abstracts, finally leaving five publications to be employed in this meta-analysis. The detailed steps of the publication retrieval are shown in Figure 1. These five publications involved one study from Japan and four studies from South Korea. The basic characteristics of the included studies are shown in Table 1. The included studies were all cohort studies, and the quality was evaluated using the Newcastle-Ottawa Scale. The Newcastle-Ottawa Scale scores are attached to Supplementary Table 1.

### Results of the meta-analysis

We compared LS and OS for T2 GBC in 11 postoperative outcomes, each of which was analyzed for sensitivity. The results of the meta-analysis are summarized in Table 2. Random effects models were used to obtain the effect sizes.

**Table 1 Basic characteristics of the included studies**

| Ref. | Country | Type | Period | Case | Age | | Sex (M/F) | | Liver resection[1] | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | LS *vs* OS | LS | OS | LS | OS | LS | OS | |
| Lee *et al*[12], 2022 | Korea | R | 2011-2018 | 20 *vs* 24 | 71.85 ± 9.11 | 68.08 ± 10.64 | 5/15 | 11/13 | 1/4/15 | 1/13/10 | 7 |
| Cho *et al*[13], 2022 | Korea | R (PSM) | 2010-2017 | 19 *vs* 19 | 69.9 ± 9.1 | 66.7 ± 7.8 | 8/11 | 12/7 | NA | NA | 6 |
| Navarro *et al*[14], 2020 | Korea | R (PSM) | 2005-2017 | 43 *vs* 43 | 66.7 ± 10.3 | 65.4 ± 7.6 | 25/18 | 28/15 | 38/5/0 | 23/12/8 | 6 |
| Jang *et al*[15], 2019 | Korea | R | 2004-2017 | 55 *vs* 44 | 70.1 ± 8.1 | 65.5 ± 10.5 | 19/36 | 23/21 | 38/16/1 | 9/32/3 | 8 |
| Itano *et al*[16], 2015 | Japan | R | 2003-2013 | 16 *vs* 14 | 68.1 ± 19.9 | 71.5 ± 13.2 | 9/7 | 5/9 | NA | NA | 7 |

[1]No/wedge/S4b or 5.

F: Female; R: Retrospective comparative studies; LS: Laparoscopic surgery; M: Male; NA: Not available; OS: Open surgery; PSM: Propensity score matching.

**Table 2 Meta-analysis results of all available studies in measured outcomes**

| Measured outcomes | Studies, *n* | Heterogeneity test | | Model | RR/WMD | 95%CI | *P* value |
|---|---|---|---|---|---|---|---|
| | | *I*² (%) | *P* value | | | | |
| Operative time | 5 | 62 | 0.03 | Random | -41.29 | -75.66, -6.92 | 0.02[a] |
| Intraoperative blood loss | 4 | 86 | 0.0001 | Random | -261.96 | -472.60, -51.31 | 0.01[a] |
| Hospital stays | 5 | 76 | 0.002 | Random | -5.67 | -8.53, -2.81 | 0.0001[a] |
| Lymph nodes retrieved | 5 | 79 | 0.0008 | Random | -1.71 | -4.27, 0.84 | 0.19 |
| Transfusion | 3 | 0 | 0.57 | Random | 0.60 | 0.31, 1.15 | 0.13 |
| Complication | 5 | 0 | 0.5 | Random | 0.72 | 0.39, 1.33 | 0.29 |
| Recurrence | 2 | 50 | 0.16 | Random | 0.41 | 0.06, 2.84 | 0.36 |
| 3-yr OS | 3 | 40 | 0.19 | Random | 0.99 | 0.82, 1.18 | 0.89 |
| 5-yr OS | 3 | 80 | 0.006 | Random | 1.02 | 0.68, 1.53 | 0.92 |
| 3-yr DFS | 3 | 29 | 0.24 | Random | 1.01 | 0.84, 1.21 | 0.93 |
| 5-yr DFS | 3 | 55 | 0.11 | Random | 1.15 | 0.90, 1.46 | 0.26 |

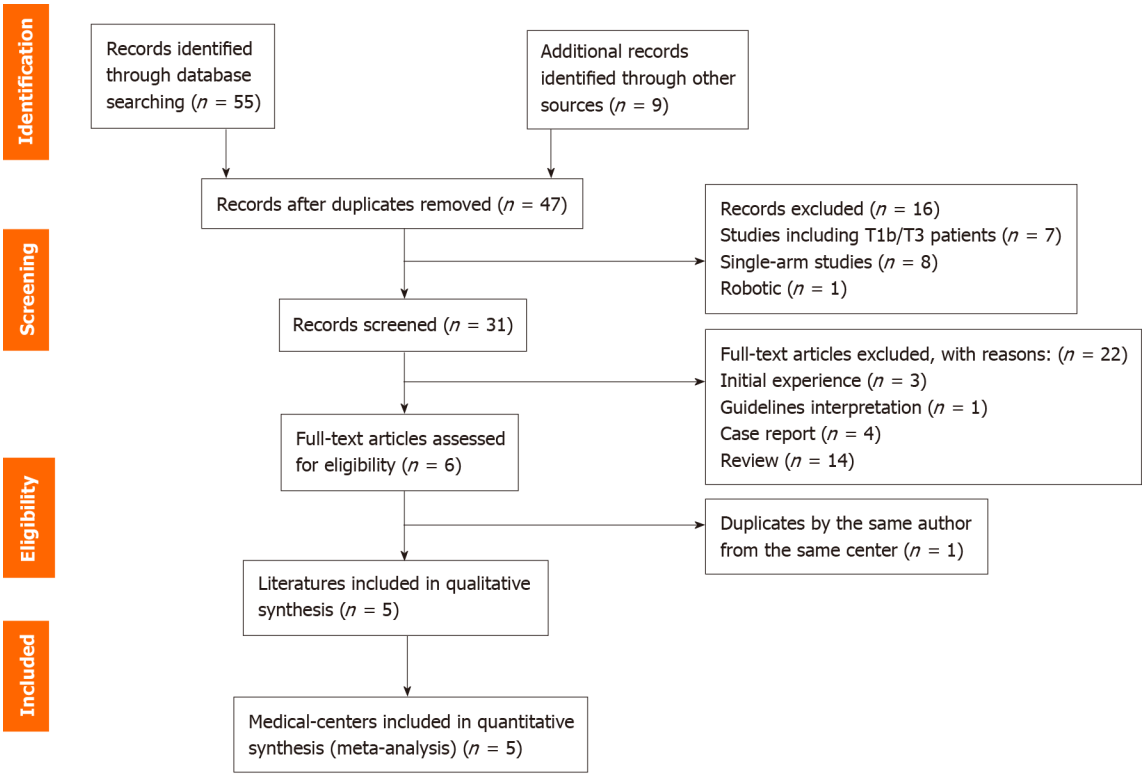
[a]Indicates statistical significance.

CI: Confidence interval; DFS: Disease-free survival; OS: Overall survival; RR/WMD: Relative risk/weighted mean difference.

**Operative time, intraoperative blood loss, and hospital stay:** Five studies reported the operative time with moderate heterogeneity (WMD = -41.29, 95%CI: -75.66 to -6.92, $P$ = 0.02)[12-16]. Four studies reported the intraoperative blood loss with moderate heterogeneity (WMD = -261.96, 95%CI: -472.60 to -51.31, $P$ = 0.01)[12,14-16]. Five studies reported the hospital stays with high heterogeneity (WMD = -5.67, 95%CI: -8.53 to -2.81, $P$ = 0.0001)[12-16]. Operative time (min), intraoperative blood loss (mL), and length of hospital stay (d) were significantly lower in LS than in OS (Figure 2A and 2B).

**Number of lymph nodes retrieved, recurrence, blood transfusion, and complications:** Five studies reported the number of lymph nodes retrieved with high heterogeneity (WMD = -1.71, 95%CI: -4.27 to 0.84, $P$ = 0.19). Three studies reported the intraoperative blood transfusion with low heterogeneity (RR = 0.56, 95%CI: 0.29-1.09, $P$ = 0.09)[12,14,15]. Five studies reported the complication rate with low heterogeneity (RR = 0.72, 95%CI: 0.39-1.33, $P$ = 0.29)[12-16]. Two studies reported the recurrence rate with moderate heterogeneity (RR = 0.41, 95%CI: 0.06-2.84, $P$ = 0.36)[12,16]. There was no significant difference between the LS and OS groups in the number of lymph nodes retrieved, recurrence, blood transfusion, or complications (Figure 2B and 2C).

**3-year and 5-year overall and disease-free survival rates:** Three studies reported the 3-year overall survival rate with moderate heterogeneity (RR = 0.99, 95%CI: 0.82-1.18, $P$ = 0.89)[12-14]. Three studies reported the 5-year overall survival rate with high heterogeneity (RR = 1.02, 95%CI: 0.68-1.53, $P$ = 0.92)[12,14,15]. Three studies reported the 3-year disease-free survival rate with low heterogeneity (RR =




**DOI:** 10.4240/wjgs.v14.i12.1387 

**Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for the literature search.**

1.01, 95%CI: 0.84-1.21, $P$ = 0.93)[12-14]. Three studies reported the 5-year disease-free survival rate with moderate heterogeneity (RR = 1.15, 95%CI: 0.90-1.46, $P$ = 0.26)[12,14,15]. There was no statistical difference between the LS and OS groups in terms of 3-year and 5-year overall and disease-free survival rates (Figure 2D).

### *Sensitivity analysis and publication bias*

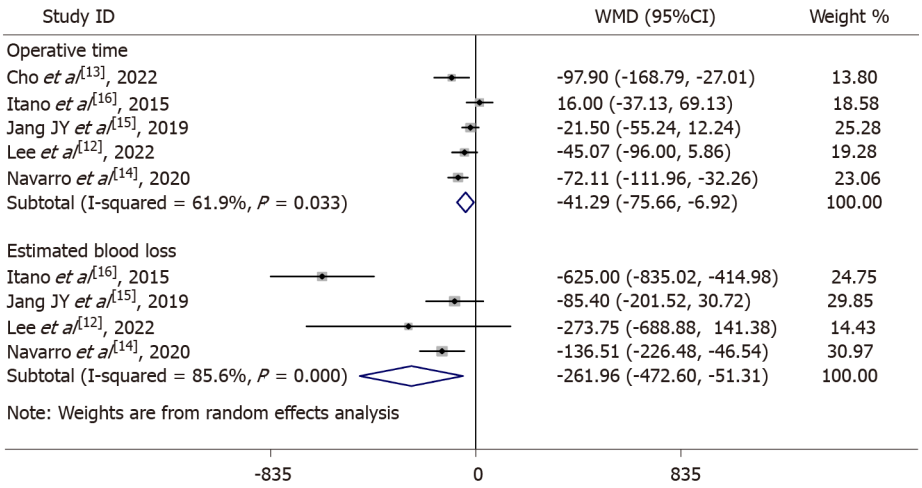
The sensitivity analysis showed that our meta-analysis was stable, and no reversal of the meta-analysis results was found. Publication bias was qualitatively assessed using funnel plots. The funnel plots were largely symmetrically distributed, with no significant extreme values (Supplementary Figure 1). Neither Begg's test nor Egger's test revealed any significant publication bias (Supplementary Table 2).

## DISCUSSION

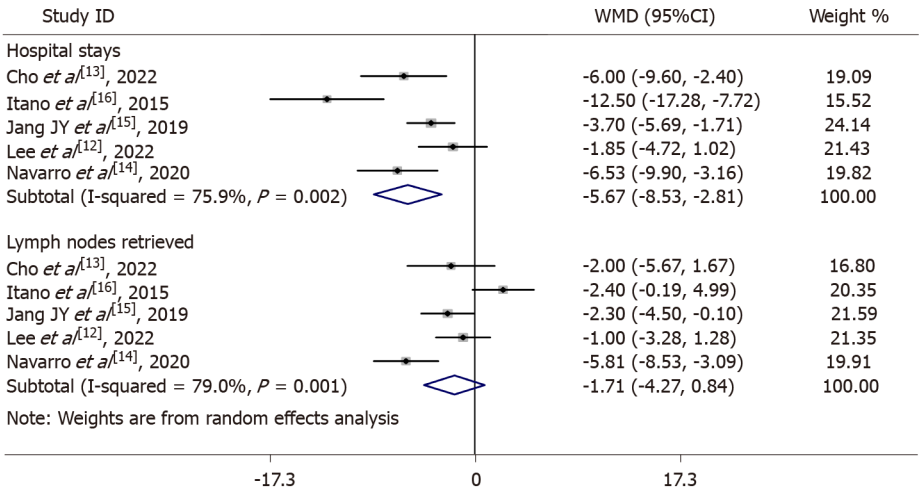
Recently, LS for patients with stage T2 GBC has become feasible in high-volume medical centers and has shown similar outcomes to those of OS[16,22-25]. However, the value of LS for T2 GBC remains controversial. The current guidelines, such as those of the National Comprehensive Cancer Network and the Japanese Society of Hepatobiliary and Pancreatic Surgery, do not recommend LS for T2 GBC[9]. Previous studies referenced by the guidelines have shown that LS is associated with a higher risk of tumor spread and incisional recurrence than OS[7,26,27]. However, tumor spread is not a complication specific to LS and can also occur in OS[28]. Currently, since specimens are often intraoperatively obtained using plastic internal bags, which can prevent tumor spread and incision site recurrence in GBC[29,30], there is no statistically significant difference in the incidence of incisional implants between LS and OS[31].

LS follows the principles of OS. Lymph node dissection and R0 rate are two important indicators to evaluate radical surgery for GBC. Studies found that the rate of lymph node metastasis in stage T2 GBC was 46%[32,33]. It has been suggested that LS is superior to OS for lymph node dissection because of the unique magnified surgical field of view[22]. However, the results of this meta-analysis showed no significant difference between the two procedures. R0 resection is also an important prognostic factor for postoperative patients. Among the analyzed studies, only the study by Lee *et al*[12] reported the R0 resection rate to be similar between the LS and OS groups, with no statistical difference.

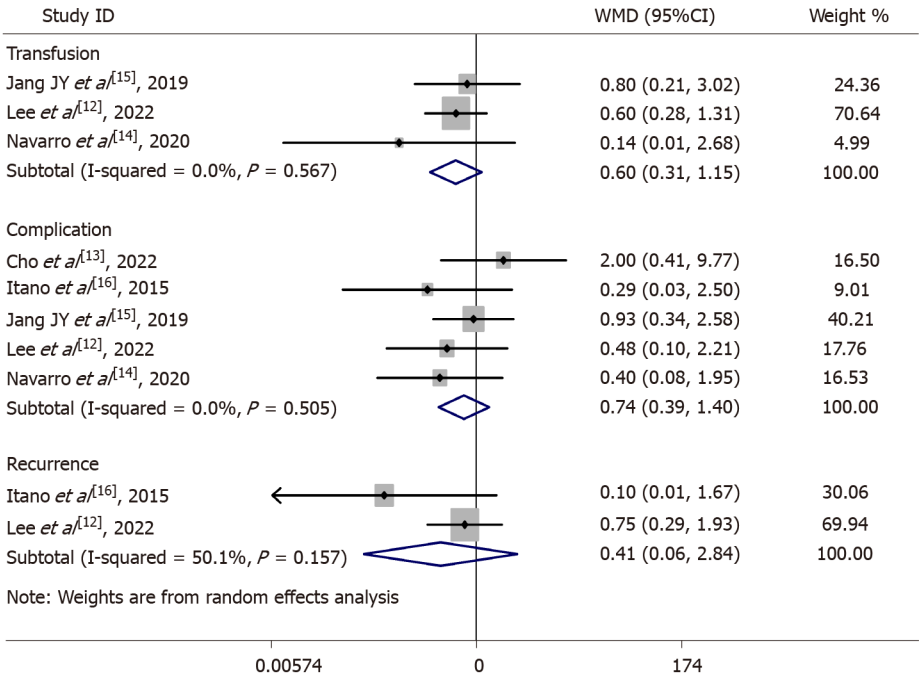
**A**


Study ID
WMD (95%CI)
Weight %
Operative time
Cho et al[13], 2022
-97.90 (-168.79, -27.01)
13.80
Itano et al[16], 2015
16.00 (-37.13, 69.13)
18.58
Jang JY et al[15], 2019
-21.50 (-55.24, 12.24)
25.28
Lee et al[12], 2022
-45.07 (-96.00, 5.86)
19.28
Navarro et al[14], 2020
-72.11 (-111.96, -32.26)
23.06
Subtotal (I-squared = 61.9%, P = 0.033)
-41.29 (-75.66, -6.92)
100.00
Estimated blood loss
Itano et al[16], 2015
-625.00 (-835.02, -414.98)
24.75
Jang JY et al[15], 2019
-85.40 (-201.52, 30.72)
29.85
Lee et al[12], 2022
-273.75 (-688.88, 141.38)
14.43
Navarro et al[14], 2020
-136.51 (-226.48, -46.54)
30.97
Subtotal (I-squared = 85.6%, P = 0.000)
-261.96 (-472.60, -51.31)
100.00
Note: Weights are from random effects analysis
-835
0
835

**B**


Study ID
WMD (95%CI)
Weight %
Hospital stays
Cho et al[13], 2022
-6.00 (-9.60, -2.40)
19.09
Itano et al[16], 2015
-12.50 (-17.28, -7.72)
15.52
Jang JY et al[15], 2019
-3.70 (-5.69, -1.71)
24.14
Lee et al[12], 2022
-1.85 (-4.72, 1.02)
21.43
Navarro et al[14], 2020
-6.53 (-9.90, -3.16)
19.82
Subtotal (I-squared = 75.9%, P = 0.002)
-5.67 (-8.53, -2.81)
100.00
Lymph nodes retrieved
Cho et al[13], 2022
-2.00 (-5.67, 1.67)
16.80
Itano et al[16], 2015
-2.40 (-0.19, 4.99)
20.35
Jang JY et al[15], 2019
-2.30 (-4.50, -0.10)
21.59
Lee et al[12], 2022
-1.00 (-3.28, 1.28)
21.35
Navarro et al[14], 2020
-5.81 (-8.53, -3.09)
19.91
Subtotal (I-squared = 79.0%, P = 0.001)
-1.71 (-4.27, 0.84)
100.00
Note: Weights are from random effects analysis
-17.3
0
17.3

**C**


Study ID
WMD (95%CI)
Weight %
Transfusion
Jang JY et al[15], 2019
0.80 (0.21, 3.02)
24.36
Lee et al[12], 2022
0.60 (0.28, 1.31)
70.64
Navarro et al[14], 2020
0.14 (0.01, 2.68)
4.99
Subtotal (I-squared = 0.0%, P = 0.567)
0.60 (0.31, 1.15)
100.00
Complication
Cho et al[13], 2022
2.00 (0.41, 9.77)
16.50
Itano et al[16], 2015
0.29 (0.03, 2.50)
9.01
Jang JY et al[15], 2019
0.93 (0.34, 2.58)
40.21
Lee et al[12], 2022
0.48 (0.10, 2.21)
17.76
Navarro et al[14], 2020
0.40 (0.08, 1.95)
16.53
Subtotal (I-squared = 0.0%, P = 0.505)
0.74 (0.39, 1.40)
100.00
Recurrence
Itano et al[16], 2015
0.10 (0.01, 1.67)
30.06
Lee et al[12], 2022
0.75 (0.29, 1.93)
69.94
Subtotal (I-squared = 50.1%, P = 0.157)
0.41 (0.06, 2.84)
100.00
Note: Weights are from random effects analysis
0.00574
0
174

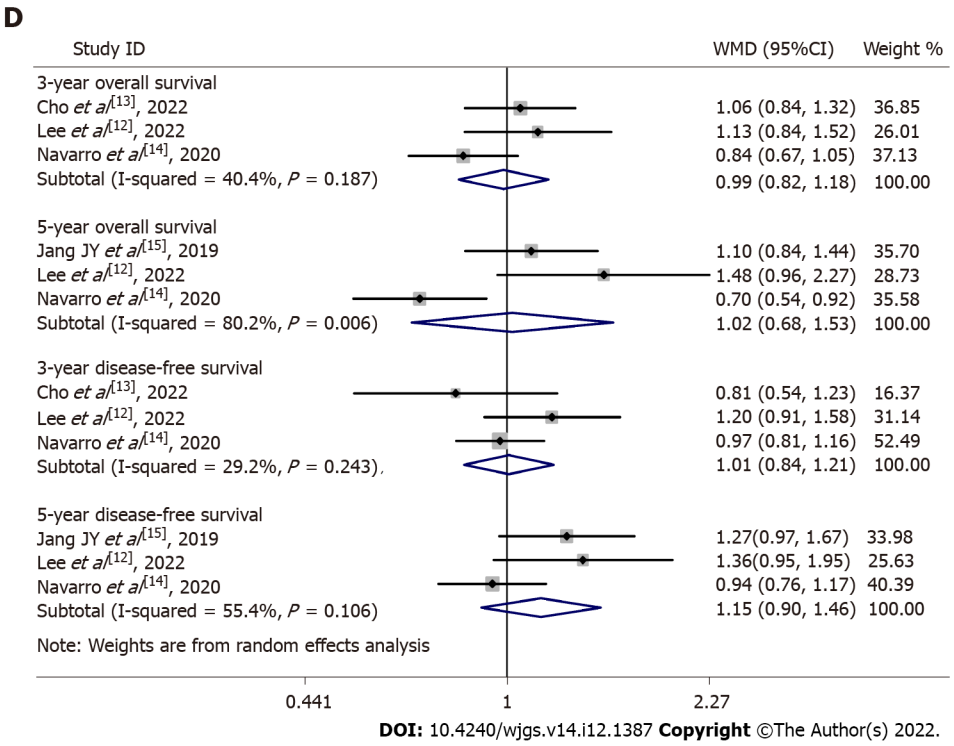



**Figure 2 Forest plot.** A: Operative time and intraoperative blood loss; B: Hospital stay and number of lymph nodes retrieved; C: Blood transfusion, complications, and recurrence; D: 3-year overall survival, 5-year overall survival, 3-year overall survival, and 5-year overall survival. CI: Confidence interval; RR: Relative risk; WMD: Weighted mean difference.

Although oncological outcomes based on surgical procedures, such as R0 rates and number of lymph nodes removed, were not significantly different between the LS and OS groups, the therapeutic effect should be based on more direct clinical evidence, such as improved survival, improved quality of life, or reduced tumor-related symptoms. These clinical benefits sometimes cannot be assessed based on intraoperative or short-term outcomes. Therefore, we explored long-term survival and found that postoperative recurrence and 3-year and 5-year overall and disease-free survival rates are not significantly different between the LS and OS groups.

In addition, our findings suggest that LS is associated with lower operation time, intraoperative blood loss, and length of hospital stay than OS. Although a random effects model was used to combine the effect sizes, there was a high degree of heterogeneity in operative time, intraoperative bleeding, and length of hospital stay, which significantly weakens the explanatory effect of the results and may cause confounding bias. The high heterogeneity may be explained by the fact that surgeons are still at the learning curve stage. As these results are prone to bias, they need to be validated *via* high-quality RCTs.

## CONCLUSION

LS for T2 GBC has similar long-term survival outcomes to those of OS but is superior to OS in terms of operative time, intraoperative bleeding, and length of hospital stay. Additional high-quality RCTs and long follow-ups are needed to further evaluate the effectiveness of LS for stage T2 GBC.

## ARTICLE HIGHLIGHTS

### *Research background*

Although laparoscopic surgery (LS) is recommended for stage T1 gallbladder cancer (GBC), the value of LS for stage T2 GBC is still controversial.

### *Research motivation*

This study evaluated the short- and long-term outcomes of LS in comparison to those of open surgery (OS) for stage T2 GBC.

### *Research objectives*

As there is still a lack of evidence from high-quality multicenter randomized controlled trials, we believe that it is necessary to conduct a meta-analysis to provide an evidence-based reference for laparoscopic radical surgery of T2 GBC.

### *Research methods*

We searched the PubMed, Embase, Cochrane Library, Ovid, Google Scholar, and Web of Science databases for published studies, with a cutoff date of September 2022.

### *Research results*

A total of 5 studies were included with a total of 297 patients, 153 in the LS group and 144 in the OS group. Meta-analysis results showed that the LS group was better than the OS group in terms of operative time, estimated blood loss, and hospital stay, whereas there was no significant difference between the two groups in terms of blood transfusion, complications, number of lymph nodes retrieved, recurrence, and 3-year and 5-year overall and disease-free survival.

### *Research conclusions*

The long-term outcomes of LS for T2 GBC are similar to those of OS, but LS is superior to OS in terms of operative time, intraoperative bleeding, and postoperative hospital stay.

### *Research perspectives*

Our meta-analysis is the first to assess the efficacy of the laparoscopic approach in the treatment of stage T2 GBC and to provide a reference for clinical management.


## FOOTNOTES


**Author contributions:** Zhang W and Ouyang DL equally contributed to this work; Zhang W and Ouyang DL drafted the manuscript and acquired and interpreted the data; Che X designed the study and revised the manuscript.

**Supported by** Shenzhen High-Level Hospital Construction Fund, and Sanming Project of Medicine in Shenzhen, No. SZSM202011010.

**Conflict-of-interest statement:** All authors report having no relevant conflicts of interest for this article.

**PRISMA 2009 Checklist statement:** This meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The data used in this study were derived from published studies and are anonymous. This study did not need informed consent from patients or a review by an institutional ethics committee. This meta-analysis was registered under the registration number CRD42022367334 on the systematic review registration platform PROSPERO (https://www.crd.york.ac.uk/PROSPERO/).





**Country/Territory of origin:** China



**ORCID number:** Wei Zhang 0000-0002-0936-0817; Xu Che 0000-0002-1634-4524.



**S-Editor:** Wang JJ
**L-Editor:** Filipodia
**P-Editor:** Wang JJ


## REFERENCES


1 **Hundal R**, Shaffer EA. Gallbladder cancer: epidemiology and outcome. *Clin Epidemiol* 2014; **6**: 99-109 [PMID: 24634588 DOI: 10.2147/CLEP.S37357]

2 **Sternby Eilard M**, Lundgren L, Cahlin C, Strandell A, Svanberg T, Sandström P. Surgical treatment for gallbladder cancer - a systematic literature review. *Scand J Gastroenterol* 2017; **52**: 505-514 [PMID: 28270039 DOI: 10.1080/00365521.2017.1284895]

3 **Wang JK**, Ma WJ, Wu ZR, Yang Q, Hu HJ, Liu F, Li FY. Is combined extra-hepatic bile-duct resection justified for

advanced gallbladder carcinoma? *Gastroenterol Rep (Oxf)* 2019; **7**: 426-433 [PMID: 31857904 DOI: 10.1093/gastro/goz018]

4 **Weiland ST**, Mahvi DM, Niederhuber JE, Heisey DM, Chicks DS, Rikkers LF. Should suspected early gallbladder cancer be treated laparoscopically? *J Gastrointest Surg* 2002; **6**: 50-6; discussion 56 [PMID: 11986018 DOI: 10.1016/s1091-255x(01)00014-2]

5 **Yokomizo H**, Yamane T, Hirata T, Hifumi M, Kawaguchi T, Fukuda S. Surgical treatment of pT2 gallbladder carcinoma: a reevaluation of the therapeutic effect of hepatectomy and extrahepatic bile duct resection based on the long-term outcome. *Ann Surg Oncol* 2007; **14**: 1366-1373 [PMID: 17260109 DOI: 10.1245/s10434-006-9219-1]

6 **D'Angelica M**, Dalal KM, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR. Analysis of the extent of resection for adenocarcinoma of the gallbladder. *Ann Surg Oncol* 2009; **16**: 806-816 [PMID: 18985272 DOI: 10.1245/s10434-008-0189-3]

7 **Reddy YP**, Sheridan WG. Port-site metastasis following laparoscopic cholecystectomy: a review of the literature and a case report. *Eur J Surg Oncol* 2000; **26**: 95-98 [PMID: 10718188 DOI: 10.1053/ejso.1999.0750]

8 **Wullstein C**, Woeste G, Barkhausen S, Gross E, Hopt UT. Do complications related to laparoscopic cholecystectomy influence the prognosis of gallbladder cancer? *Surg Endosc* 2002; **16**: 828-832 [PMID: 11997831 DOI: 10.1007/s00464-001-9085-7]

9 **Miyazaki M**, Yoshitomi H, Miyakawa S, Uesaka K, Unno M, Endo I, Ota T, Ohtsuka M, Kinoshita H, Shimada K, Shimizu H, Tabata M, Chijiiwa K, Nagino M, Hirano S, Wakai T, Wada K, Isayama H, Okusaka T, Tsuyuguchi T, Fujita N, Furuse J, Yamao K, Murakami K, Yamazaki H, Kijima H, Nakanuma Y, Yoshida M, Takayashiki T, Takada T. Clinical practice guidelines for the management of biliary tract cancers 2015: the 2nd English edition. *J Hepatobiliary Pancreat Sci* 2015; **22**: 249-273 [PMID: 25787274 DOI: 10.1002/jhbp.233]

10 **Butte JM**, Waugh E, Meneses M, Parada H, De La Fuente HA. Incidental gallbladder cancer: analysis of surgical findings and survival. *J Surg Oncol* 2010; **102**: 620-625 [PMID: 20721958 DOI: 10.1002/jso.21681]

11 **Pawlik TM**, Gleisner AL, Vigano L, Kooby DA, Bauer TW, Frilling A, Adams RB, Staley CA, Trindade EN, Schulick RD, Choti MA, Capussotti L. Incidence of finding residual disease for incidental gallbladder carcinoma: implications for re-resection. *J Gastrointest Surg* 2007; **11**: 1478-86; discussion 1486 [PMID: 17846848 DOI: 10.1007/s11605-007-0309-6]

12 **Lee JW**, Kwon JH, Lee JW. Oncologic and Long-Term Outcomes of Laparoscopic and Open Extended Cholecystectomy for Gallbladder Cancer. *J Clin Med* 2022; **11** [PMID: 35456227 DOI: 10.3390/jcm11082132]

13 **Cho JK**, Kim JR, Jang JY, Kim HG, Kim JM, Kwag SJ, Park JH, Kim JY, Ju YT, Jeong CY. Comparison of the Oncological Outcomes of Open versus Laparoscopic Surgery for T2 Gallbladder Cancer: A Propensity-Score-Matched Analysis. *J Clin Med* 2022; **11** [PMID: 35566770 DOI: 10.3390/jcm11092644]

14 **Navarro JG**, Kang I, Hwang HK, Yoon DS, Lee WJ, Kang CM. Oncologic safety of laparoscopic radical cholecystectomy in pT2 gallbladder cancer: A propensity score matching analysis compared to open approach. *Medicine (Baltimore)* 2020; **99**: e20039 [PMID: 32443308 DOI: 10.1097/MD.0000000000020039]

15 **Jang JY**, Han HS, Yoon YS, Cho JY, Choi Y. Retrospective comparison of outcomes of laparoscopic and open surgery for T2 gallbladder cancer - Thirteen-year experience. *Surg Oncol* 2019; **29**: 142-147 [PMID: 31196480 DOI: 10.1016/j.suronc.2019.05.007]

16 **Itano O**, Oshima G, Minagawa T, Shinoda M, Kitago M, Abe Y, Hibi T, Yagi H, Ikoma N, Aiko S, Kawaida M, Masugi Y, Kameyama K, Sakamoto M, Kitagawa Y. Novel strategy for laparoscopic treatment of pT2 gallbladder carcinoma. *Surg Endosc* 2015; **29**: 3600-3607 [PMID: 25740638 DOI: 10.1007/s00464-015-4116-y]

17 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700 [PMID: 19622552 DOI: 10.1136/bmj.b2700]

18 **Rahmati M**, McCarthy JJ, Malakoutinia F. Myonuclear permanence in skeletal muscle memory: a systematic review and meta-analysis of human and animal studies. *J Cachexia Sarcopenia Muscle* 2022; **13**: 2276-2297 [PMID: 35961635 DOI: 10.1002/jcsm.13043]

19 Rahmati M, Gondin J, Malakoutinia F. Effects of Neuromuscular Electrical Stimulation on Quadriceps Muscle Strength and Mass in Healthy Young and Older Adults: A Scoping Review. *Phys Ther* 2021; **101** [PMID: 34106246 DOI: 10.1093/ptj/pzab144]

20 **Rahmati M**, Malakoutinia F. Aerobic, resistance and combined exercise training for patients with amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Physiotherapy* 2021; **113**: 12-28 [PMID: 34555670 DOI: 10.1016/j.physio.2021.04.005]

21 **Rahmati M**, Keshvari M, Mirnasuri S, Yon DK, Lee SW, Il Shin J, Smith L. The global impact of COVID-19 pandemic on the incidence of pediatric new-onset type 1 diabetes and ketoacidosis: A systematic review and meta-analysis. *J Med Virol* 2022; **94**: 5112-5127 [PMID: 35831242 DOI: 10.1002/jmv.27996]

22 **Shirobe T**, Maruyama S. Laparoscopic radical cholecystectomy with lymph node dissection for gallbladder carcinoma. *Surg Endosc* 2015; **29**: 2244-2250 [PMID: 25303926 DOI: 10.1007/s00464-014-3932-9]

23 **Machado MA**, Makdissi FF, Surjan RC. Totally Laparoscopic Hepatic Bisegmentectomy (s4b+s5) and Hilar Lymphadenectomy for Incidental Gallbladder Cancer. *Ann Surg Oncol* 2015; **22** Suppl 3: S336-S339 [PMID: 26059653 DOI: 10.1245/s10434-015-4650-9]

24 **Gumbs AA**, Hoffman JP. Laparoscopic completion radical cholecystectomy for T2 gallbladder cancer. *Surg Endosc* 2010; **24**: 3221-3223 [PMID: 20499105 DOI: 10.1007/s00464-010-1102-2]

25 **Agarwal AK**, Javed A, Kalayarasan R, Sakhuja P. Minimally invasive versus the conventional open surgical approach of a radical cholecystectomy for gallbladder cancer: a retrospective comparative study. *HPB (Oxford)* 2015; **17**: 536-541 [PMID: 25727091 DOI: 10.1111/hpb.12406]

26 **Steinert R**, Nestler G, Sagynaliev E, Müller J, Lippert H, Reymond MA. Laparoscopic cholecystectomy and gallbladder cancer. *J Surg Oncol* 2006; **93**: 682-689 [PMID: 16724350 DOI: 10.1002/jso.20536]

27 **Kondo S**, Takada T, Miyazaki M, Miyakawa S, Tsukada K, Nagino M, Furuse J, Saito H, Tsuyuguchi T, Yamamoto M, Kayahara M, Kimura F, Yoshitomi H, Nozawa S, Yoshida M, Wada K, Hirano S, Amano H, Miura F; Japanese Association

of Biliary Surgery; Japanese Society of Hepato-Biliary-Pancreatic Surgery; Japan Society of Clinical Oncology. Guidelines for the management of biliary tract and ampullary carcinomas: surgical treatment. *J Hepatobiliary Pancreat Surg* 2008; **15**: 41-54 [PMID: 18274843 DOI: 10.1007/s00534-007-1279-5]

28 **Maker AV**, Butte JM, Oxenberg J, Kuk D, Gonen M, Fong Y, Dematteo RP, D'Angelica MI, Allen PJ, Jarnagin WR. Is port site resection necessary in the surgical management of gallbladder cancer? *Ann Surg Oncol* 2012; **19**: 409-417 [PMID: 21698501 DOI: 10.1245/s10434-011-1850-9]

29 **Yoon YS**, Han HS, Cho JY, Choi Y, Lee W, Jang JY, Choi H. Is Laparoscopy Contraindicated for Gallbladder Cancer? *J Am Coll Surg* 2015; **221**: 847-853 [PMID: 26272017 DOI: 10.1016/j.jamcollsurg.2015.07.010]

30 **Han HS**, Yoon YS, Agarwal AK, Belli G, Itano O, Gumbs AA, Yoon DS, Kang CM, Lee SE, Wakai T, Troisi RI. Laparoscopic Surgery for Gallbladder Cancer: An Expert Consensus Statement. *Dig Surg* 2019; **36**: 1-6 [PMID: 29339660 DOI: 10.1159/000486207]

31 **Fornara P**, Zacharias M, Wagner S. Port-site metastases: fact or fiction? *Urol Int* 2003; **71**: 136-142 [PMID: 12890948 DOI: 10.1159/000071834]

32 **Goetze TO**. Gallbladder carcinoma: Prognostic factors and therapeutic options. *World J Gastroenterol* 2015; **21**: 12211-12217 [PMID: 26604631 DOI: 10.3748/wjg.v21.i43.12211]

33 **Lee SE**, Kim KS, Kim WB, Kim IG, Nah YW, Ryu DH, Park JS, Yoon MH, Cho JY, Hong TH, Hwang DW, Choi DW; Korean Association of Hepato-Biliary and Pancreas Surgery. Practical guidelines for the surgical treatment of gallbladder cancer. *J Korean Med Sci* 2014; **29**: 1333-1340 [PMID: 25368485 DOI: 10.3346/jkms.2014.29.10.1333]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 December 27; 14(12): 1397-1410

DOI: 10.4240/wjgs.v14.i12.1397

ISSN 1948-9366 (online)

META-ANALYSIS

# Meta-analysis of transanal *vs* laparoscopic total mesorectal excision of low rectal cancer: Importance of appropriate patient selection

Pratik Bhattacharya, Ishaan Patel, Noureen Fazili, Shahab Hajibandeh, Shahin Hajibandeh

**Specialty type:** Surgery

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Lei Y, China; Yao J, China

**Received:** October 2, 2022
**Peer-review started:** October 2, 2022
**First decision:** October 30, 2022
**Revised:** November 6, 2022
**Accepted:** December 13, 2022
**Article in press:** December 13, 2022
**Published online:** December 27, 2022

**Pratik Bhattacharya,** Department of Surgery, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham B71 4HJ, United Kingdom

**Ishaan Patel, Noureen Fazili,** Department of Surgery, Queen Elizabeth Hospital Birmingham, Birmingham B15 2GW, United Kingdom

**Shahab Hajibandeh,** Department of Surgery, University Hospital of Wales, Cardiff CF14 4XW, United Kingdom

**Shahin Hajibandeh,** Department of Surgery, Royal Stoke University Hospital, Stoke-on-Trent ST4 6QG, United Kingdom

**Corresponding author:** Shahin Hajibandeh, MD, Senior Researcher, Surgeon, Department of Surgery, Royal Stoke University Hospital, Newcastle Road, Stoke-on-Trent ST4 6QG, United Kingdom. shahin_hajibandeh@yahoo.com

## Abstract

### *BACKGROUND*

Achieving a clear resection margins for low rectal cancer is technically challenging. Transanal approach to total mesorectal excision (TME) was introduced in order to address the challenges associated with the laparoscopic approach in treating low rectal cancers. However, previous meta-analyses have included mixed population with mid and low rectal tumours when comparing both approaches which has made the interpretation of the real differences between two approaches in treating low rectal cancer difficult.

### *AIM*

To investigate the outcomes of transanal TME (TaTME) and laparoscopic TME (LaTME) in patients with low rectal cancer.

### *METHODS*

A comprehensive systematic review of comparative studies was performed in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards. Intraoperative and postoperative complications, anastomotic leak, R0 resection, completeness of mesorectal excision, circumferential resection margin (CRM), distal resection margin (DRM), harvested lymph nodes, and operation time were the investigated outcome measures.

### *RESULTS*

We included twelve comparative studies enrolling 969 patients comparing TaTME ($n$ = 969) and LaTME ($n$ = 476) in patients with low rectal tumours. TaTME was associated with significantly lower risk of postoperative complications (OR: 0.74, $P$ = 0.04), anastomotic leak (OR: 0.59, $P$ = 0.02), and conversion to an open procedure (OR: 0.29, $P$ = 0.002) in comparison with LaTME. Moreover, the rate of R0 resection was significantly higher in the TaTME group (OR: 1.96, $P$ = 0.03). Nevertheless, TaTME and LaTME were comparable in terms of rate of intraoperative complications (OR: 1.87; $P$ = 0.23), completeness of mesoractal excision (OR: 1.57, $P$ = 0.15), harvested lymph nodes (MD: -0.05, $P$ = 0.96), DRM (MD: -0.94; $P$ = 0.17), CRM (MD: 1.08, $P$ = 0.17), positive CRM (OR: 0.64, $P$ = 0.11) and procedure time (MD: -6.99 min, $P$ = 0.45).

***CONCLUSION***

Our findings indicated that for low rectal tumours, TaTME is associated with better clinical and short term oncological outcomes compared to LaTME. More randomised controlled trials are required to confirm these findings and to evaluate long term oncological and functional outcomes.

**Key Words:** Total mesorectal excision; Laparoscopic; Transanal; Rectal cancer



**Core Tip:** The meta-analysis of best available evidence demonstrated that for low rectal tumours, Transanal total mesorectal excision (TaTME) is associated with better clinical and short term oncological outcomes compared to Laparoscopic TME. More randomised controlled trials with adequate power and high quality are required to not only confirm these findings, but also to evaluate long term oncological and functional outcomes.

**Citation:** Bhattacharya P, Patel I, Fazili N, Hajibandeh S, Hajibandeh S. Meta-analysis of transanal *vs* laparoscopic total mesorectal excision of low rectal cancer: Importance of appropriate patient selection. *World J Gastrointest Surg* 2022; 14(12): 1397-1410

**URL:** https://www.wjgnet.com/1948-9366/full/v14/i12/1397.htm

**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i12.1397

## INTRODUCTION

The incidence of rectal cancer is increasing making it one of the most common cancers worldwide[1]. Rapidly evolving use of total mesorectal excision (TME) and neoadjuvant chemotherapy have led to considerable improvements in the outcomes of rectal cancer surgery[2]. A clear resection margin associated with a high quality TME is important for an ideal oncological resection, reducing the incidence of local or regional recurrence, and increasing survival from cancer[3,4].

Achieving a negative resection margins during resection of low rectal tumours can be challenging due to existence of diminishing gap between the wall of the rectum and mesorectal fascia towards the anal canal[5]. This has resulted in worse oncological outcomes associated with resection of lower rectal tumours, in comparison with resection of middle or high rectal tumours, because of greater incidence of local recurrence and positive resection margin[6]. Transanal approach to TME was introduced in order to address the challenges associated with the laparoscopic and even open TME in surgical management of low rectal cancers[7].

In 2020, in a comprehensive meta-analysis of comparative studies, we reported that Transanal TME (TaTME) led to higher R0 resection rate and number of harvested lymph nodes while decreasing rates of positive circumferential resection margin (CRM) and conversion to open procedure when compared to laparoscopic TME (LaTME)[8]. Moreover, our findings indicated that TaTME and LaTME may have similar risk of perioperative morbidity[8]. Nevertheless, most of the evaluated studies in the aforementioned meta-analysis compared TaTME and LaTME in patients with middle and low rectal tumours subjecting the findings to bias. Considering the existence of new studies focusing on the clinical outcomes of TaTME and LaTME in management of low rectal cancer, conduction of another meta-analysis is worthwhile in order to help defining more appropriate patient selection.

This study aimed to systematically evaluate the best available comparative evidence surrounding TaTME and LaTME in surgical management of low rectal cancer only and compare the outcome so both approaches using meta-analytical model.

## MATERIALS AND METHODS

### Study design and selection of eligible studies

In our review protocol, we highlighted the inclusion and exclusion criteria, our methodology, and evaluated outcome measures. This study was carried out in line with standards of Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[9].

All comparative studies investigating the outcomes of transanal and laparoscopic TME in patients with low cancer were considered for inclusion. A rectal tumour within 6 cm of anal verge was considered as a low rectal tumour. We considered all adult (aged > 18 years) patients undergoing TaTME or LaTME for low rectal cancer. TaTME was the intervention of interest and LaTME was the comparison of interest.

The primary outcome measures were intraoperative and postoperative complications, and anastomotic leak. The investigated primary oncological outcome measures were R0 resection, CRM, positive CRM, distal resection margin (DRM), completeness of mesorectal excision, and number of harvested lymph nodes. Moreover, conversion to open and operative time were defined as secondary outcome measures.

### Literature search strategy

Following sources: MEDLINE, Web of Science, and CENTRAL were searched by two independent authors. Appendix 1 outlines the used search strategy (Supplementary Table 1). The most recent literature search was carried out on 08 July, 2022. Moreover, we screened the reference lists of the included studies and previous review articles in order to identify more relevant articles.

### Study selection

Two independent review authors screened the title and abstract of the identified studies. This was followed by retrieval of the full-texts of the related studies and their assessment in line with our inclusion and exclusion criteria. Discrepancies in this stage were addressed by discussion among the reviewers.

### Extraction and management of data

We created a data extraction tool and extracted details of study-related data, data regarding demographic characteristics of the included patients in each study and outcome data. Two independent reviewers were involved in this process. Disagreements between the authors were resolved following discussion. In case of no resolution, an additional reviewer was consulted.

### Assessment of risk of bias

The methodological quality of the included studies was assessed by 2 review authors who determined their associated risk of bias using the Newcastle-Ottawa scale[10] for observational studies and Cochrane's tool[11] for randomized controlled trials (RCTs). We resolved disagreements in methodological quality assessment by discussion between the reviewers. However, if disagreement remained unresolved, a third reviewer was consulted as an adjudicator.

### Summary measures and synthesis

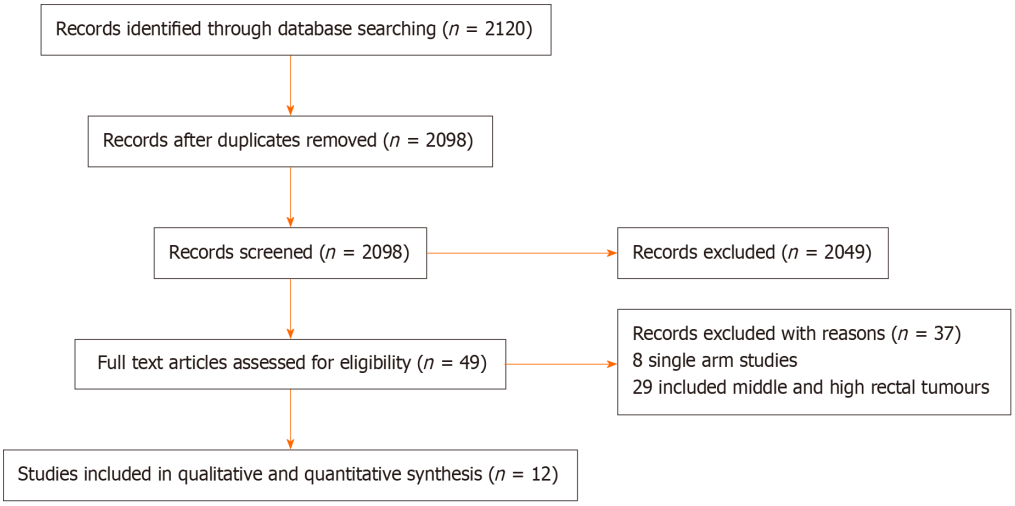
For dichotomous outcome measures the odds ratio (OR) was calculated as the summary measures. For continuous outcome parameters, the mean difference (MD) between the two groups was calculated. If mean values were not reported, we extracted data on median and interquartile range and converted those to mean and standard deviation using Hozo *et al*[12]'s equation.

The unit of analysis for all of the analyzed outcome measures in this study was an individual participant. We did not require contacting the authors of the included studies to ask for any potential missing information.

Data analysis was carried out *via* Review Manager 5.4 software[11]. One author extracted and entered the data into the software and another author cross-checked the data. Random-effects modelling were used for analysis of all outcomes. We reported outcome of analyses in Forest plots with 95% confidence intervals (CIs).

The Cochran Q test ($\chi^2$) was used to assess between-study heterogeneity. We calculated $I^2$ and used the following guide for interpreting the degree of heterogeneity: 0% to 50% might not be important; 50% to 75%: May represent moderate heterogeneity; 75% to 100% may represent substantial heterogeneity. Moreover, we constructed funnel plots for any outcome synthesis involving more than 10 studies.

We performed sensitivity analyses to assess for potential sources of heterogeneity and evaluate the robustness of our findings. Finally, we conducted leave-one-out sensitivity analysis to assess the effect of each study on the overall effect size and heterogeneity.




**DOI:** 10.4240/wjgs.v14.i12.1397 

**Figure 1 Study flow diagram.**

## RESULTS

The literature search resulted in 2120 articles. Following further assessment of the aforementioned articles, 12 comparative studies (2 randomised and 10 observational studies)[13-24] met the inclusion criteria (Figure 1). The included studies enrolled 969 patients of whom 493 underwent TaTME and the remaining 476 patients had LaTME for rectal cancer.

Table 1 presents the included studies related data. Table 2 presents baseline demographic and clinical characteristics of the included patients. The patients in the transanal and laparoscopic groups were of similar age ($P$ = 0.53), gender ($P$ = 0.19), and BMI ($P$ = 0.68). No significant difference was found between the TaTME and LaTME groups in rectal cancer stages I ($P$ = 0.29), II ($P$ = 0.30) and III ($P$ = 0.95). Furthermore, the mean distance of the tumour to the anal verge in the TaTME and LaTME groups were 3.4 cm ± 1.4 cm and 3.6 cm ± 1.5 cm, respectively, which was not significantly different ($P$ = 0.07). Neoadjuvant chemotherapy was carried our similarly between two groups ($P$ = 0.22).

### *Methodological appraisal*

The methodological assessment of 10 observational studies is presented in Table 3. In 7 studies, the risk of bias was low and in 3 studies it was moderate. Moreover, the outcome of methodological assessment of the included randomized controlled trials is demonstrated by Figure 2.

### *Data synthesis*

Outcomes are summarised in Figures 3 and 4.

**Intraoperative complications:** Six studies (382 patients) reported intraoperative complications as an outcome. The rate of intraoperative complications in the TaTME and LaTME were 7.3% and 4.2%, respectively. There was no significant difference in intraoperative complications between TaTME and LaTME (OR: 1.87; 95%CI: 0.68-5.18, $P$ = 0.23). There was low between-study heterogeneity ($I^2$ = 6%, $P$ = 0.36).

**Postoperative complications:** Eleven studies (923 patients) reported postoperative complications as an outcome. The rate of overall postoperative complications in the TaTME and LaTME were 30.0% and 35.9%, respectively. TaTME significantly reduced postoperative complications when compared to LaTME (OR: 0.74; 95%CI: 0.56-0.99, $P$ = 0.04). There was moderate heterogeneity among the included studies ($I^2$ = 2%, $P$ = 0.42).

**Anastomotic leak:** This outcome was reported by eleven studies (896 patients). Anastomotic leak occurred in 10.1% and 15.5% of patients in the TaTME and LaTME groups, respectively. TaTME was associated with a significantly lower rate of anastomotic leak compared with LaTME (OR: 0.59; 95%CI: 0.38-0.91, $P$ = 0.02). Heterogeneity among the included studies was low ($I^2$ = 0%, $P$ = 0.49).

**R0 resection**: Nine studies (609 patients) reported R0 resection as an outcome. An R0 resection was achieved in 93.5% and 87.8% of patients in the TaTME and LaTME groups, respectively. The rate of R0 resection was significantly higher in the TaTME group (OR: 1.96; 95%CI: 1.07-3.58, $P$ = 0.03). Low between-study heterogeneity was detected ($I^2$ = 0%, $P$ = 0.51).

**Table 1 Included studies related data**

| Ref. | Publication year | Journal | Country | Study design | TaTME | LaTME |
|---|---|---|---|---|---|---|
| de'Angelis *et al*[13] | 2015 | *Langenbecks Arch Surg* | France | Retrospective observational study | 32 | 32 |
| Kanso *et al*[14] | 2015 | *Dis Colon Rectum* | France | Retrospective observational study | 51 | 34 |
| Pontallier *et al*[15] | 2016 | *Surg Endosc* | France | RCT | 38 | 34 |
| Marks *et al*[16] | 2016 | *Tech. Coloproctol* | United States | Retrospective observational study | 17 | 17 |
| Lelong *et al*[17] | 2017 | *J Am Coll Surg* | France | Retrospective observational study | 34 | 38 |
| Denost *et al*[18] | 2018 | *Surg Endosc* | France | RCT | 50 | 50 |
| Mege *et al*[19] | 2018 | *Colorectal Dis* | France | Retrospective observational study | 34 | 34 |
| Rubinkiewicz *et al*[20] | 2018 | *Cancer Manag Res* | Poland | Retrospective observational study | 35 | 35 |
| Roodbeen *et al*[21] | 2019 | *Surg Endosc* | Netherlands | Retrospective observational study | 41 | 41 |
| Rubinkiewicz *et al*[22] | 2019 | *BMC Surg* | Poland | Prospective observational study | 23 | 23 |
| Ren *et al*[23] | 2021 | *Asian J Surg* | China | Prospective observational study | 32 | 32 |
| Li *et al*[24] | 2022 | *Gastroenterol Res Pract* | China | Prospective observational study | 106 | 106 |

TaTME: Transanal total mesorectal excision, LaTME: Laparoscopic total mesorectal excision; RCT: Randomised controlled trial.

**Completeness of mesorectal excision:** This outcome was reported by nine studies (766 patients). The rate of completeness of mesorectal excision in the TaTME and LaTME groups were 81.4% and 74.0%, respectively. The pooled analysis did not demonstrated similar rate of completeness of mesorectal excision between two groups (OR: 1.57; 95%CI: 0.85-2.90, $P = 0.15$). There was moderate between-study heterogeneity ($I^2 = 60\%$, $P = 0.01$).

**Number of harvested lymph nodes:** Eight studies (747 patients) reported the number of harvested lymph nodes in the TaTME and LaTME groups. The mean number of harvested lymph nodes in the TaTME was 16.1 ± 2.1, while it was 16.3 ± 3.2 in the LaTME group. The pooled analysis demonstrated no significant difference in the number of harvested lymph nodes between two groups (MD: -0.05; 95%CI: -1.98-1.89, $P = 0.96$). The between-study heterogeneity was moderate ($I^2 = 71\%$, $P = 0.001$).

**DRM:** Eight studies (745 patients) reported DRM in their study groups. The mean DRM in the TaTME group was 15.8 mm ± 3.9 mm whereas it was 17.6 mm ± 3.8 mm in the LaTME group. The pooled analysis found no significant difference in DRM between two groups (MD: -0.94; 95%CI: -2.26-0.39, $P = 0.17$). There was low heterogeneity among the included studies ($I^2 = 0\%$, $P = 0.53$).

**CRM:** Six studies (465 patients) reported CRM in their study groups. The mean CRM in the TaTME group was 8.5 mm ± 1.2 mm and it was 8.1 mm ± 2.9 mm in the LaTME group. The pooled analysis did not identify any significant difference in CRM between two groups (MD: 1.08; 95%CI: -0.46-2.61, $P = 0.17$). There was moderate between-study heterogeneity ($I^2 = 71\%$, $P = 0.004$).

**Positive CRM:** Eight studies (717 patients) reported the rate of positive CRM in their study groups. The rate of positive CRM in the TaTME group was 9.0% and it was 13.3% in the LaTME group. There was no significant difference in the rate of positive CRM between two groups (OR: 0.64; 95%CI: 0.37-1.10, $P = 0.11$). Between-study heterogeneity was low ($I^2 = 0\%$, $P = 0.59$).

**Procedure time:** Ten studies (889 patients) reported the procedure time as an outcome. The mean procedure time in the TaTME and LaTME groups were 274.1 min ± 91.8 min and 282.4 min ± 103.0 min, respectively. There was no significant difference in procedure time between two groups (MD: -6.99 min; 95%CI: -25.28-11.30, $P = 0.45$). Heterogeneity among the studies was significant ($I^2 = 86\%$, $P < 0.00001$).

**Conversion to open:** This outcome was reported by eleven studies (923 patients). The rate of conversion to an open procedure in the TaTME group was 1.5% and it was 7.5% in the LaTME group. The conversion rate was significantly lower in the TaTME group compared to the LaTME group (OR: 0.29; 95%CI: 0.13-0.64, $P = 0.002$). There was low between-study heterogeneity ($I^2 = 0\%$, $P = 0.54$).

Considering that the included study inadequately reported length of hospital stay as an outcome, we were unable to conduct an analysis on this outcome.

### *Sensitivity analysis*

There was no change in the direction of pooled effect size when the risk ratio, or risk difference was

**Table 2 Included studies related data**

| Ref. | Publication year | Age | Gender | BMI | Neoadjuvant therapy | Tumour stage | Tumour location | Distance of tumour to anal verge |
|---|---|---|---|---|---|---|---|---|
| de'Angelis[13] | 2015 | 64.91 ± 10.05 *vs* 67.16 ± 9.61 | 66% *vs* 66% | 25.19 ± 3.52 *vs* 24.53 ± 3.19 | 100% *vs* 100% | I: 65.6% *vs* 56.3%; II: 31.3% *vs* 40.6%; III: 3.1% *vs* 3.1% | Low rectum | 4 (2.5-5.0) *vs* 3.7 (2.5-5.0) |
| Kanso *et al*[14] | 2015 | 59 ± 11 (32-79) *vs* 59 ± 11 (33-82) | 71% *vs* 77% | 24 ± 4 (17-32) *vs* 24 ± 4 (15-34) | 80% *vs* 79% | NR | Lower rectum | 1.6 ± 0.8 (0-3.5) *vs* 1.8 ± 0.9 (0-3.5) |
| Pontallier *et al*[15] | 2016 | 62 (39-81) *vs* 62 (35-82) | 68% *vs* 62% | 25.5 *vs* 24.8 | 79% *vs* 88% | I: 21% *vs* 21%; II: 19% *vs* 14%; III: 60% *vs* 65% | Low rectum | 4 (2-6) *vs* 4 (2-6) |
| Marks *et al*[16] | 2016 | 60 *vs* 59 | NR | 25.9 *vs* 26.4 | NR | I: 29.4% *vs* 23.5%; II: 70.6% *vs* 76.5% | Low rectum | < 4 *vs* < 4 |
| Lelong *et al*[17] | 2017 | NR | 68% *vs* 58% | 24 (18.6-45.0) *vs* 24.2(17.7-32.7) | 88.2% *vs* 92.1% | I: 17.6% *vs* 23.7%; II: 70.6% *vs* 71.0%; III: 11.8% *vs* 5.3% | Low rectum | NR |
| Denost *et al*[18] | 2018 | 64 (39-82) *vs* 63 (31-90) | 74% *vs* 64% | 25.1 (17.3-33.2) *vs* 25.6 (18.3-38.3) | 78% *vs* 84% | NR | Low rectum | 4 (2-6) *vs* 4 (2-6) |
| Mege *et al*[19] | 2018 | 58 ± 14 *vs* 59 ± 13 | 68% *vs* 68% | 25 ± 4 *vs* 25 ± 3 | 85% *vs* 85% | I: 29.4% *vs* 11.8%; II: 67.6% *vs* 82.3%; III: 43.5% *vs* 47.8%; IV: 2.9% *vs* 5.9% | Low rectum | NR |
| Rubinkiewicz *et al*[20] | 2018 | 64.3 ± 10.1 *vs* 60.3 ± 10.2 | 69% *vs* 69% | 26.10 ± 4.09 *vs* 27.10 ± 4.71 | 88.6% *vs* 88.6% | I: 42.9% *vs* 45.7%; II: 57.1% *vs* 54.3% | Low rectum | 2.90 ± 1.17 *vs* 3.19 ± 1.47 |
| Roodbeen *et al*[21] | 2019 | 62.5 ± 10.7 *vs* 66.0 ± 9.2 | 82.9% *vs* 78% | 26.7 ± 1.9 *vs* 26.1 ± 4.0 | 43.9% *vs* 43.9% | I: 22.0% *vs* 19.5%; II: 36.6% *vs* 39%; III: 31.7% *vs* 31.7%; IV: 9.8% *vs* 9.8% | Low rectum | 2.0 (0.0-4.0) *vs* 1.5 (0.0-3.0) |
| Rubinkiewicz *et al*[22] | 2019 | 60 (51-67) *vs* 64 (58-67) | 69% *vs* 69% | 26 (22.8-29.7) *vs* 26.5 (23.8-30.6) | 78.2% *vs* 82.6% | NR | Low rectum | 3(2-4) *vs* 4 (3-5) |
| Ren *et al*[23] | 2021 | 65.78 ± 12.37 *vs* 67.16 ± 10.03 | 59.3% *vs* 56.2% | 22.87 ± 2.66 *vs* 23.05 ± 2.70 | 71.8% *vs* 65.6% | I: 34.3% *vs* 37.5%; II: 28.1% *vs* 31.2%; III: 31.2% *vs* 21.8% | Low rectum | 5.53 ± 0.98 *vs* 5.78 ± 0.94 |
| Li *et al*[24] | 2022 | 55 ± 12 (23-78) *vs* 56 ± 12 (26-79) | 100% *vs* 100% | 23:0 ± 2.9 *vs* 22:9 ± 3.2 | 100% *vs* 100% | NR | Low rectum | 3.6 ± 0.9 (2.0-5.0) *vs* 3.8 ± 0.9 (1.4-5.0) |

Transanal total mesorectal excision *vs* Laparoscopic total mesorectal excision. BMI: Body mass index; NR: Not reported.

calculated or during leave-one-out sensitivity analysis.

## DISCUSSION

In view of ongoing debates regarding the best surgical approach for resection of low rectal cancer, we conducted a comprehensive systematic review and meta-analysis to evaluate comparative outcomes of transanal *vs* laparoscopic TME in management of low rectal cancer. We identified two RCTs and 10 observational studies[13-24] enrolling 969 patients of whom 493 had TaTME and 476 patients had LaTME for low rectal tumour. The subsequent outcome synthesis showed that TaTME significantly reduced rate of postoperative complications, anastomotic leak, and conversion to open in comparison to LaTME. Moreover, TaTME resulted in significantly higher rate of R0 resection. However, no significant difference was found in intraoperative complications, completeness of mesoractal excision, harvested lymph nodes, DRM, CRM, positive CRM and procedure time between TaTME and LaTME

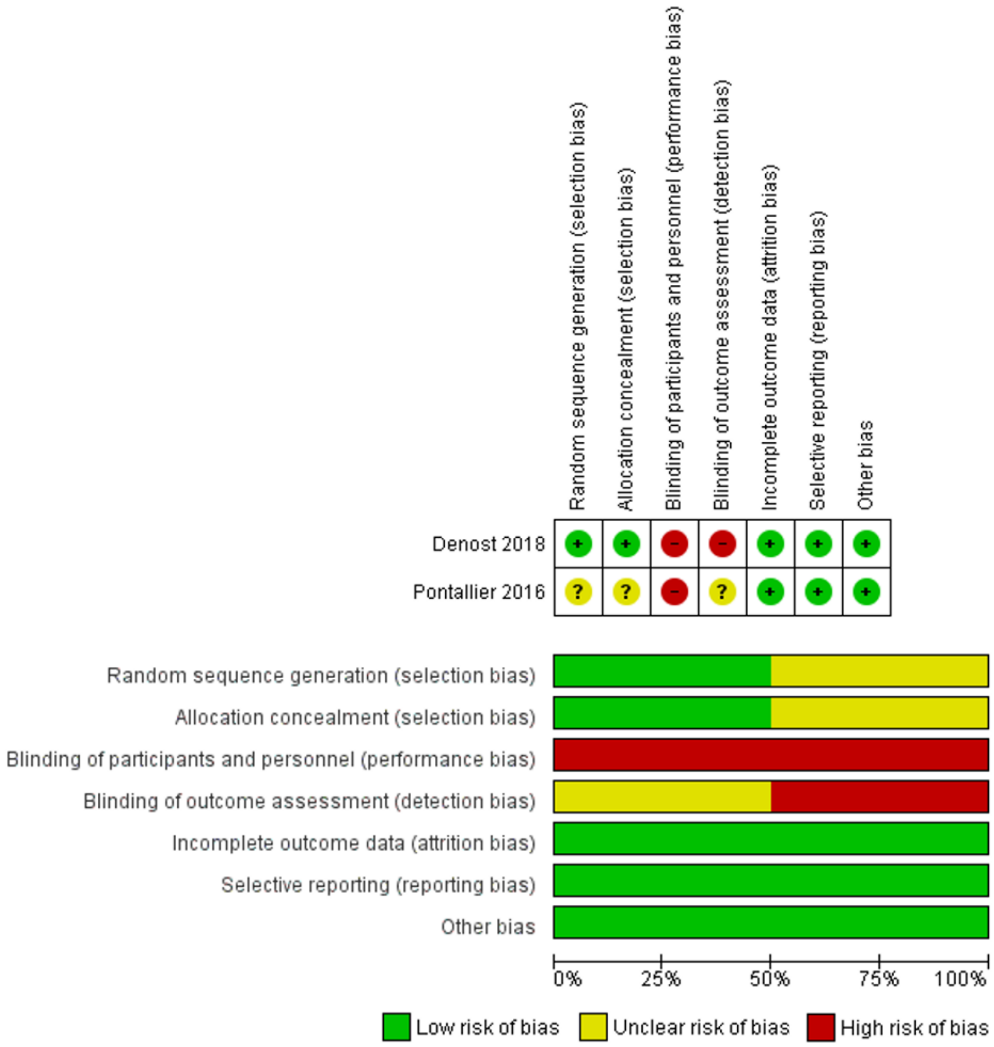
The between-study heterogeneity in the analyses of intraoperative and postoperative complications, anastomotic leak, R0 resection, DRM, positive CRM, and conversion to open were low suggesting that the reported findings with respect to these outcomes can be considered robust. Moderate heterogeneity

**Table 3 Methodological quality of the observational studies assessed with the Newcastle-Ottawa scale**

| Author | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow up of cohorts | Total score |
|---|---|---|---|---|---|---|---|---|---|
| de'Angelis[13], 2015 | * | * | * | * | ** | * | * | * | 9 |
| Kanso *et al*[14], 2015 | * | * | * | * | ** | * | * | * | 9 |
| Marks *et al*[16], 2016 | * | * | * | * | - | * | * | * | 7 |
| Lelong *et al*[17], 2017 | * | * | * | * | * | * | * | * | 8 |
| Mege *et al*[19], 2018 | * | * | * | * | ** | * | * | * | 9 |
| Rubinkiewicz *et al*[20], 2018 | * | * | * | * | ** | * | * | * | 9 |
| Roodbeen *et al* [21], 2019 | * | * | * | * | ** | * | * | * | 9 |
| Rubinkiewicz *et al*[22], 2019 | * | * | * | * | * | * | * | * | 8 |
| Ren *et al*[23], 2021 | * | * | * | * | ** | * | * | * | 9 |
| Li *et al*[24], 2022 | * | * | * | * | ** | * | * | * | 9 |

among the included studies in the analyses of completeness of mesorectal excision, and number of harvested lymph nodes may suggest variation of reporting in the included studies on these outcomes. There was high between-study heterogeneity regarding procedure time suggesting that our findings about procedure time may be less robust.

The findings of our meta-analysis are not consistent with some of the findings of our previous meta-analysis on this topic published in 2020[8]. The simple explanation for such disagreement is the difference in the inclusion criteria of the two studies with regards to the location of the rectal cancer. We only included low rectal cancer patients in this meta-analysis while previously we included both middle and low rectal cancer patients. In fact, as a direction for future research, in our previous meta-analysis we encouraged future studies to consider patients with low rectal cancer only when comparing TaTME and LaTME to evaluate a more realistic comparison between these two management approaches[8]. This is indeed reassuring to observe growing evidence in the context of comparative outcomes of TaTME and LaTME in management of low rectal cancer. The appropriate patient selection in this context is of great importance as inappropriate patient selection for TaTME has been demonstrated to result in




**DOI:** 10.4240/wjgs.v14.i12.1397 

**Figure 2 Risk of bias summary and graph showing authors' judgments about each risk of bias item.**

unfavourable outcomes of TaTME leading to suspension of TaTME in some countries. Wasmuth *et al*[25] reported high rate of anastomotic leak and local recurrence associated with TaTME, the findings that led to suspicion of TaTME in Norway. However, only 5% of their included patients had low rectal tumours with the remaining patients having middle or high rectal cancers. Moreover, the study lacked a control group, hence low level of evidence.

In the current meta-analysis, we independently evaluated the baseline characteristics of the study population to assess if the patients in the TaTME and LaTME groups were comparable. We found no significant difference in age, gender, BMI, rate of neoadjuvant chemotherapy, and stage of cancer between two groups. Moreover, we demonstrated similar distance between the distal tumour and anal verge between the TaTME and LaTME patients. This is of a cardinal importance as TaTME has been introduced to address the challenges associated with open and laparoscopic approaches in resecting very low rectal cancers, particularly in male patients with narrow pelvis[8]. Therefore, comparability of our included populations in both groups makes our findings more robust.

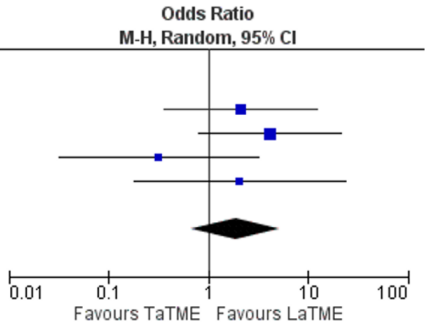
We were not able to conduct any analyses on comparative functional outcomes of TaTME and LaTME considering that only two of the included studies reported such outcomes. Lelong *et al*[17] compared functional outcomes of TaTME and LaTME and demonstrated no significant difference in urinary complications and faecal incontinence between two groups. Rubinkiewicz *et al*[22] also investigated functional outcomes in patients undergoing TaTME and LaTME for low rectal tumours and reported no significant differences in risk of low anterior resection syndrome between two groups and its severity. The authors found comparable median Wexner score in both groups[22]. Considering the current limited evidence in the context of functional outcomes of TaTME compared with LaTME, no definitive conclusions can be made.

Although we were not able to analyse long term oncological outcomes including disease recurrence, the findings of one of our included RCTs in this context is important. After 5 years follow-up, Denost *et al*[18] reported no significant differences in long-term outcomes between TaTME and LaTME. Although

**A**

| Study or Subgroup | TaTME Events | TaTME Total | LaTME Events | LaTME Total | Weight | Odds Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| de'Angelis 2015 | 0 | 32 | 0 | 32 | | Not estimable | 2015 |
| Marks 2016 | 0 | 17 | 0 | 17 | | Not estimable | 2016 |
| Rubinkiewicz 2018 | 4 | 35 | 2 | 35 | 30.5% | 2.13 [0.36, 12.46] | 2018 |
| Mege 2018 | 7 | 34 | 2 | 34 | 34.5% | 4.15 [0.79, 21.66] | 2018 |
| Roodbeen 2019 | 1 | 41 | 3 | 41 | 18.5% | 0.32 [0.03, 3.18] | 2019 |
| Ren 2020 | 2 | 32 | 1 | 32 | 16.5% | 2.07 [0.18, 24.01] | 2020 |
| **Total (95% CI)** | | **191** | | **191** | **100.0%** | **1.87 [0.68, 5.18]** | |
| Total events | 14 | | 8 | | | | |

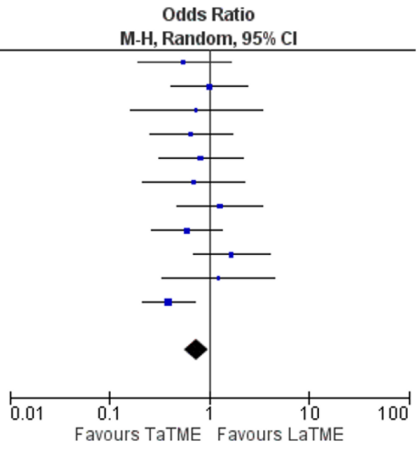
Heterogeneity: Tau² = 0.07; Chi² = 3.20, df = 3 (*P* = 0.36); I² = 6%
Test for overall effect: Z = 1.21 (*P* = 0.23)




**B**

| Study or Subgroup | TaTME Events | TaTME Total | LaTME Events | LaTME Total | Weight | Odds Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| de'Angelis 2015 | 8 | 32 | 12 | 32 | 7.0% | 0.56 [0.19, 1.63] | 2015 |
| Kanso 2015 | 24 | 51 | 16 | 34 | 10.6% | 1.00 [0.42, 2.39] | 2015 |
| Marks 2016 | 4 | 17 | 5 | 17 | 3.5% | 0.74 [0.16, 3.41] | 2016 |
| Pontallier 2016 | 12 | 38 | 14 | 34 | 8.6% | 0.66 [0.25, 1.73] | 2016 |
| Lelong 2017 | 11 | 34 | 14 | 38 | 8.5% | 0.82 [0.31, 2.17] | 2017 |
| Rubinkiewicz 2018 | 6 | 35 | 8 | 35 | 5.8% | 0.70 [0.21, 2.28] | 2018 |
| Mege 2018 | 14 | 34 | 12 | 34 | 8.4% | 1.28 [0.48, 3.42] | 2018 |
| Denost 2018 | 16 | 50 | 22 | 50 | 12.0% | 0.60 [0.27, 1.35] | 2018 |
| Roodbeen 2019 | 19 | 41 | 14 | 41 | 10.1% | 1.67 [0.68, 4.06] | 2019 |
| Ren 2020 | 6 | 32 | 5 | 32 | 4.8% | 1.25 [0.34, 4.59] | 2020 |
| Li 2022 | 21 | 106 | 41 | 106 | 20.6% | 0.39 [0.21, 0.73] | 2022 |
| **Total (95% CI)** | | **470** | | **453** | **100.0%** | **0.74 [0.56, 0.99]** | |
| Total events | 141 | | 163 | | | | |

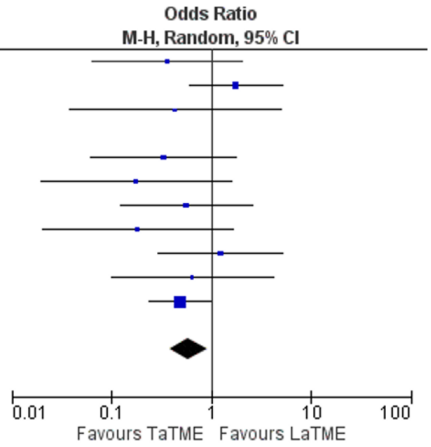
Heterogeneity: Tau² = 0.00; Chi² = 10.19, df = 10 (*P* = 0.42); I² = 2%
Test for overall effect: Z = 2.03 (*P* = 0.04)




**C**

| Study or Subgroup | TaTME Events | TaTME Total | LaTME Events | LaTME Total | Weight | Odds Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| de'Angelis 2015 | 2 | 32 | 5 | 32 | 6.3% | 0.36 [0.06, 2.01] | 2015 |
| Kanso 2015 | 14 | 51 | 6 | 34 | 16.0% | 1.77 [0.60, 5.17] | 2015 |
| Pontallier 2016 | 1 | 38 | 2 | 34 | 3.1% | 0.43 [0.04, 4.99] | 2016 |
| Marks 2016 | 0 | 17 | 0 | 17 | | Not estimable | 2016 |
| Lelong 2017 | 2 | 34 | 6 | 38 | 6.6% | 0.33 [0.06, 1.78] | 2017 |
| Mege 2018 | 1 | 34 | 5 | 34 | 3.8% | 0.18 [0.02, 1.59] | 2018 |
| Rubinkiewicz 2018 | 3 | 35 | 5 | 35 | 8.1% | 0.56 [0.12, 2.56] | 2018 |
| Denost 2018 | 1 | 50 | 5 | 50 | 3.9% | 0.18 [0.02, 1.63] | 2018 |
| Roodbeen 2019 | 5 | 28 | 4 | 27 | 9.0% | 1.25 [0.30, 5.26] | 2019 |
| Ren 2020 | 2 | 32 | 3 | 32 | 5.4% | 0.64 [0.10, 4.14] | 2020 |
| Li 2022 | 15 | 106 | 27 | 106 | 37.9% | 0.48 [0.24, 0.97] | 2022 |
| **Total (95% CI)** | | **457** | | **439** | **100.0%** | **0.59 [0.38, 0.91]** | |
| Total events | 46 | | 68 | | | | |

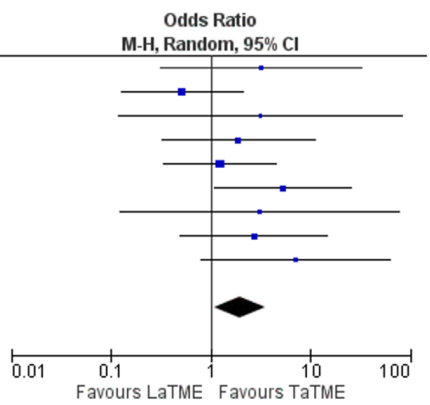
Heterogeneity: Tau² = 0.00; Chi² = 8.47, df = 9 (*P* = 0.49); I² = 0%
Test for overall effect: Z = 2.41 (*P* = 0.02)




**D**

| Study or Subgroup | TaTME Events | TaTME Total | LaTME Events | LaTME Total | Weight | Odds Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| de'Angelis 2015 | 31 | 32 | 29 | 32 | 6.8% | 3.21 [0.32, 32.60] | 2015 |
| Kanso 2015 | 43 | 51 | 31 | 34 | 18.4% | 0.52 [0.13, 2.12] | 2015 |
| Marks 2016 | 17 | 17 | 16 | 17 | 3.4% | 3.18 [0.12, 83.76] | 2016 |
| Lelong 2017 | 32 | 34 | 34 | 38 | 11.7% | 1.88 [0.32, 10.99] | 2017 |
| Mege 2018 | 29 | 34 | 28 | 34 | 21.7% | 1.24 [0.34, 4.54] | 2018 |
| Denost 2018 | 48 | 50 | 41 | 50 | 14.4% | 5.27 [1.08, 25.78] | 2018 |
| Rubinkiewicz 2018 | 35 | 35 | 34 | 35 | 3.5% | 3.09 [0.12, 78.41] | 2018 |
| Roodbeen 2019 | 39 | 41 | 36 | 41 | 12.6% | 2.71 [0.49, 14.84] | 2019 |
| Ren 2020 | 31 | 32 | 26 | 32 | 7.6% | 7.15 [0.81, 63.30] | 2020 |
| **Total (95% CI)** | | **326** | | **313** | **100.0%** | **1.96 [1.07, 3.58]** | |
| Total events | 305 | | 275 | | | | |

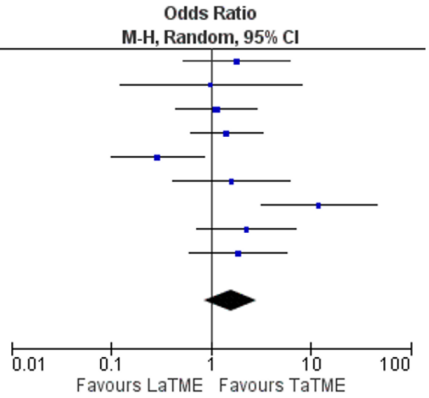
Heterogeneity: Tau² = 0.00; Chi² = 7.24, df = 8 (*P* = 0.51); I² = 0%
Test for overall effect: Z = 2.19 (*P* = 0.03)



**E**

| Study or Subgroup | TaTME Events | TaTME Total | LaTME Events | LaTME Total | Weight | Odds Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| de'Angelis 2015 | 27 | 32 | 24 | 32 | 10.8% | 1.80 [0.52, 6.25] | 2015 |
| Marks 2016 | 15 | 17 | 15 | 17 | 6.0% | 1.00 [0.12, 8.06] | 2016 |
| Lelong 2017 | 19 | 34 | 20 | 38 | 13.4% | 1.14 [0.45, 2.89] | 2017 |
| Denost 2018 | 35 | 50 | 31 | 50 | 14.3% | 1.43 [0.62, 3.29] | 2018 |
| Mege 2018 | 18 | 34 | 27 | 34 | 12.2% | 0.29 [0.10, 0.85] | 2018 |
| Rubinkiewicz 2018 | 31 | 35 | 29 | 35 | 9.9% | 1.60 [0.41, 6.26] | 2018 |
| Roodbeen 2019 | 38 | 41 | 21 | 41 | 10.2% | 12.06 [3.21, 45.40] | 2019 |
| Ren 2020 | 26 | 32 | 21 | 32 | 11.5% | 2.27 [0.72, 7.16] | 2020 |
| Li 2022 | 101 | 106 | 97 | 106 | 11.7% | 1.87 [0.61, 5.79] | 2022 |
| **Total (95% CI)** | | **381** | | **385** | **100.0%** | **1.57 [0.85, 2.90]** | |
| Total events | 310 | | 285 | | | | |

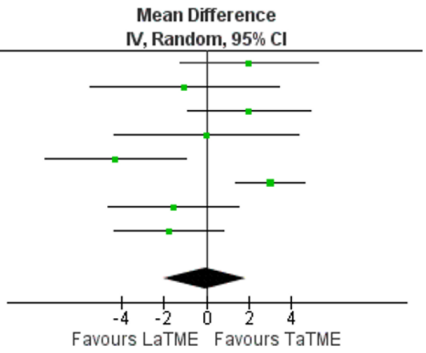
Heterogeneity: Tau² = 0.50; Chi² = 19.79, df = 8 (*P* = 0.01); I² = 60%
Test for overall effect: Z = 1.44 (*P* = 0.15)




**F**

| Study or Subgroup | TaTME Mean | TaTME SD | TaTME Total | LaTME Mean | LaTME SD | LaTME Total | Weight | Mean Difference IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| Kanso 2015 | 15 | 8 | 51 | 13 | 7 | 34 | 12.3% | 2.00 [-1.22, 5.22] | 2015 |
| de'Angelis 2015 | 17.6 | 7.14 | 32 | 18.63 | 10.7 | 32 | 9.4% | -1.03 [-5.49, 3.43] | 2015 |
| Lelong 2017 | 14 | 7 | 34 | 12 | 5.25 | 38 | 13.2% | 2.00 [-0.88, 4.88] | 2017 |
| Mege 2018 | 14 | 10 | 34 | 14 | 8 | 34 | 9.7% | 0.00 [-4.30, 4.30] | 2018 |
| Denost 2018 | 16.5 | 8 | 50 | 20.75 | 8.9 | 50 | 12.1% | -4.25 [-7.57, -0.93] | 2018 |
| Roodbeen 2019 | 18.75 | 3.75 | 41 | 15.75 | 3.76 | 41 | 16.5% | 3.00 [1.37, 4.63] | 2019 |
| Ren 2020 | 19.5 | 6.54 | 32 | 21.06 | 5.94 | 32 | 12.7% | -1.56 [-4.62, 1.50] | 2020 |
| Li 2022 | 13.75 | 7.8 | 106 | 15.5 | 10.9 | 106 | 14.1% | -1.75 [-4.30, 0.80] | 2022 |
| **Total (95% CI)** | | | **380** | | | **367** | **100.0%** | **-0.05 [-1.98, 1.89]** | |

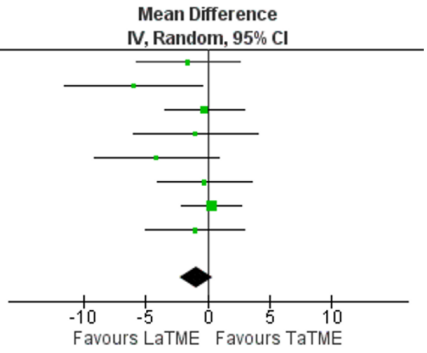
Heterogeneity: Tau² = 5.22; Chi² = 23.96, df = 7 (*P* = 0.001); I² = 71%
Test for overall effect: Z = 0.05 (*P* = 0.96)




**G**

| Study or Subgroup | TaTME Mean | TaTME SD | TaTME Total | LaTME Mean | LaTME SD | LaTME Total | Weight | Mean Difference IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| de'Angelis 2015 | 21.32 | 8.59 | 32 | 22.92 | 8.44 | 32 | 10.1% | -1.60 [-5.77, 2.57] | 2015 |
| Kanso 2015 | 12 | 9 | 51 | 18 | 15 | 34 | 5.6% | -6.00 [-11.61, -0.39] | 2015 |
| Denost 2018 | 12.5 | 8 | 50 | 12.75 | 8.38 | 50 | 17.0% | -0.25 [-3.46, 2.96] | 2018 |
| Mege 2018 | 13 | 9 | 34 | 14 | 12 | 34 | 6.9% | -1.00 [-6.04, 4.04] | 2018 |
| Rubinkiewicz 2018 | 15.7 | 9.2 | 35 | 19.8 | 12.2 | 35 | 6.8% | -4.10 [-9.16, 0.96] | 2018 |
| Roodbeen 2019 | 22.5 | 8.66 | 41 | 22.77 | 9.1 | 41 | 11.9% | -0.27 [-4.12, 3.58] | 2019 |
| Ren 2020 | 17.7 | 3.4 | 32 | 17.4 | 6 | 32 | 30.7% | 0.30 [-2.09, 2.69] | 2020 |
| Li 2022 | 12 | 9 | 106 | 13 | 19 | 106 | 11.0% | -1.00 [-5.00, 3.00] | 2022 |
| **Total (95% CI)** | | | **381** | | | **364** | **100.0%** | **-0.94 [-2.26, 0.39]** | |

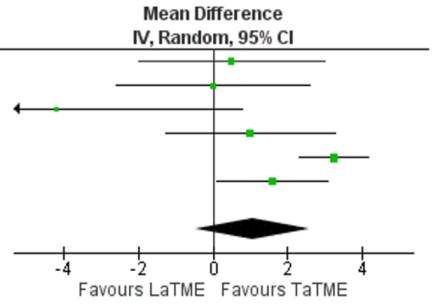
Heterogeneity: Tau² = 0.00; Chi² = 6.04, df = 7 (*P* = 0.53); I² = 0%
Test for overall effect: Z = 1.39 (*P* = 0.17)




**H**

| Study or Subgroup | TaTME Mean | TaTME SD | TaTME Total | LaTME Mean | LaTME SD | LaTME Total | Weight | Mean Difference IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| de'Angelis 2015 | 9.68 | 4.57 | 32 | 9.19 | 5.55 | 32 | 15.6% | 0.49 [-2.00, 2.98] | 2015 |
| Kanso 2015 | 7 | 6 | 51 | 7 | 6 | 34 | 15.1% | 0.00 [-2.60, 2.60] | 2015 |
| Rubinkiewicz 2018 | 9.9 | 7.8 | 35 | 14.1 | 12.9 | 35 | 7.0% | -4.20 [-9.19, 0.79] | 2018 |
| Denost 2018 | 8.5 | 5.8 | 50 | 7.5 | 5.8 | 50 | 16.8% | 1.00 [-1.27, 3.27] | 2018 |
| Roodbeen 2019 | 9 | 2.29 | 41 | 5.75 | 2.02 | 41 | 24.2% | 3.25 [2.32, 4.18] | 2019 |
| Ren 2020 | 6.81 | 2.99 | 32 | 5.22 | 3.05 | 32 | 21.3% | 1.59 [0.11, 3.07] | 2020 |
| **Total (95% CI)** | | | **241** | | | **224** | **100.0%** | **1.08 [-0.46, 2.61]** | |

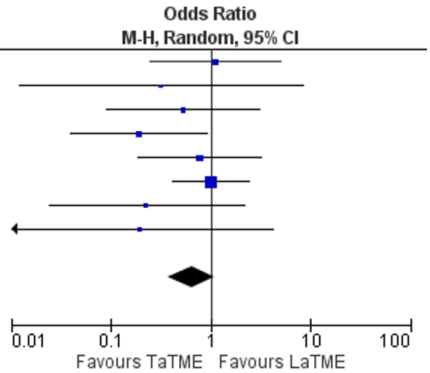
Heterogeneity: Tau² = 2.31; Chi² = 17.38, df = 5 (*P* = 0.004); I² = 71%
Test for overall effect: Z = 1.37 (*P* = 0.17)

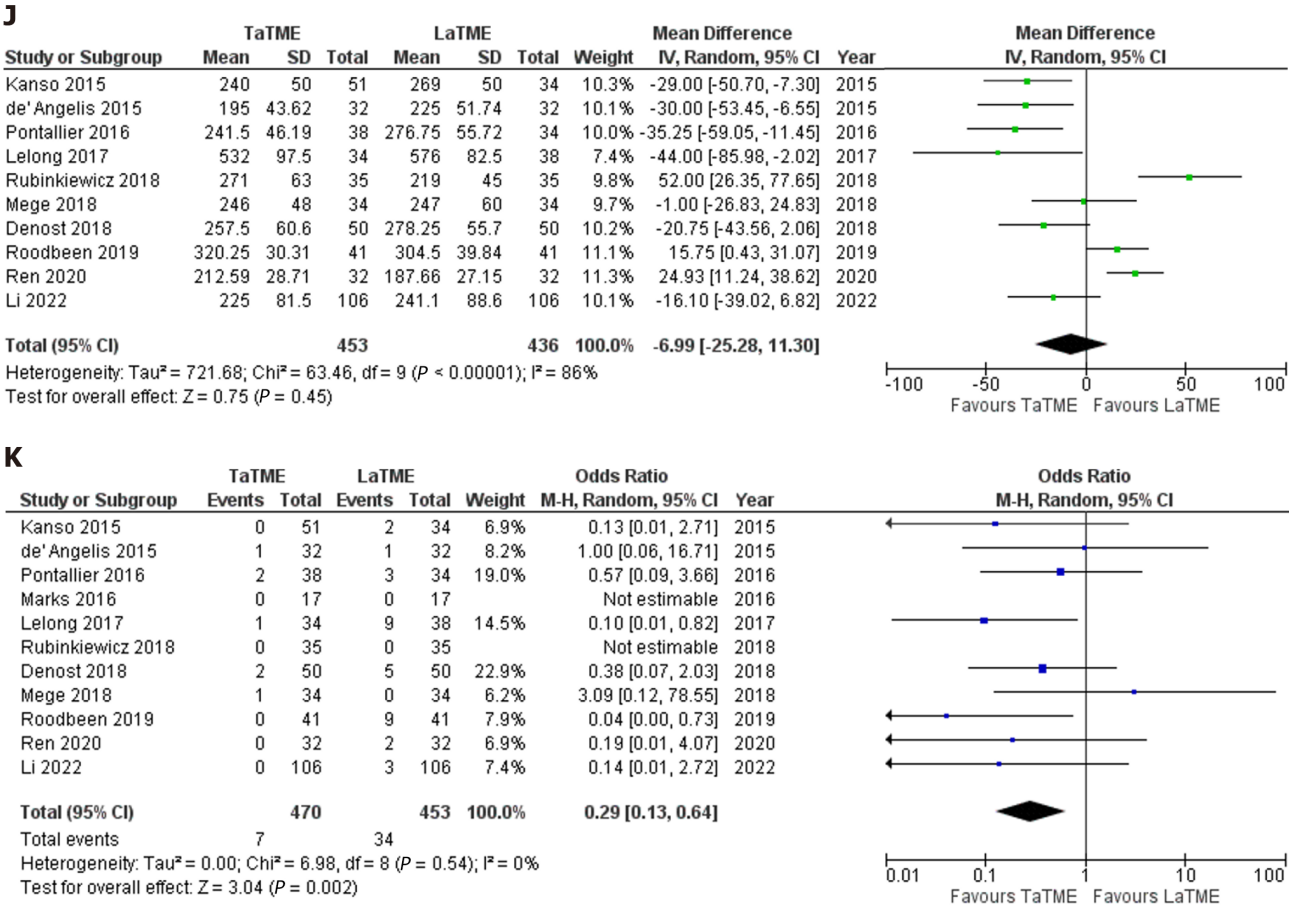



**I**

| Study or Subgroup | TaTME Events | TaTME Total | LaTME Events | LaTME Total | Weight | Odds Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Kanso 2015 | 5 | 51 | 3 | 34 | 13.1% | 1.12 [0.25, 5.04] | 2015 |
| Marks 2016 | 0 | 17 | 1 | 17 | 2.8% | 0.31 [0.01, 8.27] | 2016 |
| Lelong 2017 | 2 | 34 | 4 | 38 | 9.5% | 0.53 [0.09, 3.10] | 2017 |
| Denost 2018 | 2 | 50 | 9 | 50 | 11.7% | 0.19 [0.04, 0.93] | 2018 |
| Mege 2018 | 4 | 34 | 5 | 34 | 14.8% | 0.77 [0.19, 3.17] | 2018 |
| Roodbeen 2019 | 19 | 41 | 19 | 41 | 39.2% | 1.00 [0.42, 2.38] | 2019 |
| Ren 2020 | 1 | 32 | 4 | 32 | 5.8% | 0.23 [0.02, 2.14] | 2020 |
| Li 2022 | 0 | 106 | 2 | 106 | 3.2% | 0.20 [0.01, 4.14] | 2022 |
| **Total (95% CI)** | | **365** | | **352** | **100.0%** | **0.64 [0.37, 1.10]** | |
| Total events | 33 | | 47 | | | | |

Heterogeneity: Tau² = 0.00; Chi² = 5.56, df = 7 (*P* = 0.59); I² = 0%
Test for overall effect: Z = 1.62 (*P* = 0.11)






**DOI:** 10.4240/wjgs.v14.i12.1397 

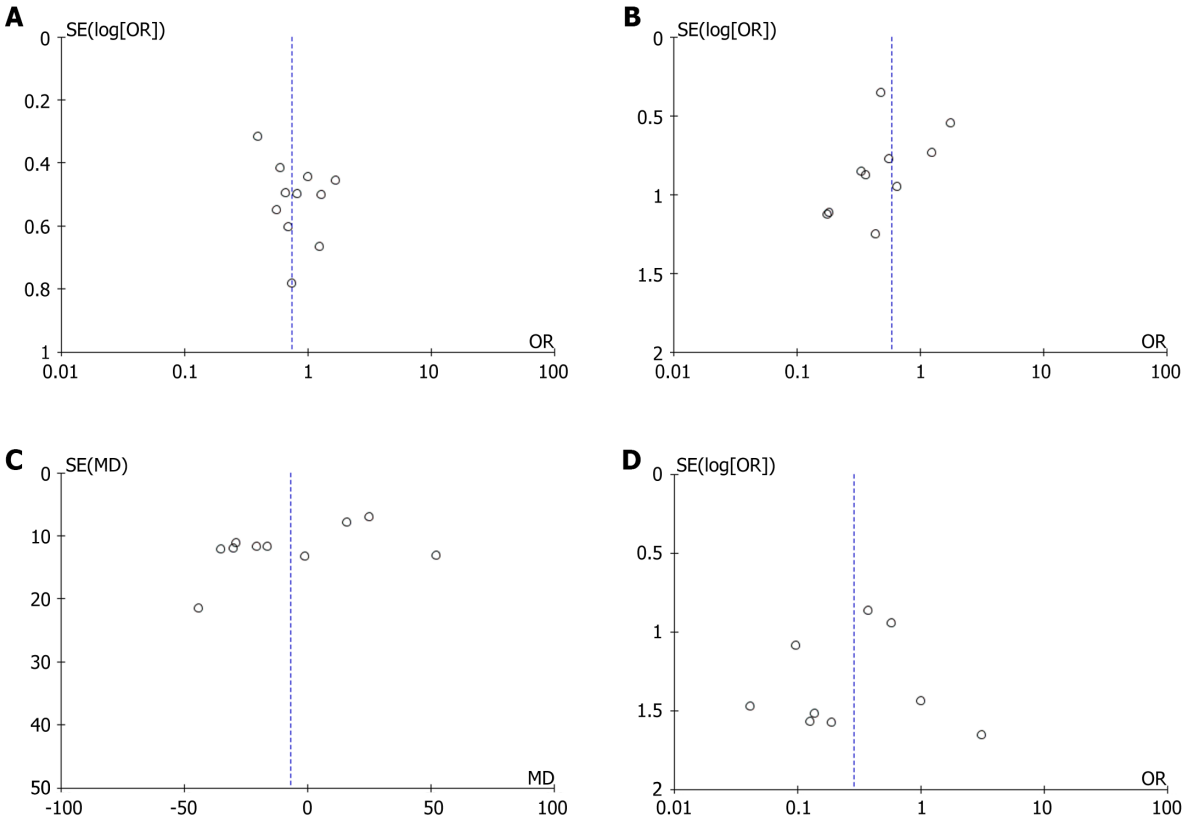
**Figure 3 Forest plots of comparison.** A: Intraoperative complications; B: Postoperative complications; C: Anastomotic leak; D: R0 resection; E: Completeness of mesorectal excision; F: Number of harvested lymph nodes; G: Distal resection margin; H: Circumferential resection margin; I: Positive circumferential resection margin; J: Procedure time; K: Conversion to an open procedure. The solid squares denote the odds ratios or mean difference. The horizontal lines represent the 95% confidence intervals, and the diamond denotes the pooled effect size. M-H: Mantel Haenszel test.

the authors found a significant association between CRM involvement and local recurrence ($P$ = 0.011), the 5-year local recurrence rate was similar between two groups (3% *vs* 5%, $P$ = 0.30). Moreover, the authors reported similar 5-year disease-free survival between two groups (72% *vs* 74%, $P$ = 0.351). The rate of local recurrence in the aforementioned RCT is comparable with the recurrence rate of 4% reported in a review by Deijen *et al*[26]. Undoubtedly, futures high quality randomized studies with adequate follow-up periods are required to investigate long term oncological outcomes of transanal and laparoscopic approaches to TME.

This study has a number of limitations. Only two of the considered studies were RCTs. Most of the included studies were observational studies with their inherited selection bias. Some of the included studies had small sample sizes which might have introduced Type 2 error to our findings. We were unable to conduct independent analyses on length of hospital stay, functional outcomes or long term oncological outcomes as the data provided by the included studies on such outcomes was inadequate. Finally, there was moderate risk of bias in 3 of our included studies.

## CONCLUSION

Our meta-analysis demonstrated that for low rectal tumours, TaTME is associated with better clinical and short term oncological outcomes compared to LaTME. More randomised controlled trials with adequate power and high quality are required to not only confirm these findings, but also to evaluate long term oncological and functional outcomes.




**DOI:** 10.4240/wjgs.v14.i12.1397 

**Figure 4 Funnel plots of comparison.** A: Postoperative complications; B: Anastomotic leak; C: Procedure time; D: Conversion to open procedure.

## ARTICLE HIGHLIGHTS

### *Research background*

Achieving a clear resection margins for low rectal cancer is technically challenging. Transanal TME (TaTME) has been introduced in order to address the chalenges associated with the open and laparoscopic TME (LaTME) in resecting low rectal tumours.

### *Research motivation*

Previous meta-analyses have included mixed patients with mid and low rectal tumours when comparing TaTME and LaTME which has made the interpretation of the real differences between two approaches in treating low rectal cancer difficult.

### *Research objectives*

To investigate the outcomes of transanal TaTME and LaTME in patients with low rectal cancer.

### *Research methods*

A comprehensive systematic review of comparative studies were conducted according to the standards of Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Intraoperative and postoperative complications, anastomotic leak, completeness of mesorectal excision, R0 resection, distal (DRM) and circumferential resection margin (CRM), number of harvested lymph nodes, and procedure time were the evaluated outcome parameters.

### *Research results*

We identified twelve comparative studies enrolling a total of 969 patients comparing the outcomes of TaTME ($n$ = 969) and LaTME ($n$ = 476) in patients with low rectal cancer. The meta-analysis demonstrated that TaTME was associated with significantly lower rate of postoperative complications (OR: 0.74, $P$ = 0.04), anastomotic leak (OR: 0.59, $P$ = 0.02), and conversion to an open procedure (OR: 0.29, $P$ = 0.002) compared with LaTME. Moreover, it was associated with significantly higher rate of R0 resection (OR: 1.96, $P$ = 0.03). However, there was no significant difference in intraoperative complications (OR: 1.87; $P$ = 0.23), completeness of mesoractal excision (OR: 1.57, $P$ = 0.15), harvested lymph nodes (MD: -0.05, $P$ = 0.96), DRM (MD: -0.94; $P$ = 0.17), CRM (MD: 1.08, $P$ = 0.17), positive CRM (OR:

0.64, $P$ = 0.11) and procedure time (MD: -6.99 minutes, $P$ = 0.45) between TaTME and LaTME.

### Research conclusions

Our findings indicated that for low rectal tumours, TaTME is associated with better clinical and short term oncological outcomes compared to LaTME.

### Research perspectives

The available evidence does not allow evaluation of long term oncological and functional outcomes. More randomized controlled trials are required to confirm the findings of this meta-analysis regarding clinical and short term oncological outcomes and to evaluate long term oncological and functional outcomes.

## FOOTNOTES

**Author contributions:** Shahi H designed the research study; Patel I, Bhattacharya P, and Fazili N collected the data for the meta-analysis; Hajibandeh S and Hajibandeh S analysed and interpreted the data, did the statistical analysis, and wrote the article; all authors critically revised the article and provided final approval for the article.

**Conflict-of-interest statement:** There are no conflicts of interest to report.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.



**Country/Territory of origin:** United Kingdom

**ORCID number:** Pratik Bhattacharya 0000-0001-9528-295X; Ishaan Patel 0000-0002-4017-1715; Noureen Fazili 0000-0002-7561-8660; Shahab Hajibandeh 0000-0002-3294-4335; Shahin Hajibandeh 0000-0001-6159-1068.

**S-Editor:** Chen YL
**L-Editor:** A
**P-Editor:** Chen YX

## REFERENCES

1 **Meyer JE**, Narang T, Schnoll-Sussman FH, Pochapin MB, Christos PJ, Sherr DL. Increasing incidence of rectal cancer in patients aged younger than 40 years: an analysis of the surveillance, epidemiology, and end results database. *Cancer* 2010; **116**: 4354-4359 [PMID: 20734460 DOI: 10.1002/cncr.25432]
2 **Heald RJ**, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. *Arch Surg* 1998; **133**: 894-899 [PMID: 9711965 DOI: 10.1001/archsurg.133.8.894]
3 **Quirke P**, Steele R, Monson J, Grieve R, Khanna S, Couture J, O'Callaghan C, Myint AS, Bessell E, Thompson LC, Parmar M, Stephens RJ, Sebag-Montefiore D; MRC CR07/NCIC-CTG CO16 Trial Investigators; NCRI Colorectal Cancer Study Group. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet* 2009; **373**: 821-828 [PMID: 19269520 DOI: 10.1016/S0140-6736(09)60485-2]
4 **Martling A**, Singnomklao T, Holm T, Rutqvist LE, Cedermark B. Prognostic significance of both surgical and pathological assessment of curative resection for rectal cancer. *Br J Surg* 2004; **91**: 1040-1045 [PMID: 15286968 DOI: 10.1002/bjs.4557]
5 **Cecil TD**, Taffinder N, Gudgeon AM. A personal view on laparoscopic rectal cancer surgery. *Colorectal Dis* 2006; **8** Suppl 3: 30-32 [PMID: 16813590 DOI: 10.1111/j.1463-1318.2006.01068.x]
6 **Nagtegaal ID**, van de Velde CJ, Marijnen CA, van Krieken JH, Quirke P; Dutch Colorectal Cancer Group; Pathology Review Committee. Low rectal cancer: a call for a change of approach in abdominoperineal resection. *J Clin Oncol* 2005; **23**: 9257-9264 [PMID: 16361623 DOI: 10.1200/JCO.2005.02.9231]
7 **Bonjer HJ**, Deijen CL, Abis GA. A randomized trial of laparoscopic vs open surgery for rectal cancer. *N Engl J Med* 2005; **372**: 1324-1332
8 **Hajibandeh S**, Hajibandeh S, Eltair M, George AT, Thumbe V, Torrance AW, Budhoo M, Joy H, Peravali R. Meta-analysis of transanal total mesorectal excision versus laparoscopic total mesorectal excision in management of rectal cancer. *Int J Colorectal Dis* 2020; **35**: 575-593 [PMID: 32124047 DOI: 10.1007/s00384-020-03545-7]
9 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D.

The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700 [PMID: 19622552 DOI: 10.1136/bmj.b2700]

10 **Wells GA**, Shea B, O'Connell D. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. November 28, 2019. [cited 3 November 2022]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [DOI: 10.7717/peerj.14320/supp-5]

11 **Cumpston M**, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev* 2019; **10**: ED000142 [PMID: 31643080 DOI: 10.1002/14651858.ED000142]

12 **Hozo SP**, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005; **5**: 13 [PMID: 15840177 DOI: 10.1186/1471-2288-5-13]

13 **de'Angelis N**, Portigliotti L, Azoulay D, Brunetti F. Transanal total mesorectal excision for rectal cancer: a single center experience and systematic review of the literature. *Langenbecks Arch Surg* 2015; **400**: 945-959 [PMID: 26497544 DOI: 10.1007/s00423-015-1350-7]

14 **Kanso F**, Maggiori L, Debove C, Chau A, Ferron M, Panis Y. Perineal or Abdominal Approach First During Intersphincteric Resection for Low Rectal Cancer: Which Is the Best Strategy? *Dis Colon Rectum* 2015; **58**: 637-644 [PMID: 26200677 DOI: 10.1097/DCR.0000000000000396]

15 **Pontallier A**, Denost Q, Van Geluwe B, Adam JP, Celerier B, Rullier E. Potential sexual function improvement by using transanal mesorectal approach for laparoscopic low rectal cancer excision. *Surg Endosc* 2016; **30**: 4924-4933 [PMID: 26944728 DOI: 10.1007/s00464-016-4833-x]

16 **Marks JH**, Montenegro GA, Salem JF, Shields MV, Marks GJ. Transanal TATA/TME: a case-matched study of taTME versus laparoscopic TME surgery for rectal cancer. *Tech Coloproctol* 2016; **20**: 467-473 [PMID: 27178183 DOI: 10.1007/s10151-016-1482-y]

17 **Lelong B**, Meillat H, Zemmour C, Poizat F, Ewald J, Mege D, Lelong JC, Delpero JR, de Chaisemartin C. Short- and Mid-Term Outcomes after Endoscopic Transanal or Laparoscopic Transabdominal Total Mesorectal Excision for Low Rectal Cancer: A Single Institutional Case-Control Study. *J Am Coll Surg* 2017; **224**: 917-925 [PMID: 28024946 DOI: 10.1016/j.jamcollsurg.2016.12.019]

18 **Denost Q**, Loughlin P, Chevalier R, Celerier B, Didailler R, Rullier E. Transanal versus abdominal low rectal dissection for rectal cancer: long-term results of the Bordeaux' randomized trial. *Surg Endosc* 2018; **32**: 1486-1494 [PMID: 29067578 DOI: 10.1007/s00464-017-5836-y]

19 **Mege D**, Hain E, Lakkis Z, Maggiori L, Prost À la Denise J, Panis Y. Is trans-anal total mesorectal excision really safe and better than laparoscopic total mesorectal excision with a perineal approach first in patients with low rectal cancer? *Colorectal Dis* 2018; **20**: O143-O151 [PMID: 29693307 DOI: 10.1111/codi.14238]

20 **Rubinkiewicz M**, Nowakowski M, Wierdak M, Mizera M, Dembiński M, Pisarska M, Major P, Małczak P, Budzyński A, Pędziwiatr M. Transanal total mesorectal excision for low rectal cancer: a case-matched study comparing TaTME versus standard laparoscopic TME. *Cancer Manag Res* 2018; **10**: 5239-5245 [PMID: 30464621 DOI: 10.2147/CMAR.S181214]

21 **Roodbeen SX**, Penna M, Mackenzie H, Kusters M, Slater A, Jones OM, Lindsey I, Guy RJ, Cunningham C, Hompes R. Transanal total mesorectal excision (TaTME) versus laparoscopic TME for MRI-defined low rectal cancer: a propensity score-matched analysis of oncological outcomes. *Surg Endosc* 2019; **33**: 2459-2467 [PMID: 30350103 DOI: 10.1007/s00464-018-6530-4]

22 **Rubinkiewicz M**, Zarzycki P, Witowski J, Pisarska M, Gajewska N, Torbicz G, Nowakowski M, Major P, Budzyński A, Pędziwiatr M. Functional outcomes after resections for low rectal tumors: comparison of Transanal with laparoscopic Total Mesorectal excision. *BMC Surg* 2019; **19**: 79 [PMID: 31277628 DOI: 10.1186/s12893-019-0550-4]

23 **Ren J**, Liu S, Luo H, Wang B, Wu F. Comparison of short-term efficacy of transanal total mesorectal excision and laparoscopic total mesorectal excision in low rectal cancer. *Asian J Surg* 2021; **44**: 181-185 [PMID: 32461015 DOI: 10.1016/j.asjsur.2020.05.007]

24 **Li Z**, Xiao J, Hou Y, Zhang X, Jie H, Liu H, Ruan L, Zeng Z, Kang L. Transanal versus Laparoscopic Total Mesorectal Excision in Male Patients with Low Tumor Location after Neoadjuvant Therapy: A Propensity Score-Matched Cohort Study. *Gastroenterol Res Pract* 2022; **2022**: 2387464 [PMID: 35265121 DOI: 10.1155/2022/2387464]

25 **Wasmuth HH**, Faerden AE, Myklebust TÅ, Pfeffer F, Norderval S, Riis R, Olsen OC, Lambrecht JR, Kørner H, Larsen SG; Norwegian TaTME Collaborative Group, on behalf of the Norwegian Colorectal Cancer Group, Forsmo HM, Baekkelund O, Lavik S, Knapp JC, Sjo O, Rashid G. Transanal total mesorectal excision for rectal cancer has been suspended in Norway. *Br J Surg* 2020; **107**: 121-130 [PMID: 31802481 DOI: 10.1002/bjs.11459]

26 **Deijen CL**, Tsai A, Koedam TW, Veltcamp Helbach M, Sietses C, Lacy AM, Bonjer HJ, Tuynman JB. Clinical outcomes and case volume effect of transanal total mesorectal excision for rectal cancer: a systematic review. *Tech Coloproctol* 2016; **20**: 811-824 [PMID: 27853973 DOI: 10.1007/s10151-016-1545-0]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 December 27; 14(12): 1411-1417

DOI: 10.4240/wjgs.v14.i12.1411

ISSN 1948-9366 (online)

CASE REPORT

# Secondary sclerosing cholangitis in a young COVID-19 patient resulting in death: A case report

Jakob Steiner, Ann-Katrin Kaufmann-Bühler, Michael Fuchsjäger, Peter Schemmer, Emina Talakić

**Specialty type:** Radiology, nuclear medicine and medical Imaging

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Barve P, United States; Saito H, Japan; Solanki SL, India

**Received:** June 13, 2022
**Peer-review started:** June 13, 2022
**First decision:** July 14, 2022
**Revised:** July 28, 2022
**Accepted:** October 4, 2022
**Article in press:** October 4, 2022
**Published online:** December 27, 2022

**Jakob Steiner, Ann-Katrin Kaufmann-Bühler, Michael Fuchsjäger, Emina Talakić,** Department of General Radiology, Medical University of Graz, Graz 8036, Austria

**Peter Schemmer,** Department of General Visceral and Transplant Surgery, Medical University of Graz, Graz 8036, Austria

**Corresponding author:** Emina Talakić, MD, Staff Physician, Department of General Radiology, Medical University of Graz, Auenbruggerplatz 9, Graz 8036, Austria.
emina.talakic@medunigraz.at

## Abstract

### *BACKGROUND*

With the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019 in Wuhan, China, liver injury in patients with coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 infection has been regularly reported in the literature. There are a growing number of publications describing the occurrence of secondary sclerosing cholangitis (SSC) after SARS-CoV-2 infection in various cases. We present a case of sudden onset SSC in a critically ill patient (SSC-CIP) following COVID-19 infection who was previously healthy.

### *CASE SUMMARY*

A 33-year old female patient was admitted to our University Hospital due to increasing shortness of breath. A prior rapid antigen test showed a positive result for SARS-CoV-2. The patient had no known preexisting conditions. With rapidly increasing severe hypoxemia she required endotracheal intubation and developed the need for veno-venous extracorporeal membrane oxygenation in a setting of acute respiratory distress syndrome. During the patient´s 154-d stay in the intensive care unit and other hospital wards she underwent hemodialysis and extended polypharmaceutical treatment. With increasing liver enzymes and the development of signs of cholangiopathy on magnetic resonance cholangiopancreatography (MRCP) as well as endoscopic retrograde cholangiopancreatography (ERCP), the clinical setting was suggestive of SSC. At an interdisciplinary meeting, the possibility of orthotopic liver transplantation and additional kidney transplantation was discussed due to the constant need for hemodialysis. Following a deterioration in her general health and impaired respiratory function with a reduced chance of successful surgery and rehabilitation, the plan for transplantation was discarded. The patient passed away due to multiorgan failure.

*CONCLUSION*
SSC-CIP seems to be a rare but serious complication in patients with SARS-CoV-2 infection, of which treating physicians should be aware. Imaging with MRCP and/or ERCP seems to be indicated and a valid method for early diagnosis. Further studies on the effects of early and late SSC in (post-) COVID-19 patients needs to be performed.

**Key Words:** Secondary sclerosing cholangitis; COVID-19; Liver failure; Critically ill patients; Magnetic resonance cholangiopancreatography; Endoscopic retrograde cholangiopancreatography; Case report



**Core Tip:** Secondary sclerosing cholangitis in critically ill patients is an important complication in patients requiring intensive care treatment. With the ongoing coronavirus disease 2019 pandemic we will see increasing complications regarding the liver and the biliary system. Our case report hopes to aid other surgeons, radiologists and intensive care physicians in their decision making.

**Citation:** Steiner J, Kaufmann-Bühler AK, Fuchsjäger M, Schemmer P, Talakić E. Secondary sclerosing cholangitis in a young COVID-19 patient resulting in death: A case report. *World J Gastrointest Surg* 2022; 14(12): 1411-1417
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i12/1411.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i12.1411

## INTRODUCTION

With the emergence of an unknown respiratory virus of the corona group in late 2019 in Wuhan, China, an undetected spread of the newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been observed, which was declared a pandemic by the WHO in March 2020.

Common signs of SARS-CoV-2 infection include flu-like symptoms, dyspnea, fatigue, anosmia, headache and fever, with potentially life-threatening acute respiratory distress syndrome (ARDS) developing in some cases, requiring intensive medical care. During this ongoing crisis, and due to the nature of a novel virus infection, the scientific community has been able to identify a wide range of different symptoms and features attributable to the later and rarer hyperinflammatory phase in some cases. In particular, the diffuse inflammatory phase appears to be a multiorgan problem that is not limited to the lungs or upper respiratory tract[1,2].

Liver injury in patients with SARS-CoV-2 infection has been regularly reported in the literature during the course of the ongoing coronavirus disease 2019 (COVID-19) pandemic. The occurrence of elevated and abnormal liver parameters has been demonstrated in 14% to 76% of patients. Recent case reports and series have investigated and discussed the probability of increased risk for permanent damage to the hepatobiliary system[1-4].

There are a growing number of publications in the literature describing the occurrence of secondary sclerosing cholangitis (SSC) after SARS-CoV-2 infection in various cases, particularly after severe COVID-19-associated ARDS with a reported incidence of up to 2.6% of intensive care unit (ICU) patients [5].

We report the sudden onset of SSC in a critically ill patient (SSC-CIP) following severe COVID-19 infection ultimately resulting in death.

## CASE PRESENTATION

### *Chief complaints*

A 33-year-old female patient was admitted to our University Hospital by emergency medical services (EMS) due to shortness of breath.

### *History of present illness*

According to her relatives, she had been feeling ill for a week, and her general health deteriorated rapidly and she developed a high fever. She had tested positive for the novel coronavirus (SARS-CoV-2) 7 d prior to admission.

### History of past illness

The patient had an elevated body mass index of 34 (1.68 m/95 kg), and was previously healthy with no preexisting conditions, particularly no known liver damage or respiratory problems.

### Personal and family history

No relevant personal or family history was recorded.

### Physical examination

On arrival of the EMS, respiratory function was already compromised by severe hypoxemia requiring endotracheal intubation and mechanical ventilation onsite, which did not improve on admission with high ventilation pressure and poor $O_2$ saturation. Veno-venous extracorporeal membrane oxygenation (vvECMO) was administered, which provided acceptable oxygenation in the setting of severe acute respiratory distress syndrome (COVID-19-ARDS) with a persistent need of continuous catecholamines. During the patient´s 154-d stay in the ICU and other hospital wards, hemodialysis was initiated on day 4, ECMO was removed on day 14, and successful weaning was achieved on day 15 (Figure 1).

### Laboratory examinations

During the patient's treatment for severe COVID-19-associated ARDS in the ICU, impaired liver function with elevated liver and cholestasis parameters (bilirubin, gamma-glutamyl transferase (GGT) and alkaline phosphatase (AP)) was detected. Due to the polypharmaceutical therapy regime with additional ECMO treatment, toxic/ischemic liver injury was initially suspected.

Following ECMO removal and reduction of sedation (particularly ketamine), elevated liver enzymes persisted indicating SSC-CIP. Laboratory parameters continued to show slightly elevated bilirubin (1.4 mg/dL), GGT (1299 U/L), AP (1883 U/L), aspartate aminotransferase (AST) (162 U/L) and alanine aminotransferase (ALT) (119 U/L).

Treatment for SSC-CIP with Ursofalk® 1000 mg was initiated.

### Imaging examinations

A computed tomography of the abdomen on day 10 showed no signs of parenchymal damage or cholestasis (Figure 2A).

After prolonged treatment in the ICU, the patient underwent magnetic resonance cholangiopancreatography (MRCP) on day 47 after admission, which revealed no signs of liver injury or intrahepatic cholestasis but mild stenosis of the distal common bile duct (CBD) and suspected stricture of prepapillary CBD main.

Endoscopic retrograde cholangiopancreatography (ERCP) was performed on day 60 and showed rarefication of intrahepatic bile ducts, suggesting SSC-CIP (Figure 2C). An additional MRCP follow-up on day 105 after the initial admission confirmed SSC-CIP with worsening of multiple diffuse stricture of the CBD and entire intrahepatic biliary tree compared to the initial MRCP. Round T2-signal changes with restricted diffusion were identified, suggestive of additional cholangetic abscess formation (Figure 2B and D).

Magnetic resonance imaging (MRI) follow-up on day 129 depicted progressive encapsulated intrahepatic fluid accumulation with restricted diffusion and rim-contrast enhancement, associated with progressive intrahepatic abscess.

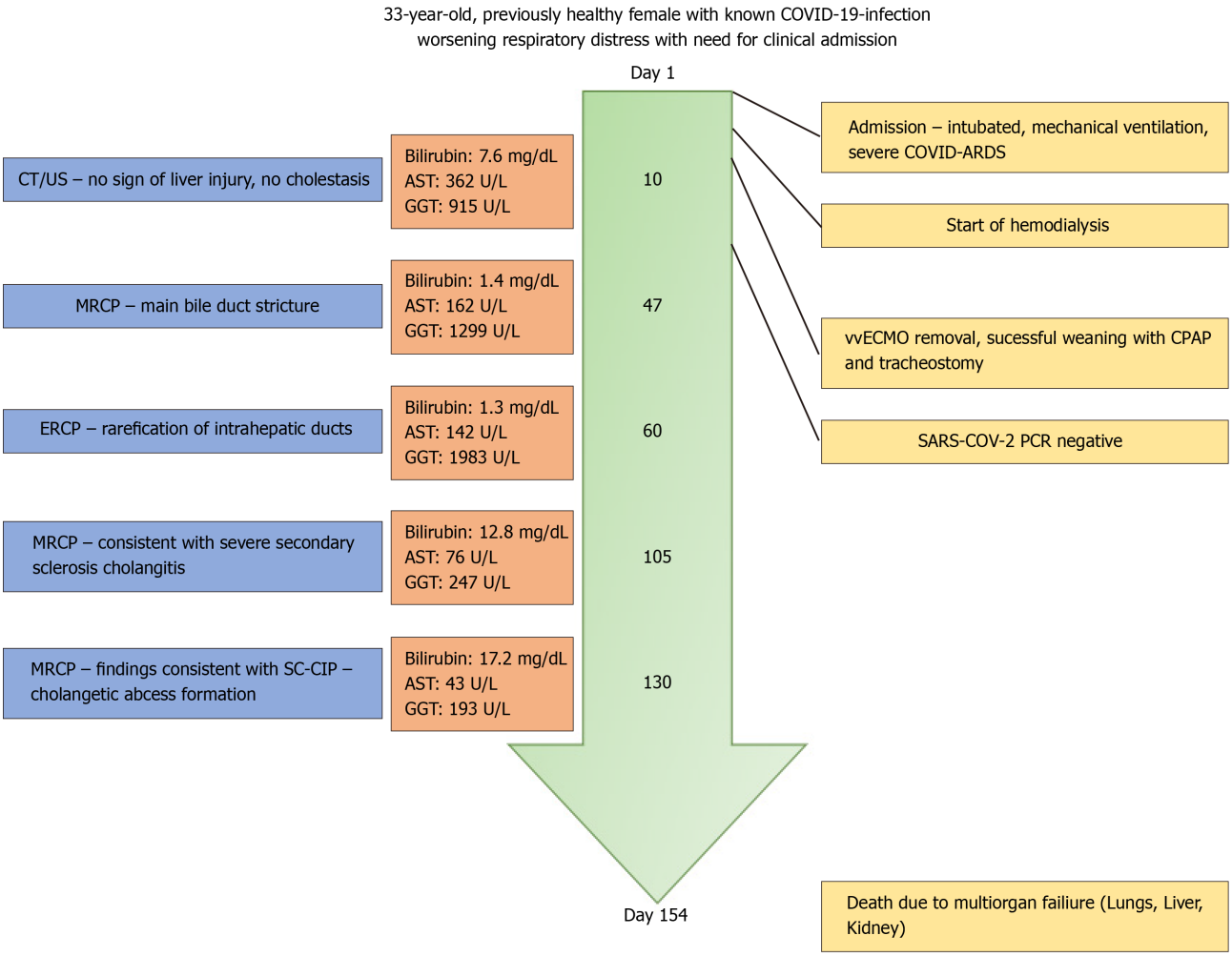
## MULTIDISCIPLINARY EXPERT CONSULTATION

In the following weeks, our patient suffered from persistent and undulating elevated inflammatory parameters [especially C-reactive protein (CRP), peak 217 mg/L] and overall worsening of her general condition. Due to renal failure, hemodialysis was performed three times a week. Liver parameters remained elevated (*e.g.*, bilirubin peak 17.29 mg/dL on day 139).

At an interdisciplinary meeting, the possibility of orthotopic liver transplantation and additional kidney transplantation was discussed due the constant need for hemodialysis. As a result of a deterioration in general health and impaired respiratory function with a reduced chance of successful surgery and rehabilitation, the plan for transplantation was discarded.

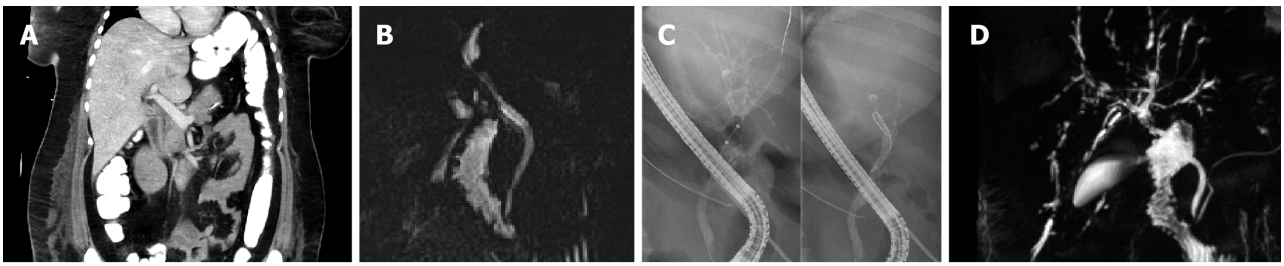
## FINAL DIAGNOSIS

Due to the rapid acceleration and worsening of SSC-CIP, we strongly suspected the presence of post-COVID-19 cholangiopathy with the development of SSC-CIP.




**DOI:** 10.4240/wjgs.v14.i12.1411 **Copyright** ©The Author(s) 2022.

**Figure 1 The chart shows the chronological timeline of patient treatment with adjacent changes in laboratory parameters and imaging as well as intensive care unit interventions.** MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.




**DOI:** 10.4240/wjgs.v14.i12.1411 **Copyright** ©The Author(s) 2022.

**Figure 2 Imaging throughout the hospital treatment.** A: The image shows early contrast enhanced computed tomography of the upper abdomen on day 10 after admission without significant cholangetic stasis or narrowing of the common bile duct (CBD); B: A prepapillary narrowing of the CBD can be identified with at that point suspected CBD stricture (day 47); C: The image shows a rarefication of the peripheral bile ducts indicating early secondary sclerosing cholangitis on day 60; D: The image shows magnetic resonance cholangiopancreatography at day 105 after admission with classical appearance of secondary sclerosing cholangitis.

## TREATMENT

Throughout the ICU period, she was treated according to guidelines, with additional remdesivir, a nucleotide analogue prodrug with broad-spectrum antiviral activity and Convalescent Plasma Transfusion as well as various treatments with additional antibiotics, including Noxafil®, Piperacillin/Tazobactam®, Tygacil® and Curam® due to superinfection.

## OUTCOME AND FOLLOW-UP

On day 154, our patient passed away due to organ failure involving the respiratory system, kidneys and liver. No autopsy was performed.

## DISCUSSION

SSC-CIP is a recently included form of cholestatic liver disease in a patient population undergoing prolonged intensive care for various reasons without known hepatic or biliary disease. It is usually the result of trauma, burn injuries, or major surgical procedures such as cardiothoracic surgery or transplantation procedures[6,7].

While up to 60% of SSC-CIP patients survive to ICU discharge, the need for later transplantation is high at up to 20%. One-year survival without transplantation has been reported to be 55%[8].

SSC-CIP is thought to be the result of direct damage to cholangiocytes, either by ischemia/hypoxia or by toxic bile with changes in bile composition or by infection. There is no single predisposing or causative factor for the development of SSC-CIP. Severe hypotension seems to directly cause ischemic bile duct damage and contribute to it by altering hepatobiliary transporters. Sepsis and microcirculatory disturbances have also been attributed to transporter alteration[9].

Liver damage resulting from SARS-CoV-2 infection has been described in the literature. Throughout the pandemic, many publications have described a close association between SARS-CoV-2 and elevated liver enzymes in the early stages of infection and liver parenchymal injury. Most authors theorize that increased angiotensin-converting enzyme 2 receptor expression in hepatocytes and even more in cholangiocytes leads to direct damage of cells by the virus, possibly causing cell destruction[2,10,11].

Additional changes in microvascular steatosis due to the thrombogenic characteristics of the novel coronavirus 19 appear to play a role in this parenchymal damage[10,11].

As described by Kaltschmidt *et al*[12], SARS-CoV-2 replicates in the liver parenchyma and is secreted into the bile ducts, which in combination with platelet activation and parenchymal injury appears to result in direct damage to the biliary system. The accompanying necrosis with the development of stenosis seem to directly promote the occurrence of sclerosing cholangitis[12].

SSC, as in our case, is usually diagnosed by imaging techniques such as ERCP and MRI. Distinguishing features include strictures and stenosis as well as newly developed dilations of intra- and extrahepatic bile ducts[13].

While ERCP offers the possibility of direct intervention such as stent placement, MRI, particularly MRCP, is a noninvasive modality for early diagnosis and follow-up, widely available in Western countries. With protocols starting at 15 min, it is also within a reasonable timeframe for monitoring intensive care patients.

Although our patient was ultimately not a candidate for transplantation, there are a growing number of case reports showing promising results with orthotopic liver transplantation for SSC-CIP following COVID-19[14,15].

As mentioned above SSC-CIP can occur due to various underlying conditions including pharmacological toxicity, prolonged intensive care treatment and interventions. In our case, the rapid onset of liver parameter changes with early elevated GGT/AST compared with relatively low bilirubin, followed by subsequent increasing bilirubin levels and textbook appearance on MRCP strongly suggest a close correlation between SSC-CIP and SARS-CoV-2 infection. In our case, this was most likely due to recently described post-COVID-19 cholangiopathy, in which early cholangiocytic injury leads to late stenosis and sclerosis, ultimately resulting in death. Differential diagnoses of the cause could include the mentioned prolonged intensive treatment, which seemed in our experience less likely.

Due to the lack of autopsy or biopsy, the major limitation in our case is the lack of confirmation of histopathological findings suggestive of SSC-CIP with liver parenchymal changes associated with viral damage, such as the presence of cytokeratin 7 metaplasia of periportal hepatocytes, compared with SCC with a possible other cause, most likely caused by drugs - due to prolonged mechanical ventilation and sedation.

## CONCLUSION

Despite its limitations, our case fits other cases and case series in the current literature and demonstrates the importance of early and regular evaluation of cholestatic parameters. SSC-CIP seems to be a rare but serious complication in patients with SARS-CoV-2 infection, of which treating physicians should be aware.

Imaging with MRCP and/or ERCP seems to be indicated and a valid method for early diagnosis. Although our case resulted in death as the patient was unfit for transplantation, liver transplantation seems to be a promising treatment in severe cases.

Given the still unknown long time span after complications in a post-pandemic medical world, the awareness of secondary liver injury and cholestatic damage should be monitored and further studies on the effects of early and late SSC in (post-) COVID-19 patients need to be performed.

## FOOTNOTES

**Author contributions:** Talakić E and Steiner J were responsible for the conceptualization, data acquisition and original manuscript drafting; Kaufmann-Bühler AK and Fuchsjäger M reviewed and edited the manuscript, and provided helpful discussions; Schemmer P was responsible for data acquisition and both reviewed and edited the manuscript; all authors have read and approved the final version of the manuscript.

**Informed consent statement:** No informed consent was required as the study was approved by the local IRB.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).



**Country/Territory of origin:** Austria

**ORCID number:** Jakob Steiner 0000-0001-6612-4418; Peter Schemmer 0000-0002-4192-6155; Emina Talakić 0000-0002-9948-138X.

**S-Editor:** Gong ZM
**L-Editor:** Webster JR
**P-Editor:** Gong ZM

## REFERENCES

1 **Zhong P**, Xu J, Yang D, Shen Y, Wang L, Feng Y, Du C, Song Y, Wu C, Hu X, Sun Y. COVID-19-associated gastrointestinal and liver injury: clinical features and potential mechanisms. *Signal Transduct Target Ther* 2020; **5**: 256 [PMID: 33139693 DOI: 10.1038/s41392-020-00373-7]
2 **Sharma A**, Jaiswal P, Kerakhan Y, Saravanan L, Murtaza Z, Zergham A, Honganur NS, Akbar A, Deol A, Francis B, Patel S, Mehta D, Jaiswal R, Singh J, Patel U, Malik P. Liver disease and outcomes among COVID-19 hospitalized patients - A systematic review and meta-analysis. *Ann Hepatol* 2021; **21**: 100273 [PMID: 33075578 DOI: 10.1016/j.aohep.2020.10.001]
3 **Fix OK**, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, Pratt DS, Russo MW, Schilsky ML, Verna EC, Loomba R, Cohen DE, Bezerra JA, Reddy KR, Chung RT. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. *Hepatology* 2020; **72**: 287-304 [PMID: 32298473 DOI: 10.1002/hep.31281]
4 **Li Y**, Xiao SY. Hepatic involvement in COVID-19 patients: Pathology, pathogenesis, and clinical implications. *J Med Virol* 2020; **92**: 1491-1494 [PMID: 32369204 DOI: 10.1002/jmv.25973]
5 **Meersseman P**, Blondeel J, De Vlieger G, van der Merwe S, Monbaliu D; Collaborators Leuven Liver Transplant program. Secondary sclerosing cholangitis: an emerging complication in critically ill COVID-19 patients. *Intensive Care Med* 2021; **47**: 1037-1040 [PMID: 34185115 DOI: 10.1007/s00134-021-06445-8]
6 **Gupta A**, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020; **26**: 1017-1032 [PMID: 32651579 DOI: 10.1038/s41591-020-0968-3]
7 **Esposito I**, Kubisova A, Stiehl A, Kulaksiz H, Schirmacher P. Secondary sclerosing cholangitis after intensive care unit treatment: clues to the histopathological differential diagnosis. *Virchows Arch* 2008; **453**: 339-345 [PMID: 18769938 DOI: 10.1007/s00428-008-0654-1]
8 **Kulaksiz H**, Heuberger D, Engler S, Stiehl A. Poor outcome in progressive sclerosing cholangitis after septic shock. *Endoscopy* 2008; **40**: 214-218 [PMID: 18264887 DOI: 10.1055/s-2007-967024]
9 **Leonhardt S**, Veltzke-Schlieker W, Adler A, Schott E, Eurich D, Faber W, Neuhaus P, Seehofer D. Secondary Sclerosing Cholangitis in Critically Ill Patients: Clinical Presentation, Cholangiographic Features, Natural History, and Outcome: A Series of 16 Cases. *Medicine (Baltimore)* 2015; **94**: e2188 [PMID: 26656347 DOI: 10.1097/MD.0000000000002188]
10 **Chan HL**, Kwan AC, To KF, Lai ST, Chan PK, Leung WK, Lee N, Wu A, Sung JJ. Clinical significance of hepatic derangement in severe acute respiratory syndrome. *World J Gastroenterol* 2005; **11**: 2148-2153 [PMID: 15810082 DOI:

10.3748/wjg.v11.i14.2148]
11 **Zhao B**, Ni C, Gao R, Wang Y, Yang L, Wei J, Lv T, Liang J, Zhang Q, Xu W, Xie Y, Wang X, Yuan Z, Zhang R, Lin X. Recapitulation of SARS-CoV-2 infection and cholangiocyte damage with human liver ductal organoids. *Protein Cell* 2020; **11**: 771-775 [PMID: 32303993 DOI: 10.1007/s13238-020-00718-6]
12 **Kaltschmidt B**, Fitzek ADE, Schaedler J, Förster C, Kaltschmidt C, Hansen T, Steinfurth F, Windmöller BA, Pilger C, Kong C, Singh K, Nierhaus A, Wichmann D, Sperhake J, Püschel K, Huser T, Krüger M, Robson SC, Wilkens L, Schulte Am Esch J. Hepatic Vasculopathy and Regenerative Responses of the Liver in Fatal Cases of COVID-19. *Clin Gastroenterol Hepatol* 2021; **19**: 1726-1729.e3 [PMID: 33516952 DOI: 10.1016/j.cgh.2021.01.044]
13 **Kim HJ**, Park MS, Son JW, Han K, Lee JH, Kim JK, Paik HC. Radiological patterns of secondary sclerosing cholangitis in patients after lung transplantation. *Abdom Radiol (NY)* 2019; **44**: 1361-1366 [PMID: 30377725 DOI: 10.1007/s00261-018-1819-2]
14 **Lee A**, Wein AN, Doyle MBM, Chapman WC. Liver transplantation for post-COVID-19 sclerosing cholangitis. *BMJ Case Rep* 2021; **14** [PMID: 34446515 DOI: 10.1136/bcr-2021-244168]
15 **Durazo FA**, Nicholas AA, Mahaffey JJ, Sova S, Evans JJ, Trivella JP, Loy V, Kim J, Zimmerman MA, Hong JC. Post-Covid-19 Cholangiopathy-A New Indication for Liver Transplantation: A Case Report. *Transplant Proc* 2021; **53**: 1132-1137 [PMID: 33846012 DOI: 10.1016/j.transproceed.2021.03.007]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 December 27; 14(12): 1418-1424

DOI: 10.4240/wjgs.v14.i12.1418

ISSN 1948-9366 (online)

CASE REPORT

# Rectal tubular adenoma with submucosal pseudoinvasion misdiagnosed as adenocarcinoma: A case report

Dan Chen, Ding-Fu Zhong, Hong-Ying Zhang, Ying Nie, Dong Liu

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** El-Azeem MAA, Egypt; Osera S, Japan; Yap RVC, Philippines

**Received:** July 29, 2022
**Peer-review started:** July 29, 2022
**First decision:** October 5, 2022
**Revised:** October 18, 2022
**Accepted:** November 20, 2022
**Article in press:** November 20, 2022
**Published online:** December 27, 2022

**Dan Chen, Ding-Fu Zhong, Hong-Ying Zhang, Ying Nie,** Department of Gastroenterology, Affiliated Jinhua Hospital of Wenzhou Medical University, Jinhua People's Hospital, Jinhua 321000, Zhejiang Province, China

**Dong Liu,** Department of Hepatobiliary and Pancreatic Gastroenterology, Affiliated Jinhua Hospital of Wenzhou Medical University, Jinhua People's Hospital, Jinhua 321000, Zhejiang Province, China

**Corresponding author:** Dong Liu, MD, Doctor, Department of Hepatobiliary and Pancreatic Gastroenterology, Affiliated Jinhua Hospital of Wenzhou Medical University, Jinhua People's Hospital, No. 267 Danxi East Road, Jindong District, Jinhua 321000, Zhejiang Province, China. li375dong@163.com

## Abstract

*BACKGROUND*

Differential diagnosis of colorectal intramucosal tumors from invasive adenocarcinoma is important in clinical practice due to the different risks of lymph node metastasis and different treatment options. The phenomenon of a colorectal adenoma with part of the gland entering the submucosa is known as pseudoinvasion of the adenoma, which is a major challenge for pathological diagnosis. It is essential to raise awareness of colorectal adenoma with submucosal pseudoinvasion clinically to avoid overtreatment.

*CASE SUMMARY*

We describe a case of rectal adenoma with submucosal pseudoinvasion in a 48-year-old man. The patient was admitted to Jinhua People's Hospital due to a change in stool habit for 5 d. We performed colonoscopy, and the results suggested a submucosal bulge approximately 1.0 cm × 1.0 cm in size in the rectum 8 cm from the anal verge, with red surface erosion. Ultrasound colonoscopy was also performed and a homogeneous hypoechoic mass about 0.52 cm × 0.72 cm in size was seen at the lesion, protruding into the lumen with clear borders and invading the submucosa. Endoscopic surgery was then performed and the pathological specimen showed a tubular adenoma with high-grade intraepithelial neoplasia (intramucosal carcinoma) involving the adenolymphatic complex. In addition, we performed a literature review of rectal tubular adenoma with submucosal pseudoinvasion to obtain a deeper understanding of this disease.

*CONCLUSION*

The aim of this study was to improve awareness of this lesion for clinicians and

pathologists to reduce misdiagnosis.

**Key Words:** Colorectal adenoma; Submucosal pseudoinvasion; Ultrasound endoscopy; Pathological diagnosis; Treatment; Case report



**Core Tip:** Colorectal adenoma with submucosal pseudoinvasion has only been studied in a small number of small cases in the current national and international literature. At present, endoscopists diagnose our patient's lesion by electronic staining endoscopy (NBI), magnification endoscopy and ultrasound enteroscopy. A more accurate diagnosis of the depth of infiltration was obtained by pathological support. And if the pathologist misjudges, it will lead to overtreatment in clinical practice.

**Citation:** Chen D, Zhong DF, Zhang HY, Nie Y, Liu D. Rectal tubular adenoma with submucosal pseudoinvasion misdiagnosed as adenocarcinoma: A case report. *World J Gastrointest Surg* 2022; 14(12): 1418-1424
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i12/1418.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i12.1418

## INTRODUCTION

Both neoplastic and non-neoplastic epithelium of the mucosa may enter the submucosa for some reason, a phenomenon known as pseudoinvasion or misplaced epithelium of the submucosa. When part of the gland of a colorectal adenoma mistakenly enters the submucosa, it is called pseudoinvasion of the adenoma[1]. The incidence of colorectal adenoma with submucosal pseudoinvasion is low, and those occurring in the rectal region are extremely rare, with few reports in the national and international literature. The definitive diagnosis relies mainly on pathological support[2]. If the pathologist misjudges, this will lead to overtreatment in clinical practice. Here we present a case of rectal adenoma with submucosa pseudoinvasionin order to benefit both patients andpractitioners.

## CASE PRESENTATION

### *Chief complaints*

A 48-year-old man was admitted to Jinhua People's Hospital on June 29, 2021 due to change in stool habit for 5 d.

### *History of present illness*

His symptoms started 5 d previously and were accompanied by a change in stool habit (yellow, thin, pasty stools 3-5 times a day, without mucus and blood). No significant change in body weight was noted.

### *History of past illness*

The patient had a history of surgery for hypofractionated adenocarcinoma of the stomach 6 mo ago. According to the World Health Organization (WHO) Classification of Digestive System Tumor, hypofractionated adenocarcinoma is defined as the cancer cells are short columnar or indefinite, arranged in small nests or strands, and basically without glandular tube structure.

### *Personal and family history*

The patient had no relevant personal and family history.

### *Physical examination*

On examination, his abdomen was soft, old surgical scars were visible in the upper abdomen, and no pressure pain, rebound pain, or masses were found.

### *Laboratory examinations*

Laboratory examinationsshowed that routine blood, urine, stool, liver and kidney function, carcinoembryonic antigen, alpha-fetoprotein and carbohydrate antigen 199 were all within the normal range.

### *Imaging examinations*

The patient was advised to undergo abdominal enhanced computed tomography (CT) and colonoscopy, and the results of colonoscopy on July 1, 2021 suggested a submucosal bulge approximately 1.0 cm × 1.0 cm in the rectum 8 cm from the anal verge, with red surface erosion (Figure 1A). Narrow band imaging (NBI) and magnification colonoscopy showed uneven caliber and distribution of blood vessels. Type2B was considered according to JNET staging (Figure 1B).

## MULTIDISCIPLINARY EXPERT CONSULTATION

Ultrasound colonoscopy was performed on July 1, 2021 and a homogeneous hypoechoic mass about 0.52 cm × 0.72 cm in size was seen at the lesion, protruding into the lumen with clear borders and invading the submucosa (Figure 1C). CT on June 30, 2021 (enhancement of two sites) showed a nodule in the posterior rectal wall (Figure 1D and E).

## FINAL DIAGNOSIS

Postoperative pathological results in our hospital [rectal endoscopic submucosal dissection (ESD) specimen] showed moderately differentiated adenocarcinoma with significant hyperplasia of lymphoid tissue, about 1.0 cm × 0.8 cm in size, infiltrated to the submucosa. No cancer thrombus was seen in the vasculature, and the surrounding cut edge was not involved approximately 200 μm from the basal cut edge. Immunohistochemical results were as follows: CD10 (-), CD56 (-), CDX2 (+), CgA (-), CK20 (+), CK7 (-), EGFR (1+), Ki67 (30%+), P53 (missense expression), and Syn (-).

In order to quickly improve the pathological understanding of early GI tumors in our hospital and better carry out our ESD surgery, the pathological specimen was sent to the Department of Pathology of the Second Affiliated Hospital of Zhejiang University School of Medicine and the results suggested (rectal ESD specimen) tubular adenoma with high-grade intraepithelial neoplasia (intramucosal carcinoma) involving the adenolymphatic complex. No clear vascular invasion was seen. The horizontal and vertical margins were negative (Figure 1F-I). Based on the above pathological findings, the patient was advised to undergo repeat colonoscopy. A follow-up colonoscopy on January 12, 2022 showed post-rectal scar formation and no local recurrence. A repeat pelvic MRI on April 12, 2022 suggested post-rectal changes and no lymphatic metastases were found.

## TREATMENT

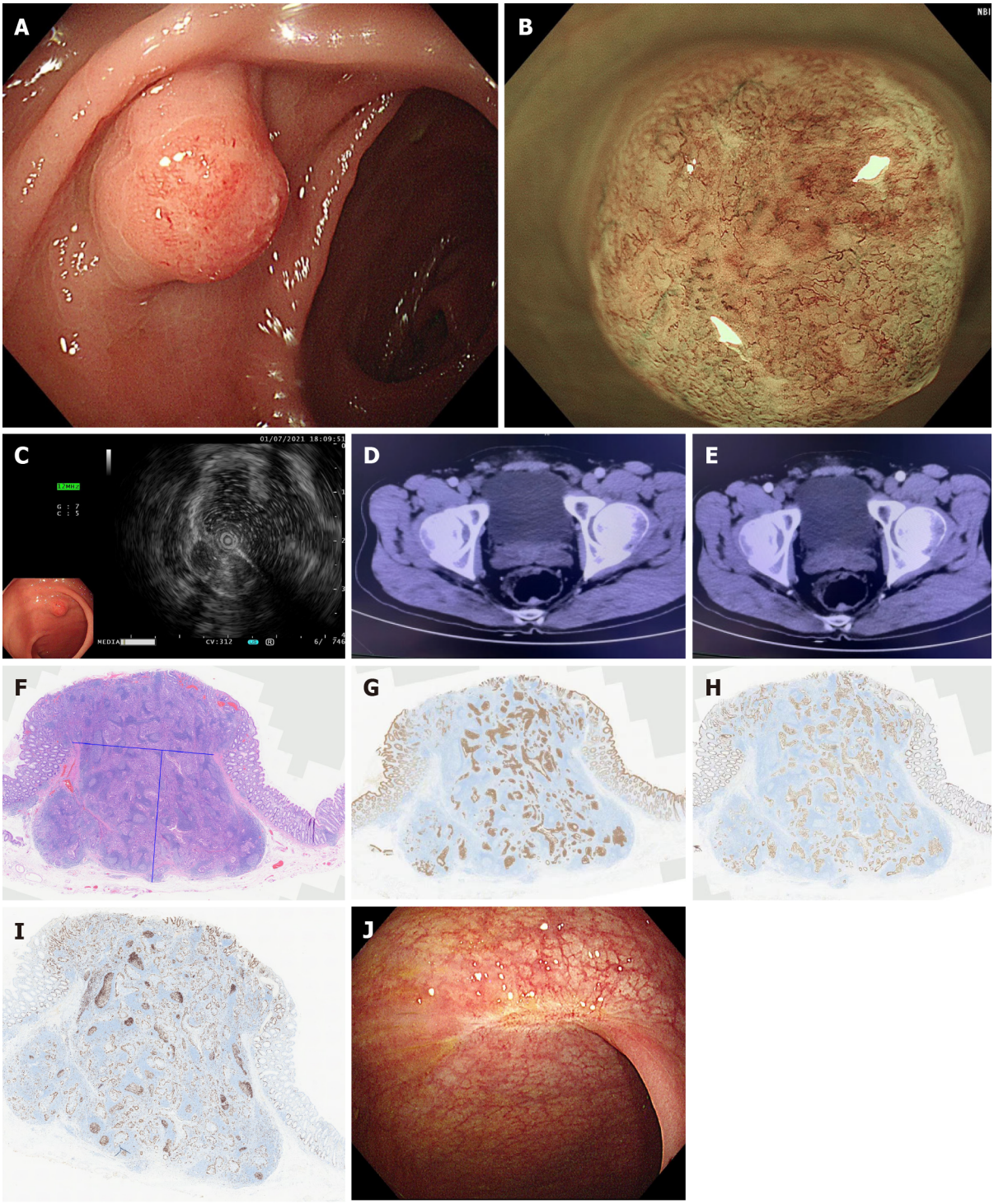
After full communication with the patient and obtaining his consent, ESD was performed on July 5, 2021.

## OUTCOME AND FOLLOW-UP

One year after ESD, colonoscopy showed a postoperative scar in the rectum without local recurrence (Figure 1J).

## DISCUSSION

Pseudoinvasion or misplaced epithelium of the submucosa was first described by Muto *et al*[3] in 1972 and its characteristic histological manifestation was defined as the mislocation of non-neoplastic or adenomatous epithelium into the submucosa for some reasons. Its predilection is in the sigmoid colon, accounting for about 85% of cases, followed by the descending colon, accounting for about 10%, and the rectum is relatively uncommon[2]. The average age of patients is 60 years for men and 56 years for women, similar to the average age of patients with common adenomatous polyps, with a male to female ratio of 3:1. Single lesion resection or local excision was effective, with no recurrence or metastasis at follow-up[3]. In 2006, a national colorectal cancer screening program was launched in the United Kingdom, and as the program progressed, an increasing number of difficult cases emerged, among which the differential diagnosis of epithelial malposition of colonic adenoma and adenocarcinoma was the most difficult. Therefore, an Expert Board was established to analyze and discuss the pathologies with diagnostic doubts. The percentage of misplaced epithelium diagnosed by the original pathologists increased from 30.6% to 80.3%, indicating that pathologists lack sufficient knowledge of this pathology and a number of misdiagnoses occurred[4]. This is undoubtedly a major challenge in clinical and




**DOI**: 10.4240/wjgs.v14.i12.1418 

**Figure 1 Clinical data of the patient with rectal tubular adenoma and submucosal pseudoinvasion.** A: Normal colonoscopy showing Is-type lesion; B: Narrow band imaging magnification colonoscopy; C: Ultrasound colonoscopy image; D: Posterior rectal wall in the venous phase showing the lesion; E: Posterior rectal wall in the arterial phase showing the lesion; F: The epithelial tumors seen microscopically are glandular ductal and sieve shaped with a high-grade heterogeneous morphology. The tumors are located in the lymphatic interstitium rich in lymphoid follicles. The lymphoid interstitium is located in the deep mucosal and submucosal layers with smooth and well-defined borders, H&E × 200 magnification; G: Immunohistochemistry CK20 (+), magnification × 200; H: Immunohistochemistry CDX2 (+), magnification × 200; I: Immunohistochemistry Ki67 (30%+), magnification × 200; J: Colonoscopy results after the operation.

pathological diagnosis.

Colorectal adenoma with submucosal pseudoinvasion has only been studied in a small number of cases in the current national and international literature. The morphological patterns were sorted and categorized in a limited number of cases, and two patterns of pseudoinvasion were summarized[5,6]. One type is lobulated, defined as a submucosal neoplastic gland forming a lobulated or nested mass. This type is more prevalent in the sigmoid colon with leptomeningeal lesions. The mechanism of onset may be increased luminal pressure due to intestinal contractility and repeated physical injury due to

traction, or tip torsion due to intestinal peristalsis, impaired blood flow, and subsequent entry of the gland into the submucosa through a relaxed mucosal muscle gap or weak area. Therefore, this type of pseudoinvasion may occur with ruptured glandular necrosis and hemorrhage, causing an inflammatory reaction and fibrosis[1,2,5,7]. The other type is lymphoglandular complex-like, in which the adenoma participates in the formation of a lymphoglandular complex into the submucosa, which can mimic invasive adenocarcinoma with lymphatic metastasis, with broad-based elevated lesions being the most common[5]. The available case studies show that almost all adenomas with pseudoinvasion have a maximum diameter greater than 10 mm, which means that there is a correlation between the size of the adenoma and the presence of submucosal pseudoinvasion. It can be inferred that even in the absence of excessive pressure or mechanical force, adenomas can easily enter the submucosa through the mucosal weak zone when they exceed a certain size[1,4,5,8]. When diagnosing colorectal adenoma with submucosal pseudoinvasion, it is important to be alert to the possibility that both patterns of pseudoinvasion components may have direct true infiltration in the submucosa, which should be treated as invasive adenocarcinoma, and therefore the pathology report needs to reflect the presence or absence of true infiltration[9]. In addition to the pathomorphological features of interest, in a small number of case studies of submucosal pseudoinvasion[6], immunohistochemical testing was performed and a Ki-67 positivity index of 25%-80% was found. P53 showed a wild-type pattern in positive cells within adenoma tissue and a missense mutation pattern in tumor tissue within a pooled lymph node that continued with a region of high-grade heterogeneous hyperplasia in one case.

The principles of the treatment options for colorectal adenoma with submucosal pseudoinvasion are consistent with those for colorectal intramucosal tumors, with endoscopic mucosal resection or ESD being the mainstay. Colorectal intramucosal tumors are defined as tumor infiltration confined to the mucosal layer (M-stage carcinoma). Those infiltrating into the submucosal layer without invading the intrinsic muscular layer are called submucosal carcinoma (SM-stage carcinoma)[10]. Those infiltrating into the upper 1/3, middle 1/3, and lower 1/3 of the submucosal layer are defined as SM1-stage carcinoma, SM2-stage carcinoma, and SM3-stage carcinoma, respectively[11]. The WHO classification of gastrointestinal tumors describes colorectal carcinoma as "epithelial malignant tumors originating from the colorectum which are diagnosed as cancer when they penetrate the mucosal muscle and infiltrate into the submucosa"[9]. Colorectal intramucosal tumors and invasive adenocarcinoma both have significantly different risks in terms of local recurrence and lymph node metastasis[12,13]. The absence of lymph node as well as vascular metastasis in intramucosal carcinoma is an absolute indication for endoscopic treatment. The percentage of lymph node metastasis from tumor infiltration to the superficial submucosa (SM1) is only 3.3%. Therefore, it can be a relative indication for endoscopic treatment. However, a rigorous pathological evaluation is required to determine whether lymphatic and vascular infiltration is present, and the need for additional surgical procedures will be determined on a situational basis. A previous report[14] showed no significant difference in the efficacy of endoscopic and surgical treatment for intramucosal and superficial submucosal carcinoma. For highly infiltrative submucosal lesions, additional surgery is required for submucosal infiltrations of 1000 μm or more[15].

Our patient's rectal lesion was diagnosed based on the morphology, vascular configuration, and surface structure in terms of pathological type by plain endoscopy, electronic staining endoscopy (NBI), and magnification endoscopy. A more direct diagnosis of the depth of infiltration was obtained vertically by ultrasound enteroscopy. Ultrasound can clearly display the structure of each layer of the colorectal wall and accurately determine the depth of lesion invasion and infiltration of surrounding organs[16-18]. Although crystal violet staining is suitable for the precise diagnosis of glandular duct openings in the pit pattern, it is currently not recommended *in vivo* due to its toxicity; therefore, it was not performed in this patient. After comprehensive evaluation, the preoperative lesion was considered to be superficial submucosal invasive carcinoma, and endoscopic ESD surgery is still indicated. Endoscopic surgery was performed after fully informing the patient of his condition and obtaining his consent. The postoperative pathological findings showed specific changes that led us to misdiagnose it as an invasive moderately differentiated adenocarcinoma. Fortunately, the pathological staging, basal cut margins, depth of submucosal invasion, and vascular invasion of this lesion did not suggest the need for additional surgery and did not result in overtreatment. The lesion was found to be a rare high-grade tubular adenoma of the rectum with pseudoinvasion of the submucosa only after late review of the pathology. To date, no effective clinical adjuvant examination has been availableto confirm whether the lesion is pseudoinvasion or not[2,4,14,19], and the definitive diagnosis still relies to a great extent on the pathologists' knowledge of its pathology.

## CONCLUSION

The aim of this study was to improve the awareness of clinicians and pathologists regarding this type of lesion, in order to reduce the probability of misdiagnosis as invasive adenocarcinoma and avoid overtreatment.

## ACKNOWLEDGEMENTS

The authors sincerely thank the participants for their help and willingness to participate in this study.

## FOOTNOTES

**Author contributions:** Chen D, Zhong DF, Zhang HY, Nie Y, and Liu D collected and analyzed the data; Chen D and Liu D drafted the manuscript; Liu D critically revised and gave final approval for publication of the paper.

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest related to this article.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).



**Country/Territory of origin:** China

**ORCID number:** Dan Chen 0000-0001-7910-9161; Dong Liu 0000-0002-7890-8209.

**S-Editor:** Gong ZM
**L-Editor:** A
**P-Editor:** Gong ZM

## REFERENCES

1 **Panarelli NC**, Somarathna T, Samowitz WS, Kornacki S, Sanders SA, Novelli MR, Shepherd NA, Yantiss RK. Diagnostic Challenges Caused by Endoscopic Biopsy of Colonic Polyps: A Systematic Evaluation of Epithelial Misplacement With Review of Problematic Polyps From the Bowel Cancer Screening Program, United Kingdom. *Am J Surg Pathol* 2016; **40**: 1075-1083 [PMID: 26975041 DOI: 10.1097/PAS.0000000000000641]

2 **Shepherd NA**, Griggs RK. Bowel cancer screening-generated diagnostic conundrum of the century: pseudoinvasion in sigmoid colonic polyps. *Mod Pathol* 2015; **28** Suppl 1: S88-S94 [PMID: 25560603 DOI: 10.1038/modpathol.2014.138]

3 **Muto T**, Bussey HJ, Morson BC. Pseudo-carcinomatous invasion in adenomatous polyps of the colon and rectum. *J Clin Pathol* 1973; **26**: 25-31 [PMID: 4540378 DOI: 10.1136/jcp.26.1.25]

4 **Griggs RK**, Novelli MR, Sanders DS, Warren BF, Williams GT, Quirke P, Shepherd NA. Challenging diagnostic issues in adenomatous polyps with epithelial misplacement in bowel cancer screening: 5 years' experience of the Bowel Cancer Screening Programme Expert Board. *Histopathology* 2017; **70**: 466-472 [PMID: 27676454 DOI: 10.1111/his.13092]

5 **Lee HE**, Wu TT, Chandan VS, Torbenson MS, Mounajjed T. Colonic Adenomatous Polyps Involving Submucosal Lymphoglandular Complexes: A Diagnostic Pitfall. *Am J Surg Pathol* 2018; **42**: 1083-1089 [PMID: 29738362 DOI: 10.1097/PAS.0000000000001081]

6 **Hou WH**, Song SJ, Hou WD, Shen MQ, Ma LJ, Niu JW, Zhang XL, Wang GW, Jin ML. [Pathological characteristics of colorectal adenoma with submucosal pseudoinvasion]. *Zhonghua Bing Li Xue Za Zhi* 2021; **50**: 32-37 [PMID: 33396984 DOI: 10.3760/cma.j.cn112151-20201021-00800]

7 **Yantiss RK**, Goldman H, Odze RD. Hyperplastic polyp with epithelial misplacement (inverted hyperplastic polyp): a clinicopathologic and immunohistochemical study of 19 cases. *Mod Pathol* 2001; **14**: 869-875 [PMID: 11557782 DOI: 10.1038/modpathol.3880403]

8 **Zhou S**, Ma Y, Chandrasoma P. Inverted lymphoglandular polyp in descending colon. *Case Rep Pathol* 2015; **2015**: 646270 [PMID: 25767731 DOI: 10.1155/2015/646270]

9 **WHO Classification of Tumours Editorial Board**. WHO classification of tumours. Digestive system tumours. 5th ed. Lyon: IARC Press 2019: 60-95

10 **Intestinal Study Group**, Chinese Society of Digestive Endoscopy; Jiang B, Liu SD. Chinese consensus: endoscopic diagnosis and treatment of early large bowel cancer. *Zhonghua Xiaohua Neijing Zazhi* 2008; **25**: 617-620 [DOI: 10.3760/cma.j.issn.1007-5232.2008.12.001]

11 **Endoscopic Submucosal Dissection Experts' Cooperation Group**. Consensus: Endoscopic submucosal dissection of Gastrointestinal mucous membrane. *Zhonghua Weichang Waike Zazhi* 2012; **15**: 1083-1086 [DOI: 10.1016/j.gii.2012.09.001]

12 **Choi DH**, Sohn DK, Chang HJ, Lim SB, Choi HS, Jeong SY. Indications for subsequent surgery after endoscopic resection of submucosally invasive colorectal carcinomas: a prospective cohort study. *Dis Colon Rectum* 2009; **52**: 438-445 [PMID:

19333043 DOI: 10.1007/DCR.0b013e318197e37f]
13 **Loughrey MB**, Shepherd NA. Problematic Colorectal Polyps: Is It Cancer and What Do I Need to Do About It? *Surg Pathol Clin* 2017; **10**: 947-960 [PMID: 29103541 DOI: 10.1016/j.path.2017.07.009]
14 **Zhang YH**, Sheng JQ, Chen ZM, Yan W, Yu DL, Li AQ, Wang HH, Han Y, Li SR. Clinical Evaluation of Traetment on Early-Stage Colorectal Cancer by Endoscopic Resection. *Weichangbing Xue* 2007; **12**: 5-8 [DOI: 10.3816/ccc.2011.n.005]
15 **Shinei K**, Meng N. Endoscopic treatment of neoplasms in colon and rectum. Liaoning Science and Technology Press 2007: 31-38 [DOI: 10.3109/9781420017984-1]
16 **Zhou PH**, Yao LQ, Xu MD, Liang Z, Qin XY. Endoscopic ultrasound diagnosis of colorectal cancer invasion depth and surrounding lymph nodes metastasis (with 60 cases report). *Zhongguo Neijing Zazhi* 2001; **7**: 12-14 [DOI: 10.3969/j.issn.1007-1989.2001.05.007]
17 **Zhou PH**, Yao LQ. The value of ultrasonic mini probe in the diagnosis of lesions of lower digestive tract. *Zhonghua Xiaohua Neijing Zazhi* 2002; **19**: 205-207 [DOI: 10.3760/cma.j.issn.1007-5232.2002.04.004]
18 **Xia L**, Dai X, Liu HL, Lin MB, Yin L, Zhu Q. Endoscopic ultrasonography with combination of miniature probe and radial scanning in preoperative staging for rectal cancer. *Zhonghua Xiaohua Neijing Zazhi* 2009; **26**: 175-179 [DOI: 10.3760/cma.j.issn.1007-5232.2009.04.003]
19 **Kealy WF**. Colonic lymphoid-glandular complex (microbursa): nature and morphology. *J Clin Pathol* 1976; **29**: 241-244 [PMID: 1270606 DOI: 10.1136/jcp.29.3.241]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 December 27; 14(12): 1425-1431

DOI: 10.4240/wjgs.v14.i12.1425

ISSN 1948-9366 (online)

CASE REPORT

# Malignant transformation of perianal tailgut cyst: A case report

Yuan Fang, Yong Zhu, Wei-Zhen Liu, Xia-Qing Zhang, Yu Zhang, Kang Wang

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C, C, C
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Jiang Y, China; Piltcher-da-Silva R, Brazil; Tajiri K, Japan; Tangsuwanaruk T, Thailand; Tsujinaka S, Japan;

**Received:** August 19, 2022
**Peer-review started:** August 19, 2022
**First decision:** September 4, 2022
**Revised:** September 17, 2022
**Accepted:** October 25, 2022
**Article in press:** October 25, 2022
**Published online:** December 27, 2022

**Yuan Fang, Yong Zhu, Wei-Zhen Liu, Xia-Qing Zhang, Yu Zhang,** Colorectal Surgery Center, Nanjing Hospital of Chinese Medicine Affiliated to Nanjing University of Chinese Medicine, Nanjing 210022, Jiangsu Province, China

**Kang Wang,** Department of Pathology, Nanjing Hospital of Chinese Medicine Affiliated to Nanjing University of Chinese Medicine, Nanjing 210022, Jiangsu Province, China

**Corresponding author:** Yong Zhu, MD, Doctor, Colorectal Surgery Center, Nanjing Hospital of Chinese Medicine Affiliated to Nanjing University of Chinese Medicine, No. 157 Daming Road, Nanjing 210022, Jiangsu Province, China. zhuyong839@sina.com

## Abstract

### *BACKGROUND*

Tailgut cyst is a congenital enterogenous cyst that rarely undergoes malignant transformation. Its clinical manifestations mainly correlate to the mass effect caused by the development of cysts and the infections that originate from these. Furthermore, the complete resection of this cyst is curative. We report our diagnostic and treatment experience with one case of malignant transformation of a perianal tailgut cyst, which was initially misdiagnosed as perianal abscess.

### *CASE SUMMARY*

A 72-year-old woman visited our institution with complaints of a refractory nonhealing lesion on the right hip, which repeatedly broke and suppurated for more than 70 years, and aggravated in 4 mo. The patient was given a diagnosis of refractory perianal abscess with repeated incision and drainage procedures. Computed tomography of the pelvic cavity revealed a giant perianal cyst. Subsequent biopsy revealed a tumor with moderate-to-severe glandular epithelial dysplasia, and suggested that this was derived from the developmental cysts in the posterior rectal space. After further clarifying the nature and extent of the tumor by magnetic resonance imaging, total cystic resection was performed. Postoperative histopathological examination confirmed the malignancy, dictating the investigators to add postoperative chemotherapy to the treatment regimen.

### *CONCLUSION*

The malignant transformation of perianal tailgut cysts is very uncommon, and this should be differentiated from perianal abscess. Complete surgical removal is curative, and postoperative pathology may determine the necessity of additional postoperative chemotherapy or radiotherapy, which may be beneficial for preventing local recurrence and metastasis.

**Key Words:** Tailgut cyst; Perianal cyst; Perianal abscess; Adenocarcinoma; Chemotherapy; Case report



**Core Tip:** We report our diagnostic and treatment experience with a unique case of malignant transformation of perianal tailgut cyst. Since perianal tailgut cysts are difficult to differentiate from other perianal diseases, the reported case was initially misdiagnosed as perianal abscess with repeated incision and drainage procedures. The patient underwent complete resection and received salvage chemotherapy for 3 mo after the surgery.

**Citation:** Fang Y, Zhu Y, Liu WZ, Zhang XQ, Zhang Y, Wang K. Malignant transformation of perianal tailgut cyst: A case report. *World J Gastrointest Surg* 2022; 14(12): 1425-1431
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i12/1425.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i12.1425

## INTRODUCTION

Tailgut cysts are developmental congenital enterogenous cysts that mostly occur in the retrorectal or presacral space[1]. The clinical features include the mass effect caused by the development of cysts, and the infection that originates from these[2]. Magnetic resonance imaging (MRI) can display the typical cyst appearance, which is crucial for distinguishing the cyst from perianal abscess. Complete resection of the cyst is curative and clinically preferred[3]. Postoperative histopathological analysis is routinely performed to pathologically confirm the diagnosis and mainly rule out the chance of malignancy. Clinically, this entity is not complicated in its diagnosis and treatment. We report a case of malignant transformation after the perianal tailgut cyst was misdiagnosed as perianal abscess, in which total resection was performed and postoperative chemotherapy was added.

## CASE PRESENTATION

### *Chief complaints*

A 72-year-old woman was transferred to our hospital with complaints of a tumor on the right hip, which repeatedly broke and suppurated for more than 70 years, and aggravated in 4 mo.

### *History of present illness*

The patient was born with a 5 mm × 5 mm mass under the right hip, which covered the skin. Perianal distending pain and discomfort were experienced by the patient with the gradual increase of the tumor. At a local hospital, the patient was diagnosed with perianal abscess due to its fluctuating feature. During the incision and drainage procedures, copious brownish pus was repeatedly drained out from the mass. In particular, during the recent 4 mo, the mass progressively become larger, with multiple ulcers on its surface, cauliflower-like objects at its base, and jelly-like liquid inside.

### *History of past illness*

The patient had a history of hypertension, and her daily blood pressure was maintained at approximately 120/60 mmHg with regular oral medication.

### *Personal and family history*

The patient denied any family history of malignancy.

### *Physical examination*

The physical examination did not unveil any significant finding, except for the 5 cm ulcerative mass under the right hip.

### *Laboratory examinations*

The patient had a slightly elevated carbohydrate antigen 7-24 of 23.04 U/mL, but no abnormalities were detected in other blood and urine analyses.

### *Imaging examinations*

Computed tomography (CT) revealed a multilocular cystic soft tissue mass in the right hip, which extended into the sacrococcygeal region, with an enhanced edge and a size of 6.0 cm × 5.8 cm × 9.5 cm (Figure 1A and B). In order to establish a diagnosis, biopsy was performed on the cystic mass. The results revealed a tumor with moderate-to-severe glandular epithelial dysplasia, and suggested the origin of developmental cysts in the posterior rectal space (Figure 2A). After the patient was transferred to our hospital, intestinal lesions were further excluded by proctoscopy. Endorectal ultrasonography further revealed multiple hypoechoic areas (diameter: 1.0-2.5 cm), with clear boundaries in the sacrococcygeal region, and uneven echo areas in the right hip with unclear boundaries (Figure 1C and D). MRI revealed an abnormal hypointense T1 and hyperintense T2 signal shadow in irregular quasi-circular lesion, and diffusion-weighted imaging (DWI) revealed a size of 107 mm in the sagittal position with wall enhancement (Figure 1E-H).

## MULTIDISCIPLINARY EXPERT CONSULTATION

Through the discussion of the multidisciplinary team, enterogenous cyst with malignant transformation was suggested as the preliminary diagnosis. The patient underwent a transperineal operation, during which the tailgut cyst was identified to extend into the posterior rectal space, and reach the sacral vertebrae at the 4th-5th levels above the tip of the coccyx. Since the sacrococcyx fascia was considered to be the origin of the cyst and attached to the coccyx, a part of this was resected to expose the surgical field. After radically resecting the cystic lesion with the surrounding tissues without injuring the posterior rectal wall, endorectal ultrasonography was performed to confirm that no cystic remnants were present, and a free-flap procedure to reconstruct the extensive resection site was performed by co-operating with the plastic surgery team (Figure 3). The operation lasted for approximately 270 min, with an unexpected intraoperative blood loss of more than 600 mL. The patient was hospitalized for 36 d for postoperative recovery.

Postoperatively, pathological examination revealed a diagnosis of malignant transformation of the perianal tailgut cyst, and this was identified as mucinous adenocarcinoma, with a size of 6.5 cm × 4.0 cm × 6.0 cm, without local infiltration (Figure 2B). Histologically, tumorous cells were found 0.2 cm away from the resection margin, confirming a pathological R0 resection. Further immune-histological examinations were paneled, as follows: MLH1 (+), MSH2 (+), MSH6 (+), PMS2 (+), P53S100 (-), CD34 (-), D2-40 (-), Ki-67 (70%), CDH-17 (+), CDX-2 (+), CK7 (+), CK20 (+), and SATB-2 (+).

## FINAL DIAGNOSIS

Pathologically, the patient was given a final diagnosis of malignant transformation of the perianal tailgut cyst.

## TREATMENT

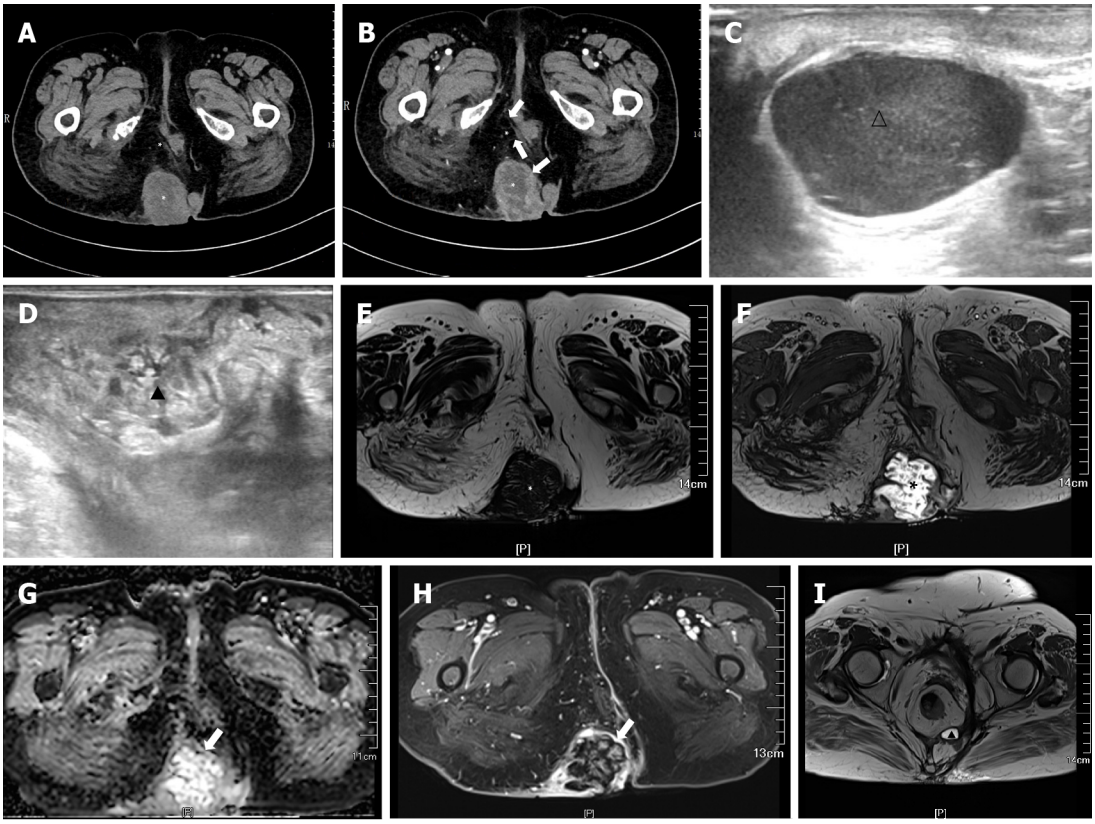
Three months after the surgery, MRI revealed a small cyst under the right levator ani (Figure 1I), and the carbohydrate antigen 7-24 decreased to normal. According to the postoperative pathology, oral salvage chemotherapy with capecitabine 1000 mg, twice per day, for eight cycles, was added, and an MRI examination was recommend every 3 mo to monitor the change in size of the cyst.

## OUTCOME AND FOLLOW-UP

After the 3$^{rd}$ cycle of chemotherapy with capecitabin, the patient did not have any special complaints or discomfort.

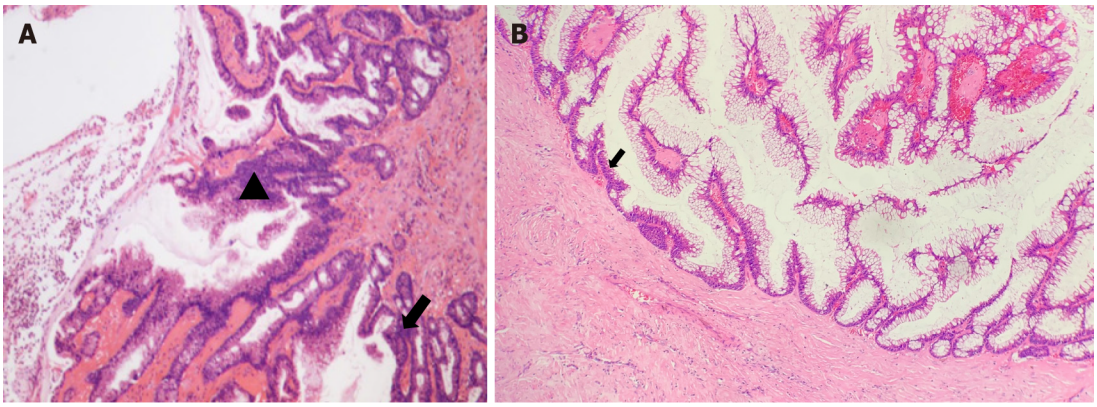
## DISCUSSION

As a rare congenital disease, tailgut cyst originates from the tailgut and neurenteric canal[4], and most likely occurs in the retrorectal or presacral space[1]. Clinically, this disease is more commonly observed in middle-aged females with the presentation of a mass lesion, with or without infection[2]. Malignancy infrequently occurs in presacral tailgut cysts, at a rate of less than 8%, and when this occurs, it may most likely be adenocarcinoma or carcinoid[3]. For the present case, the patient presented with an infected and inflammatory mass, with the dissemination of cells from the cyst wall as the result of repeated




**DOI**: 10.4240/wjgs.v14.i12.1425 **Copyright** © The Author(s) 2022.

**Figure 1 Computed tomography and magnetic resonance imaging.** A: A soft tissue mass and cystic density shadow were observed in the right hip and sacrococcygeal region (*), and the largest range was approximately 6.0 cm × 5.8 cm × 9.5 cm; B: The cyst was uneven, and the edge and septal of the focus were enhanced (↑); C and D: Multiple hypoechoic areas with a clear boundary (1.0–2.5 cm) were observed in the sacral region (Δ) (C), and uneven echo areas in the right hip (▲) (D); E and F: The lesion had low-attenuation on T1 (*) (E) and high-attenuation on T2 (*) (F); G: Diffusion weighted image (↑). The longest diameter of the sagittal position was approximately 107 mm; H: The edge of the lesion was obviously enhanced (↑); I: Magnetic resonance imaging (T2) revealed a small cyst (▲) under the right levator ani.

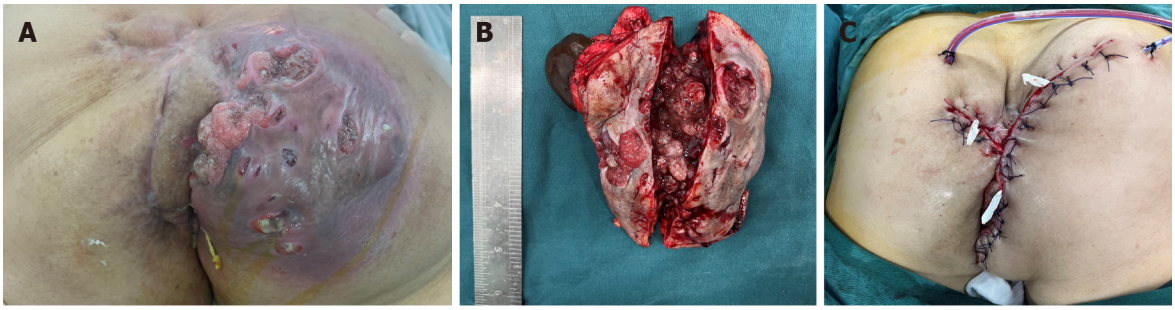



**DOI:** 10.4240/wjgs.v14.i12.1425 **Copyright** ©The Author(s) 2022.

**Figure 2 Histopathological analysis.** A: Moderate (▲)-to-severe (↑) dysplasia of the glandular epithelium; B: The columnar epithelial lining of the cyst wall had a large amount of mucus secretion, some of the epithelium had moderate dysplasia, and deranged smooth muscle bundles could be observed in the cyst wall (↑).

incision, and this might have been the main cause of the local recurrence that contributed to the malignant transformation[5].

The present report emphasizes the differentiation of a perianal tailgut cyst from a perianal abscess. For perianal abscess in the retrorectal space, when it exhibits the reluctance to complete healing due to the discharge of residual pus, when no anal fistula is found, or when this recurs multiple times after repeated surgical treatment, tailgut cyst should be suspected and completely resected for further pathological diagnosis. Since the specimens obtained from the biopsy often contain merely the inflamed fibrous tissue without the epithelia, or merely one type of epithelium, which may not consequently




**DOI:** 10.4240/wjgs.v14.i12.1425 

**Figure 3 Macroscopic examination.** A: A 13 cm × 12 cm lesion was found on the right hip, with obvious fluctuation, reddish skin on the surface, multiple ruptures, jelly-like fluid outflow, and cauliflower-like objects attached to the base; B: Gross examination of the specimen revealed brown and jelly-like fluid in the cyst; C: The orthopedists assisted with the free skin flap, and closed the incision.

support any diagnosis[6], the biopsy of the cystic lesion is not recommended.

Pathohistologically, the cyst would be filled with brown and jelly-like fluid from the wall of the tailgut cyst[6], which would be partially or completely covered with intestinal epithelium, and this may contain columnar cells, squamous cells, and transitional cells with mucus secretion function[2], while the smooth muscle fibers in the cyst wall would be disorganized without the nerve plexus[7]. The canceration of caudal cysts is mostly focal, allowing for a thorough postoperative histopathological analysis of the resected specimen to be mandated, in order to confirm the diagnosis and rule out malignant tumors. Unlike perianal abscesses, tailgut cysts possess a multilocular nature, which demands preoperative endorectal ultrasonography, or pelvic MRI or CT imaging studies[8]. MRI can reveal the typical cyst appearance as low attenuation on T1 and high-attenuation on T2, and DWI can allow for the tailgut cyst to be distinguished from a perianal abscess[9]. Furthermore, although the importance of MRI in the diagnosis of tailgut cysts has been emphasized, endorectal ultrasonography is more convenient and accessible than MRI, especially in operations for complete cyst resection[10].

For the risk of malignant transformation of a cyst, surgical resection is the first choice for the treatment of tailgut cysts[3], and the surgical approach should be selected according to the location of the cyst shown in the imaging studies. Since the incidence of canceration of the tailgut cyst remains low, there is still a risk of local recurrence and distant metastasis. At present, three cases of local recurrence and two cases of distant metastasis have been reported[11-14]. Among these cases (Table 1), a patient with pseudomyxoma peritonei benefited from chemotherapy. After 3 mo, MRI revealed a small cyst under the right levator ani, which might putatively be correlated to the local implantation of cyst wall cells caused by the partial rupture of the cyst wall during the operation. Since the preoperative carbohydrate antigen 724 was also slightly elevated, with a Ki-67 index of 70%, oral capecitabine chemotherapy was given to the patient, who refused to undergo a reoperation for the relatively tiny lesion, as a salvage chemotherapy. In addition, close follow-up with MRI study was recommended. Indeed, a study suggested that postoperative adjuvant radiotherapy be recommended for patients with canceration of the tailgut cyst and remnant lesions for incomplete lesion resection, in order to achieve good outcomes, with or without chemotherapy[15].

## CONCLUSION

In summary, perianal caudal cysts are difficult to differentiate from other perianal diseases, especially perianal abscesses. Due to the risk of cancerization of the cyst, multi-disciplinary treatment should be emphasized clinically.

**Table 1 Characteristics of patients with perianal tailgut cyst who accepted chemotherapy therapy**

| Ref. | Gender | Age (yr) | Pathology | Cause of chemotherapy | Scheme | Follow-up | PMID |
|---|---|---|---|---|---|---|---|
| Akira *et al* [14], 1998 | Female | 66 | Moderately differentiated adenocarcinoma | Elevated carcinoembryonic antigen level | Oral tegafur, 200 mg daily | 3.2 yr | 9872560 |
| Luis *et al* [13], 2009 | Female | 37 | Mucinous adenocarcinoma | Resection was complete, but not *en bloc* | Intraperitoneal mitomycin C and doxorubicin plus systemic 5-fluorouracil and leucovorin | 3.0 yr | 19856666 |
| Zhao *et al* [5], 2015 | Female | 44 | Moderately differentiated adenocarcinoma | Elevated carcinoembryonic antigen level | Intracapsular tumor necrosis factor and raltitrexed plus systemic oxaliplatin 3-cycles (130 mg/m$^2$) | 9.0 wk | 26656372 |

## FOOTNOTES

**Author contributions:** Fang Y contributed to data curation and writing of the original draft; Liu WZ, Zhang XQ, and Zhang Y contributed to data curation; Zhang Y contributed to manuscript review and editing; Wang K contributed to evaluation of the histopathology; all authors have read and approved the final manuscript.

**Informed consent statement:** Informed written consent was obtained from the patient and her family for publication of this report and any accompanying images.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).



**Country/Territory of origin:** China

**ORCID number:** Yuan Fang 0000-0002-3825-3770; Yong Zhu 0000-0003-3039-5413; Wei-Zhen Liu 0000-0003-3720-2493; Xia-Qing Zhang 0000-0002-0842-5463; Yu Zhang 0000-0001-8739-9541; Kang Wang 0000-0002-5246-0338.

**S-Editor:** Liu GL
**L-Editor:** Wang TQ
**P-Editor:** Liu GL

## REFERENCES

1 **Sung MT**, Ko SF, Niu CK, Hsieh CS, Huang HY. Perirenal tailgut cyst (cystic hamartoma). *J Pediatr Surg* 2003; **38**: 1404-1406 [PMID: 14523832 DOI: 10.1016/s0022-3468(03)00408-1]
2 **Dahan H**, Arrivé L, Wendum D, Docou le Pointe H, Djouhri H, Tubiana JM. Retrorectal developmental cysts in adults: clinical and radiologic-histopathologic review, differential diagnosis, and treatment. *Radiographics* 2001; **21**: 575-584 [PMID: 11353107 DOI: 10.1148/radiographics.21.3.g01ma13575]
3 **Broccard SP**, Colibaseanu DT, Behm KT, Mishra N, Davis P, Maimone KL, Mathis KL, Stocchi L, Dozois EJ, Merchea A. Risk of malignancy and outcomes of surgically resected presacral tailgut cysts: A current review of the Mayo Clinic experience. *Colorectal Dis* 2022; **24**: 422-427 [PMID: 34941020 DOI: 10.1111/codi.16030]
4 **Hjermstad BM**, Helwig EB. Tailgut cysts. Report of 53 cases. *Am J Clin Pathol* 1988; **89**: 139-147 [PMID: 3277378 DOI: 10.1093/ajcp/89.2.139]
5 **Zhao XR**, Gao C, Zhang Y, Yu YH. The Malignant Transformation of Retrorectal Cystic Hamartomas With Blood Irregular Antibodies Positive: A Case Report. *Medicine (Baltimore)* 2015; **94**: e2253 [PMID: 26656372 DOI: 10.1097/MD.0000000000002253]
6 **Prasad AR**, Amin MB, Randolph TL, Lee CS, Ma CK. Retrorectal cystic hamartoma: report of 5 cases with malignancy arising in 2. *Arch Pathol Lab Med* 2000; **124**: 725-729 [PMID: 10782156 DOI: 10.5858/2000-124-0725-RCH]
7 **Hufkens AS**, Cools P, Leyman P. Tailgut cyst: report of three cases and review of the literature. *Acta Chir Belg* 2019; **119**: 110-117 [PMID: 30776969 DOI: 10.1080/00015458.2017.1353758]
8 **Li Z**, Lu M. Presacral Tumor: Insights From a Decade's Experience of This Rare and Diverse Disease. *Front Oncol* 2021; **11**: 639028 [PMID: 33796466 DOI: 10.3389/fonc.2021.639028]
9 **Shetty AS**, Loch R, Yoo N, Mellnick V, Fowler K, Narra V. Imaging of tailgut cysts. *Abdom Imaging* 2015; **40**: 2783-2795

[PMID: 26017036 DOI: 10.1007/s00261-015-0463-3]

10 **Visscher AP**, Felt-Bersma RJ. Endoanal ultrasound in perianal fistulae and abscesses. *Ultrasound Q* 2015; **31**: 130-137 [PMID: 25364961 DOI: 10.1097/RUQ.0000000000000124]

11 **Liessi G**, Cesari S, Pavanello M, Butini R. Tailgut cysts: CT and MR findings. *Abdom Imaging* 1995; **20**: 256-258 [PMID: 7620420 DOI: 10.1007/BF00200409]

12 **Erdrich J**, Schaberg KB, Khodadoust MS, Zhou L, Shelton AA, Visser BC, Ford JM, Alizadeh AA, Quake SR, Kunz PL, Beausang JF. Surgical and molecular characterization of primary and metastatic disease in a neuroendocrine tumor arising in a tailgut cyst. *Cold Spring Harb Mol Case Stud* 2018; **4** [PMID: 30087100 DOI: 10.1101/mcs.a003004]

13 **Zappa L**, Godwin TA, Sugarbaker PH. Tailgut cyst, an unusual cause of pseudomyxoma peritonei. *Tumori* 2009; **95**: 514-517 [PMID: 19856666]

14 **Maruyama A**, Murabayashi K, Hayashi M, Nakano H, Isaji S, Uehara S, Kusuda T, Miyahara S, Kondo A, Yabana T. Adenocarcinoma arising in a tailgut cyst: report of a case. *Surg Today* 1998; **28**: 1319-1322 [PMID: 9872560 DOI: 10.1007/bf02482826]

15 **Martins P**, Canotilho R, Peyroteo M, Afonso M, Moreira A, de Sousa A. Tailgut cyst adenocarcinoma. *Autops Case Rep* 2020; **10**: e2019115 [PMID: 32039057 DOI: 10.4322/acr.2019.115]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 December 27; 14(12): 1432-1437

DOI: 10.4240/wjgs.v14.i12.1432

ISSN 1948-9366 (online)

CASE REPORT

# Acute appendicitis in the short term following radical total gastrectomy misdiagnosed as duodenal stump leakage: A case report

Jun Ma, Zhen-Ping Zha, Chao-Ping Zhou, Xiang Miao, Shu-Qiang Duan, Ya-Ming Zhang

**Specialty type:** Surgery

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Arigami T, Japan; Moshref RH, Saudi Arabia; Straksyte V, Lithuania

**Received:** September 15, 2022
**Peer-review started:** September 15, 2022
**First decision:** October 21, 2022
**Revised:** October 28, 2022
**Accepted:** November 22, 2022
**Article in press:** November 22, 2022
**Published online:** December 27, 2022

**Jun Ma, Chao-Ping Zhou, Xiang Miao, Ya-Ming Zhang,** Department of General Surgery, Anqing Municipal Hospital, Anqing 246000, Anhui Province, China

**Zhen-Ping Zha,** Department of Vascular Surgery, Anqing Municipal Hospital, Anqing 246000, Anhui Province, China

**Shu-Qiang Duan,** Department of Pathology, Anqing Municipal Hospital, Anqing 246000, Anhui Province, China

**Corresponding author:** Ya-Ming Zhang, MD, Chief Doctor, Surgeon, Surgical Oncologist, Department of General Surgery, Anqing Municipal Hospital, No. 352 Ren-Ming Road, Anqing 246000, Anhui Province, China. zhangyaming2014@163.com

## Abstract

*BACKGROUND*

Common diseases after radical gastrectomy include cholecystitis and pancreatitis, but the sudden onset of acute appendicitis in a short period following radical gastrectomy is very rare, and its clinical symptoms are easily misdiagnosed as duodenal stump leakage.

*CASE SUMMARY*

This is a case report of a 77-year-old woman with lower right abdominal pain 14 d after radical resection of gastric cancer. Her pain was not relieved by conservative treatment, and her inflammatory markers were elevated. Computed tomography showed effusion in the perihepatic and hepatorenal spaces, right paracolic sulcus and pelvis, as well as exudative changes in the right iliac fossa. Ultrasound-guided puncture revealed a slightly turbid yellow-green fluid. Laparoscopic exploration showed a swollen appendix with surrounding pus moss and no abnormalities of the digestive anastomosis or stump; thus, laparoscopic appendectomy was performed. The patient recovered well after the operation. Postoperative pathology showed acute purulent appendicitis. The patient continued adjuvant chemotherapy after surgery, completing three cycles of oxaliplatin plus S-1 (SOX regimen).

*CONCLUSION*

Acute appendicitis in the short term after radical gastrectomy needs to be differentiated from duodenal stump leakage, and early diagnosis and surgery are the

most important means of treatment.

**Key Words:** Gastric cancer; Acute appendicitis; Surgery; Complications; Case report



**Core Tip:** Common forms of abdominal inflammation occurring after radical gastrectomy are cholecystitis and pancreatitis, of which cholecystitis has the highest incidence. In contrast, the incidence of appendicitis in the short term after radical gastrectomy is rare and has not been reported before. Herein, we present a case of acute appendicitis in the short term following radical total gastrectomy. We suggest that acute appendicitis in the short term after gastric cancer surgery needs to be differentiated from duodenal stump leakage and that early diagnosis and surgery are the most important means of treatment.

**Citation:** Ma J, Zha ZP, Zhou CP, Miao X, Duan SQ, Zhang YM. Acute appendicitis in the short term following radical total gastrectomy misdiagnosed as duodenal stump leakage: A case report. *World J Gastrointest Surg* 2022; 14(12): 1432-1437
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i12/1432.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i12.1432

## INTRODUCTION

Acute appendicitis is mainly caused by bacteria, fecal stones, and malformations, and the pathogenic condition must be mucosal damage and bacterial invasion[1]. Common forms of abdominal inflammation occurring after radical gastrectomy are cholecystitis and pancreatitis, of which cholecystitis has the highest incidence[2]. In contrast, the incidence of appendicitis in the short term after radical resection of gastric cancer is rare and has not been reported. The lack of typical symptoms of metastatic lower right abdominal pain is attributed to resection of the stomach and greater omentum. The symptoms mainly manifest as persistently aggravated right-sided abdominal pain and a high perforation rate; therefore, the inflammation is not easily confined, and the clinical symptoms are easily misdiagnosed as duodenal stump leakage.

## CASE PRESENTATION

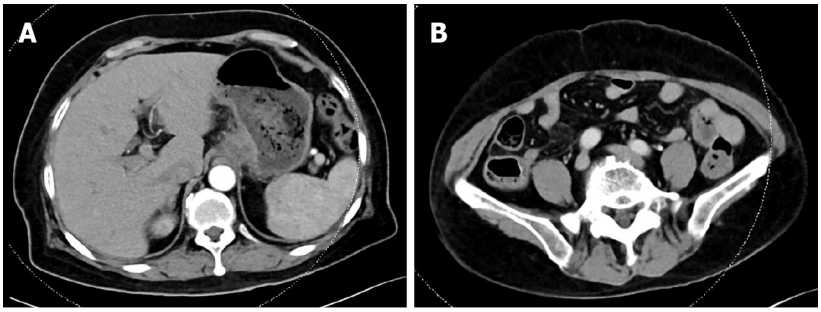
### *Chief complaints*

Durative pain in the lower right abdomen 14 d after radical total gastrectomy.

### *History of present illness*

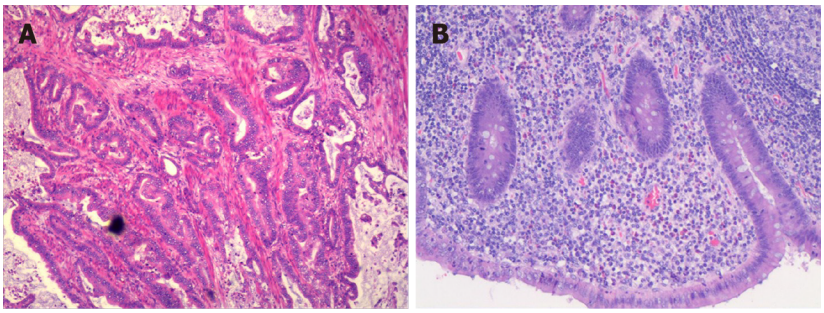
A 77-year-old woman was diagnosed with gastric cancer, and preoperative pathology showed adenocarcinoma, moderately differentiated, HP (-). On May 23, 2022, computed tomography (CT) showed that the cardia was thickened and reinforced (Figure 1A), and the appendix was normal (Figure 1B). Preoperative clinical staging showed cT4Nx; preoperative neoadjuvant therapy was recommended, but the patient refused due to advanced age, and "radical total gastrectomy (D2 lymph node dissection)" was performed under general anesthesia on May 26, 2022. Intraoperative exploration: The gallbladder had been removed; the omentum was adhered to the gallbladder bed, no ascites was seen, and no metastatic nodules were seen in the liver or peritoneum. Postoperative pathology indicated stage IIIB, moderately differentiated, intestinal-type adenocarcinoma with lymph node involvement (7/30) (Figure 2A). The resection margin was negative. The immunohistochemical marker results were as follows: CK (+), Her-2 (3+), MSH2 (+), MSH6 (+), PMS2 (+), MLH1 (+), and Ki-67 (approximately 70%).

The patient recovered well after the operation; all inflammatory indexes gradually decreased, and her blood sugar was well controlled. On June 3, 2022, her D-dimer level was significantly elevated, and ultrasound showed intermuscular thrombosis located in the lower right extremity, which was treated with low-molecular-weight heparin. On June 4, 2022, CT showed no abnormalities around the anastomosis or stump, no leakage of oral pantothenic glucosamine into the abdominal cavity, no abnormalities in the ileocecal region or appendix, and no significant fluid accumulation in the abdominopelvic cavity (Figure 3). On June 8, 2022, her blood count, calcitonin and C-reactive protein (CRP) levels were normal, and she was ready to be discharged. However, during the night of June 9, 2022, the patient complained of persistent pain on the right side of the abdomen, and the abdominal pain became



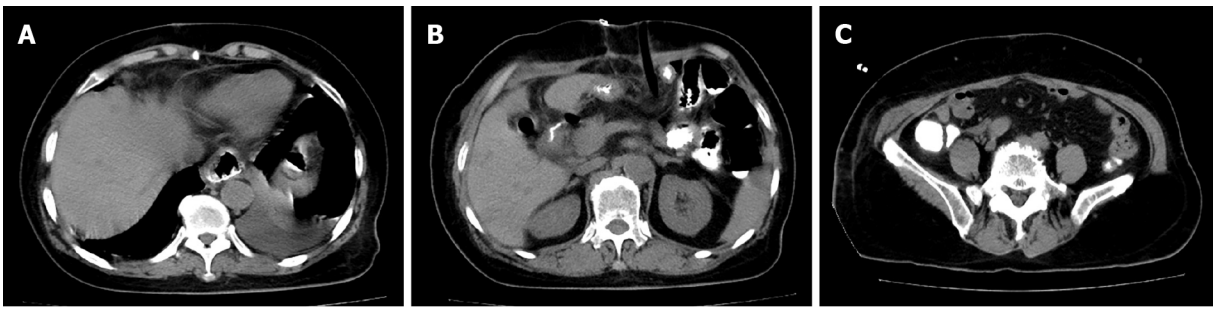

**DOI:** 10.4240/wjgs.v14.i12.1432 **Copyright** ©The Author(s) 2022.

**Figure 1 Imaging data of May 23, 2022.** A: Computed tomography (CT) showed that the cardia was thickened and reinforced; B: CT showed that the appendix was normal.




**DOI:** 10.4240/wjgs.v14.i12.1432 **Copyright** ©The Author(s) 2022.

**Figure 2 Photomicrographs (hematoxylin and eosin, × 200 magnification).** A: Moderately differentiated tubular adenocarcinoma; B: Acute purulent appendicitis and periapical inflammation.




**DOI:** 10.4240/wjgs.v14.i12.1432 **Copyright** ©The Author(s) 2022.

**Figure 3 Imaging data of June 4, 2022.** A: Computed tomography showed no abnormalities around the anastomosis or stump, no leakage into the abdominal cavity from oral pantothenic glucosamine, no abnormalities in the ileocecal region or appendix, and no significant fluid accumulation in the abdominopelvic cavity; B: No abnormalities were found in the ileocecal region or duodenal stump; C: No abnormalities were found in the appendix.

significantly worse on the morning of June 10, 2022.

### *History of past illness*

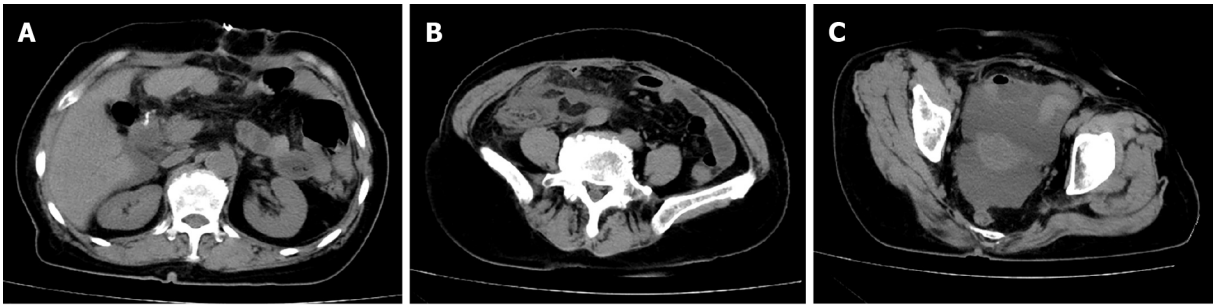
The patient had a previous history of diabetes, hypertension, cholecystectomy and no history of chronic appendicitis.

### *Personal and family history*

There was no family history of tumors.

### *Physical examination*

On June 6, the abdominal incision was healing well, and the patient reported tenderness in the lower right abdomen, muscle tension and rebound pain.




**DOI:** 10.4240/wjgs.v14.i12.1432 

**Figure 4 Imaging data of June 10, 2022.** A: Computed tomography showed that there was effusion in the perihepatic and hepatorenal interstitial areas; B: There was effusion in the right paracolic sulcus and exudative changes in the right iliac fossa; C: Effusion was seen in the pelvis.

### *Laboratory examinations*

The patient's leukocyte level was 17.18 × $10^9$/L; neutrophil ratio, 88.4%; calcitonin level, 0.19 ng/mL; and CRP level, 65.20 mg/L.

### *Imaging examinations*

On June 10, 2022, CT showed effusion in the perihepatic and hepatorenal spaces, right paracolic sulcus and pelvis and exudative changes in the right iliac fossa (Figure 4). Subsequent ultrasound-guided puncture revealed a slightly turbid yellow-green fluid.

## FINAL DIAGNOSIS

Acute suppurative appendicitis after radical gastrectomy.

## TREATMENT

On June 10, 2022, laparoscopic exploration revealed yellow-green fluid in the perihepatic and pelvic cavities (Figure 5A and B); the duodenal stump was wrapped in tissue and did not show leakage (Figure 5C), and there were no abnormalities in the esophageal-jejunal anastomosis or jejunal-jejunal anastomosis. A large amount of pus moss was seen in the ileocecal region, and the terminal ileum wrapped around the appendix (Figure 6A). A septic and swollen appendix was seen after careful laparoscopic separation of the adhesions (Figure 6B). The appendiceal mesentery was treated with harmonic scissors and absorbable clips, the root of the appendix was ligated with thread, and the appendiceal stump was cauterized (Figure 6C). A pelvic drainage tube was placed after aspiration of intra-abdominal fluid.

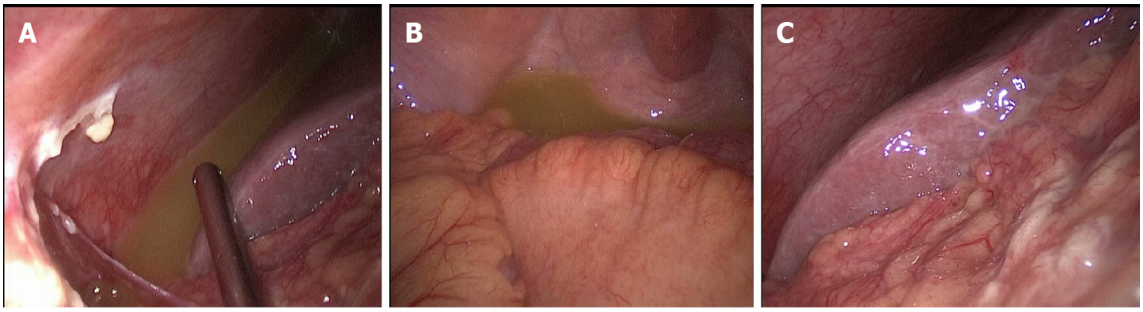
## OUTCOME AND FOLLOW-UP

Postoperative pathology showed acute purulent appendicitis and periapical inflammation (Figure 2B). The patient recovered well after surgery and was successfully discharged two weeks later. Follow-up CT showed no significant abnormalities in the abdominal cavity (Figure 7). The patient continued adjuvant chemotherapy after surgery, completing three cycles of oxaliplatin and S-1 (SOX regimen).

## DISCUSSION

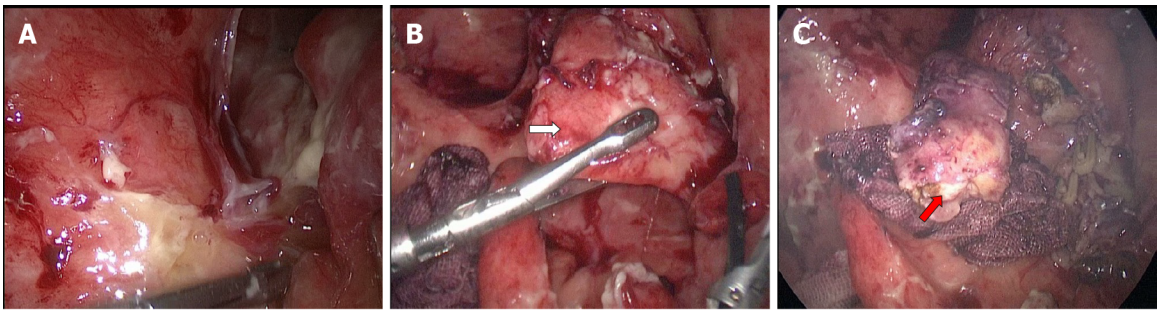
Cholecystitis and pancreatitis are common diseases after radical resection of gastric cancer. Appendicitis occurs rarely, as early as several months later, and perioperative combined episodes of appendicitis are even rarer.

There were several reasons for misdiagnosis in this case. First, we usually used one etiology to explain all the symptoms of the patient; we would focus on postoperative complications but might ignore the possibility of common diseases. Second, the most common abdominal complication after radical gastrectomy is duodenal stump leakage[3]. The patient had a history of diabetes and presented with postoperative right abdominal pain. CT showed hepatorenal and pelvic effusion, and the puncture



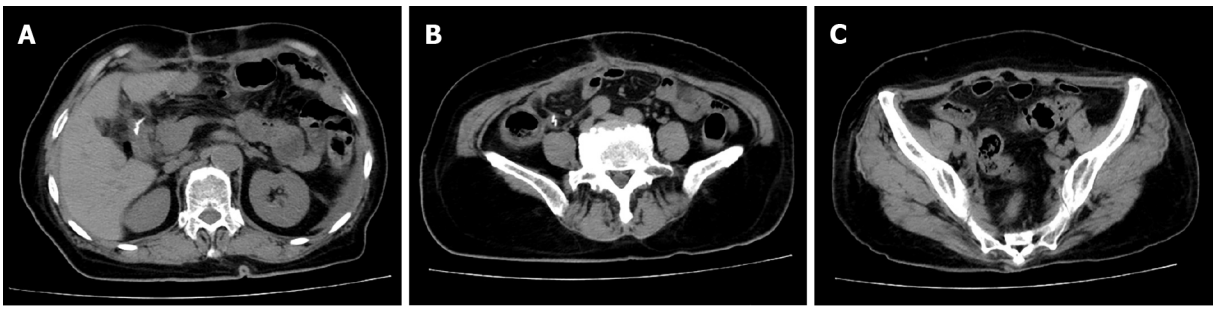

**DOI:** 10.4240/wjgs.v14.i12.1432 **Copyright** ©The Author(s) 2022.

**Figure 5 laparoscopic exploration.** A and B: Yellow-green fluid could be found in the perihepatic and pelvic cavities; C: The duodenal stump was wrapped in tissue and did not show leakage.




**DOI:** 10.4240/wjgs.v14.i12.1432 **Copyright** ©The Author(s) 2022.

**Figure 6 Surgical procedure.** A: A large amount of pus moss was seen around the ileocecal region, and the terminal ileum wrapped around the appendix; B: A septic and swollen appendix was seen after careful laparoscopic separation of the adhesions (white arrow); C: Resected appendix (red arrow) and treated appendiceal stump and mesentery.




**DOI:** 10.4240/wjgs.v14.i12.1432 **Copyright** ©The Author(s) 2022.

**Figure 7 Imaging data of July 12, 2022.** Computed tomography showed no significant abnormalities of the duodenal stump, appendiceal stump or pelvic. A: Duodenal stump; B: Appendiceal stump; C: Pelvic.

revealed yellow-green turbid fluid, which could not exclude the occurrence of duodenal stump leakage.

This is a successful case in which laparoscopic exploration was promptly performed to clarify the diagnosis. This case is enlightening for the following reasons: (1) For patients with a history of diabetes and postoperative lower right abdominal pain, the possibility of appendicitis must be considered, as diabetes is a high-risk factor for appendicitis[4]; (2) Patients with appendicitis following gastrectomy have atypical abdominal pain due to surgical removal of all or a large part of the stomach, and reconstruction of the digestive tract alters the original physiological structure; (3) The large omentum was removed and could no longer easily confine the acute inflammation of the appendix; thus, as the disease worsened, diffuse peritonitis developed; (4) The occurrence of appendicitis has been reported in conjunction with several other diseases, such as colon cancer, tuberculosis, herniation and gynecological diseases[5-8]; and (5) Gastric cancer combined with appendiceal metastasis would cause symptoms of acute appendicitis, but in this case, there was no peritoneal or appendiceal metastasis[9]. In conclusion, acute appendicitis occurring within a short period after radical gastrectomy has its own characteristics and is easily confused with postoperative complications of gastric cancer; thus, a clear diagnosis and

early surgical treatment are needed.

## CONCLUSION

Acute appendicitis in the short term after gastric cancer is rare and easily ignored clinically and needs to be differentiated from duodenal stump leakage.

## FOOTNOTES

**Author contributions:** Ma J wrote and edited the original draft; Duan SQ and Miao X contributed to data collection and analysis; Zhou CP and Zha ZP reviewed the literature; Zhang YM reviewed and approved the final manuscript; All authors have read and approve the final manuscript.

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** The authors declare that they have no conflicts of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).



**Country/Territory of origin:** China

**ORCID number:** Jun Ma 0000-0003-2547-8257; Chao-Ping Zhou 0000-0001-6610-2091; Shu-Qiang Duan 0000-0002-9333-3626; Ya-Ming Zhang 0000-0002-7020-7379.

**S-Editor:** Zhang H
**L-Editor:** A
**P-Editor:** Zhang H

## REFERENCES

1 **Bhangu A**, Søreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. *Lancet* 2015; **386**: 1278-1287 [PMID: 26460662 DOI: 10.1016/S0140-6736(15)00275-5]
2 **Seo HS**, Na Y, Jung J. Analysis of the Occurrence of Diseases Following Gastrectomy for Early Gastric Cancer: a Nationwide Claims Study. *J Gastric Cancer* 2021; **21**: 279-297 [PMID: 34691812 DOI: 10.5230/jgc.2021.21.e29]
3 **Ramos MFKP**, Pereira MA, Barchi LC, Yagi OK, Dias AR, Szor DJ, Zilberstein B, Ribeiro-Júnior U, Cecconello I. Duodenal fistula: The most lethal surgical complication in a case series of radical gastrectomy. *Int J Surg* 2018; **53**: 366-370 [PMID: 29653246 DOI: 10.1016/j.ijsu.2018.03.082]
4 **Tseng CH**. Metformin use is associated with a reduced risk of acute appendicitis in Taiwanese patients with type 2 diabetes mellitus. *Sci Rep* 2021; **11**: 12400 [PMID: 34117321 DOI: 10.1038/s41598-021-91902-z]
5 **Hajibandeh S**, Hajibandeh S, Morgan R, Maw A. The incidence of right-sided colon cancer in patients aged over 40 years with acute appendicitis: A systematic review and meta-analysis. *Int J Surg* 2020; **79**: 1-5 [PMID: 32387215 DOI: 10.1016/j.ijsu.2020.04.065]
6 **Chiș B**, Dudric V, Fodor D. Tuberculous appendicitis. A case report. *Med Ultrason* 2017; **19**: 333-335 [PMID: 28845503 DOI: 10.11152/mu-1085]
7 **Bettini A**, Ulloa JG, Harris H. Appendicitis within Morgagni Hernia and simultaneous Paraesophageal Hernia. *BMC Surg* 2015; **15**: 15 [PMID: 25644716 DOI: 10.1186/1471-2482-15-15]
8 **Noor M**, Chen A, Gonzalez RS. Clinicopathologic findings in gynecologic proliferations of the appendix. *Hum Pathol* 2019; **92**: 101-106 [PMID: 31430494 DOI: 10.1016/j.humpath.2019.08.004]
9 **Wang W**, Cui T, Mao W. Acute appendicitis caused by metastatic gastric adenocarcinoma: a case report and literature review. *Ann Palliat Med* 2021; **10**: 7132-7137 [PMID: 34154334 DOI: 10.21037/apm-21-1098]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
**Telephone:** +1-925-3991568
**E-mail:** bpgoffice@wjgnet.com
**Help Desk:** https://www.f6publishing.com/helpdesk
https://www.wjgnet.com