ANASTOMOTIC AND INTESTINAL WOUND HEALING: RECENT ADVANCES AND FUTURE DIRECTIONS

EDITED BY: Sven Flemming and Hans Martin Schardey
PUBLISHED IN: Frontiers in Surgery

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-83250-572-4
DOI 10.3389/978-2-83250-572-4

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

ANASTOMOTIC AND INTESTINAL WOUND HEALING: RECENT ADVANCES AND FUTURE DIRECTIONS

Topic Editors:
Sven Flemming, University Hospital of Wuerzburg, Germany
Hans Martin Schardey, Agatharied Hospital GmbH, Germany

Citation: Flemming, S., Schardey, H. M., eds. (2022). Anastomotic and Intestinal Wound Healing: Recent Advances and Future Directions. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83250-572-4

Table of Contents

frontiers | Frontiers in Surgery

TYPE Editorial
PUBLISHED 14 September 2022
DOI 10.3389/fsurg.2022.922090

OPEN ACCESS

EDITED BY
Sven Flemming,
University Hospital of Wuerzburg, Germany

REVIEWED BY
Matthias Kelm,
University Hospital Würzburg, Germany

*CORRESPONDENCE
Peter C. Ambe
peter.ambe@uni-wh.de

SPECIALTY SECTION
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

RECEIVED 17 April 2022
ACCEPTED 29 August 2022
PUBLISHED 14 September 2022

CITATION
Ambe PC (2022) Editorial: Increasing patient's safe in colorectal surgery *via* real-time bowel perfusion using near infrared ICG fluorescence studies.
Front. Surg. 9:922090.
doi: 10.3389/fsurg.2022.922090

Editorial: Increasing patient's safe in colorectal surgery *via* real-time bowel perfusion using near infrared ICG fluorescence studies

Peter C. Ambe[1,2]*

[1]Chair of Surgery II, Witten/Herdecke University, Witten, Bergische Gladbach, Germany, [2]Department of General, Visceral and Colorectal Surgery, GFO Kliniken Rhein Berg, Witten, Bergische Gladbach, Germany

KEYWORDS

ICG = near-infrared indocyanine green, anastomotic leak in colorectal surgery, patients safety, colorectal surgery, left colectomy

Editorial on the Research Topic
Increasing patient's safe in colorectal surgery *via* real-time bowel perfusion using near infrared ICG fluorescence studies

by Ambe PC. (2022) Front. Surg. 9: 922090. doi: 10.3389/fsurg.2022.922090

Anastomotic leakage (AL) is the most feared complication in colorectal surgery and preventing this serious morbidity is a primary goal. Although the etiology of AL is multifactorial, three categories of risk factors can be identified. The first group includes "patient-related factors" like advanced age, male gender, obesity, concomitant diseases, etc. The second group is directly associated with the underlying pathology e.g., low rectal cancer and prior radiation, while the third group is surgery-related. The third group may include all perioperative aspects from preoperative preparation, surgical technique, postoperative management, etc and is therefore not limited to the expertise of the operating surgeon alone.

Anastomotic leakage is a complication that has probably been encouraged by almost every colorectal or gastrointestinal surgeon. Ever wondered why an AL develops even after creating a vital, tension-free and air-tight anastomosis? Maybe the perfusion was not as good as you conceived! Our judgement of bowel perfusion at the anastomotic site may not be always objective.

Over the last years objective real-time studies of bowel perfusion during the creation of an anastomosis has been increasingly reported. Fluorescent studies using indocyanine green (ICG) is one method of judging bowel perfusion during surgery. While the application of ICG is not new in medicine and surgery, its application in colorectal surgery is being advocated as a new standard with regard to evaluation of bowel perfusion.

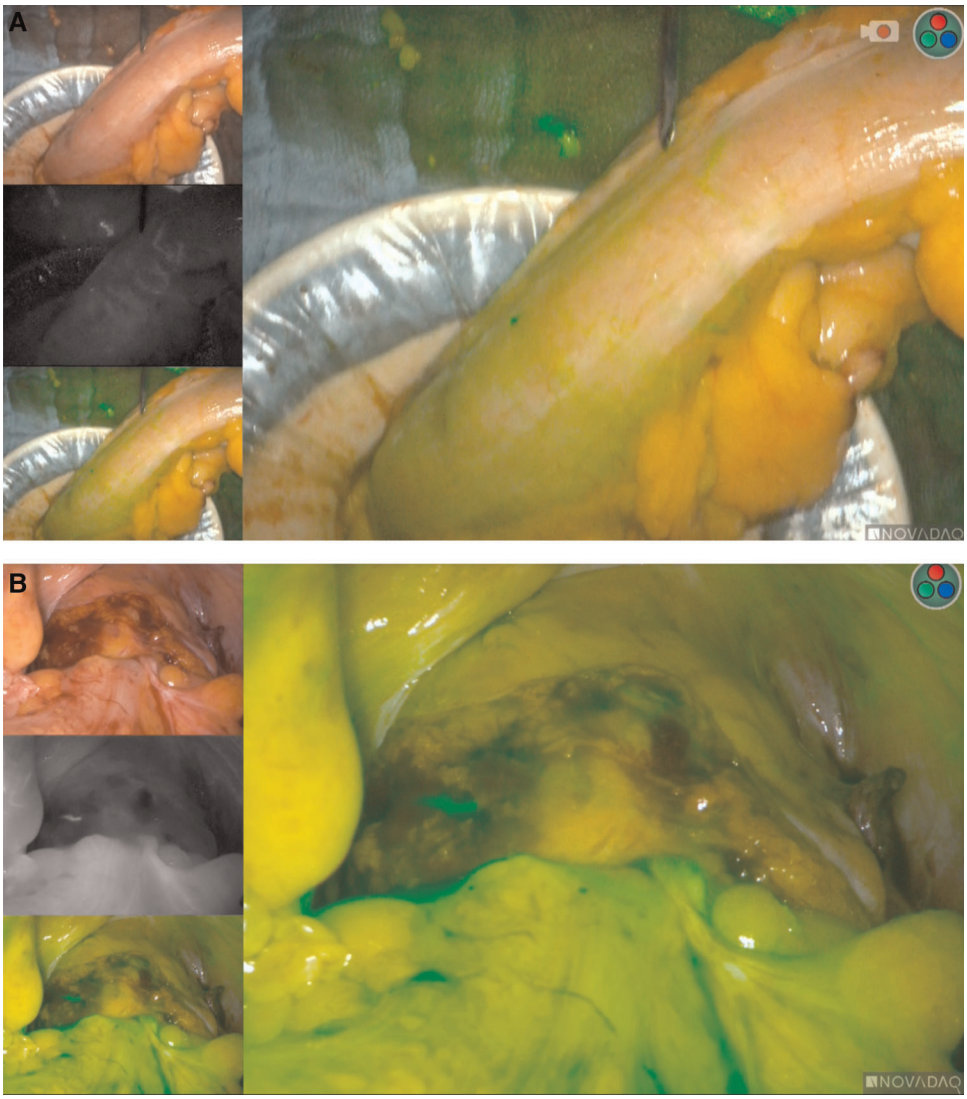

FIGURE 1
(A) real-time ICG fluorescence studies prior to bowel transection. (B) ICG-Studies during colorectal Anastomosis.

In a recently published retrospective study Neddermeyer et al. (1) compared the outcomes of two cohorts with and without ICG imaging prior to colorectal or coloanal anastomosis following left-sided colectomy or rectal resection with respect to the rate of AL. Patients with benign (mostly diverticular disease) and malignant pathologies (colorectal cancer) were included in this study. The primary endpoint was the rate of AL.

The transection line was chosen by the leading surgeon based on bowel coloration in white-light, pulsation of end vessels and peristaltic waves prior to bowel transection. Then ICG was injected for perfusion studies. Per institutional protocol 5 ml ICG (5 mg/ml) was injected to judge the perfusion of the proximal colon after the anvil has been implanted. The degree of fluorescence of the colon was compared and judged with that of the small bowel. Using this algorithm, the future anastomosis site at the proximal colon was deemed as poorly perfused and was corrected in 12.9% of cases following ICG- imaging. Overall, a statistically significant lower rate of AL was documented in the ICG group compared to the non-ICG cohort (1.4 vs. 14.5%).

This study, albeit its retrospective design aimed at investigating the rate of AL in cases with ICG vs. no-ICG and represents one of the first studies of its kind. The main result confirms the importance of ICG imaging as a simple and effective means of reducing the risk of AL in colorectal surgery. This finding is even more compelling considering the fact that a correction of the transection line was performed in

12.9% in the ICG group. If perfusion was the sole reason for AL in colorectal surgery, which is not, this finding would have meant 12.9% more cases of AL in the ICG cohort.

Despite the magnitude of the main finding from this study, some methodological aspects in the study by Neddermeyer et al. (1) may are worth discussing. My personal approach is to perform ICG prior to bowel transection (**Figure 1A**). This eliminates the need for correcting the transection line prior to anastomosis. Also, the perfusion of the distal bowel (usually the rectum) was not accessed by Neddermeyer et al. (1). The rectal stump could as well be poorly perfused, especially following radical resection for cancer. I therefore advocate a second perfusion study, again with 2.5 ml ICG just before complete closure of the stapling device (**Figures 1A,B**).

Despite different application methods, studying bowel perfusion objectively prior to creating an anastomosis and ensuring viable bowel perfusion is crucial in reducing the risk of AL. However, it must be clearly stated that, if sub-optimal perfusion was the only culprit, the rate of AL would be zero in all ICG cohorts. This emphasizes the multifactorial cause of AL. Nevertheless, real-time perfusion studies using ICG can be seen as an additional means of increasing patient's safety in colorectal surgery.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Neddermeyer M, Kanngießer V, Maurer E, Bartsch DK. Indocyanine green near-infrared fluoroangiography is a useful tool in reducing the risk of anastomotic leakage following left colectomy. *Front Surg.* (2022) 9. doi: 10.3389/fsurg.2022.850256

frontiers in Surgery

SYSTEMATIC REVIEW
published: 15 March 2022
doi: 10.3389/fsurg.2022.815753

Effect of Indocyanine Green Fluorescence Angiography on Anastomotic Leakage in Patients Undergoing Colorectal Surgery: A Meta-Analysis of Randomized Controlled Trials and Propensity-Score-Matched Studies

Gang Tang[1], *Donglin Du*[1], *Jie Tao*[2] *and Zhengqiang Wei*[1]*

[1] Department of Gastrointestinal Surgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China,
[2] Department of Hepatobiliary Surgery, Chongqing Medical University, Chongqing, China

OPEN ACCESS

Edited by:
Hans Martin Schardey,
Agatharied Hospital GmbH, Germany

Reviewed by:
Kazuhiro Hanazaki,
Kochi University, Japan
Gaetano Luglio,
University of Naples Federico II, Italy

***Correspondence:**
Zhengqiang Wei
1980900547@qq.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: 15 November 2021
Accepted: 15 February 2022
Published: 15 March 2022

Citation:
Tang G, Du D, Tao J and Wei Z (2022) Effect of Indocyanine Green Fluorescence Angiography on Anastomotic Leakage in Patients Undergoing Colorectal Surgery: A Meta-Analysis of Randomized Controlled Trials and Propensity-Score-Matched Studies. Front. Surg. 9:815753. doi: 10.3389/fsurg.2022.815753

Background: Meta-analyses have demonstrated that indocyanine green (ICG) can effectively prevent anastomotic leakage (AL) after colorectal surgery. However, recent evidence from large randomized controlled trial (RCT) has suggested that ICG fluorescence angiography does not reduce the incidence of AL in colorectal surgery. This study was conducted to evaluate the value of ICG for the prevention of AL following colorectal surgery.

Methods: Up to September 16, 2021, PubMed, Embase, China National Knowledge Infrastructure, Web of Science, Scopus, Cochrane Library, and VIP databases were searched for RCTs and propensity-score matched (PSM) studies evaluating the use of ICG for prevention of AL after colorectal surgery. Mean differences (MDs) or odds ratios (ORs) and 95% confidence intervals (CI) were calculated.

Results: Twenty studies (5 RCTs and 15 PSM studies) with a total of 5,125 patients were included. ICG did not reduce the reoperation rate (OR, 0.71; 95% CI, 0.38, 1.30), conversion rates (OR, 1.34; 95% CI, 0.65, 2.78), or mortality (OR, 0.50; 95% CI, 0.13, 1.85), but ICG did reduce the incidence of AL (OR, 0.46; 95% CI, 0.36, 0.59) and symptomatic AL (OR, 0.48; 95% CI, 0.33, 0.71), and reduced the length of hospital stay (MD,−1.21; 95% CI,−2.06,−0.35) and intraoperative blood loss (MD,−9.13; 95% CI,−17.52,−0.74). In addition, ICG use did not increase the incidence of total postoperative complications (OR, 0.93; 95% CI, 0.64, 1.35), postoperative ileus (OR, 1.26; 95% CI, 0.53, 2.97), wound infection (OR, 0.76; 95% CI, 0.44, 1.32), urinary tract infection (OR, 0.87; 95% CI, 0.30, 2.59), pulmonary infection (OR, 0.23; 95% CI, 0.04, 1.45), urinary retention (OR, 1.08; 95% CI, 0.23, 5.04), anastomotic bleeding (OR, 1.53; 95% CI, 0.27, 8.60), anastomotic stricture (OR, 0.74; 95% CI, 0.24, 2.29), or operative time (MD,−9.64; 95% CI,−20.28, 1.01).

Conclusions: ICG can effectively reduce the incidence of AL, without prolonging the operation time or increasing postoperative complications in colorectal surgery.

Systematic Review Registration: www.crd.york.ac.uk/prospero/#recordDetails, identifier: CRD42021279064.

Keywords: indocyanine green fluorescence angiography, anastomotic leakage, colorectal surgery, meta-analysis, randomized controlled trial

INTRODUCTION

Anastomotic leakage (AL) is one of the most destructive complications of colorectal surgery, which is associated with increased length of hospital stay, hospitalization costs, postoperative morbidity and mortality (1, 2). More worryingly, studies have shown that AL can also harm patient's long-term outcomes (3, 4). The incidence of AL after colorectal surgery is as high as 3–20%, especially in rectal surgery (5, 6). The risk factors for AL include male, age, preoperative chemotherapy and radiotherapy, high ASA score, advanced tumor, malnutrition, smoking, alcoholism, obesity, complications, intraoperative sepsis, immunosuppression, blood loss, prolonged operation time, perioperative blood transfusion, diverticutis and inadequate anastomotic blood supply (6, 7). Adequate blood perfusion is the key to good anastomotic healing (1). Therefore, detection of intestinal segments with poor blood supply during surgery can effectively reduce the incidence of AL. Traditionally, surgeons have assessed the blood supply of the anastomotic site primarily by the color of the intestinal mucosa, marginal bleeding, and palpable arterial pulses in the mesentery (8). However, this assessment strategy is susceptible to the clinician's experience and has low accuracy (9). Therefore, it is urgent to find reliable strategies to evaluate anastomotic perfusion.

Indocyanine green (ICG) is a water-soluble tricarbine compound that rapidly binds to plasma proteins when administered intravenously. ICG can absorb near-infrared light, and fluorescence angiography of ICG enables real-time evaluation of blood perfusion during surgery (10, 11). ICG has been widely used in various surgical procedures (12–14). Several cohort studies have suggested that ICG fluorescein angiography may be a potential strategy for preventing AL after colorectal surgery (15–19). However, baseline data from most cohort studies (15–19) do not match, which has stimulated the interest of investigators in conducting high-quality randomized controlled trials (RCTs) to investigate the effect of ICG on AL prevention. Two large and highly anticipated RCTs (20, 21) published recently have shown that ICG fluorescein angiography does not reduce the incidence of postoperative AL, nor does it reduce postoperative complications or mortality. Existing meta-analyses include either low-quality evidence or a limited number of RCTs, so the results of these meta-analyses (4, 5, 8, 22, 23) are not convincing. Propensity-score matched (PSM) study was able to eliminate baseline differences between the experimental and control groups, there is plenty of evidence that PSM studies are almost equivalent to RCTs in evaluating the efficacy of interventions (24).

In order to resolve the current conflicting findings and overcome the lack of high-quality evidence, we conducted a comprehensive literature search and analyzed data from RCTs and PSM studies to clarify the prophylactic effect of ICG on postoperative anastomotic leakage in colorectal surgery.

METHODS

Search Strategy

Our meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (25). We successfully registered this study protocol on PROSPERO (registration no. CRD42021279064). The Embase, China National Knowledge Infrastructure, Web of Science, Scopus, PubMed, Cochrane Library, and VIP databases were searched to identify RCTs and PSM studies evaluating the effect of ICG in colorectal surgery from inception to September 16, 2021. There are no language restrictions on retrieval. The search terms were: (stomal leak OR anastomotic leakage) AND (indocyanine green OR ICG). To identify potential relevant trials, the reference lists of all included articles were reviewed.

Study Selection

Literatures were screened by two independent authors according to the following inclusion criteria: (1) patients undergoing colorectal surgery; (2) intervention with ICG fluorescence angiography; (3) compare with surgeon's judgement visually; (4) the outcomes included any of the following: AL rate, symptomatic anastomotic leakage (SAL) rate, postoperative complications, conversion rates, length of postoperative hospital stay, reoperation rate, blood loss mortality and operative time. (5) the study design was RCT or PSM. Meeting abstract, letters, reviews, Studies involving non-human subjects, and case reports were excluded.

Data Extraction

The following data were extracted: first author, year, type of study, sample, age, gender, primary disease, type of surgery and outcomes. AL is defined as the communication between the intestinal lumen and the outside due to the defect of the integrity of the intestinal wall at the anastomosis (23). AL can be classified into three different grades: grade A, grade B and grade C. Grade A AL, also known as asymptomatic AL, referred to leakage detected only by imaging examination without clinical manifestations or abnormal laboratory examination. Grade B AL was defined as leakage that requires active intervention but does not require reoperation. Grade C AL was defined as leakage

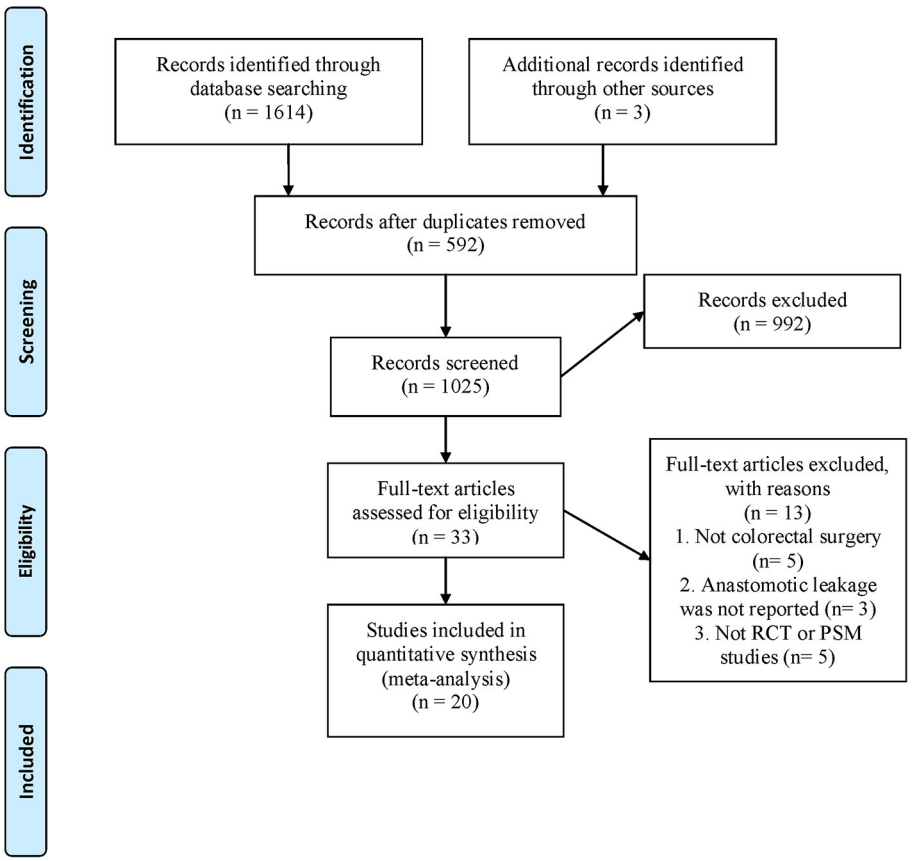

FIGURE 1 | Flow chart of literature search and screening.

requiring reoperation. Grade B and C AL were referred to as SAL (26). If some necessary information could not be extracted from the article, we would contact the corresponding author to try to obtain the missing data.

Quality Assessment

The Cochrane Collaboration tool for risk of bias was used to assess the risk of bias in RCTs, including the following domains: (a) sequence generation; (b) allocation concealment; (c) blinding of participants and personnel; (d) blinding of outcome assessment; (e) incomplete outcome data; (f) selective outcome reporting; (g) other potential sources of bias. We used the Newcastle-Ottawa score (NOS) to assess the risk of bias in PSM. Three methodological aspects (selection of participants, groups comparability, and outcome) were assessed using a 9-point scale. During the process of literature retrieval, screening, information extraction and quality assessment, any differences between the two authors (Tang and Du) were discussed and resolved with the third author (Tao).

Statistical Analysis

For dichotomous data, the odds ratio (OR) and 95% confidence intervals (CIs) was calculated. The mean difference (MD) associated 95% confidence intervals (CI) was calculated for continuous outcome data (27). Heterogeneity was assessed using the chi-square test and I^2. When $I^2 > 50\%$, heterogeneity was considered significant (28). We selected the random-effects model and carried out all statistical analyses taking into account heterogeneity within and between studies. Subgroup analysis was based on type of surgery (low anterior resection only) and type of study design (RCT only). To evaluate the impact of each study on the pooled effect size, sensitivity analysis was conducted using 1-study excluded approach. Analyses were conducted using Review Manager (RevMan) Version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration 2014; Copenhagen, Denmark). Funnel plots was performed to evaluate publication bias. $P < 0.05$ was considered statistically significant.

RESULTS

Selected Studies

A total of 1,617 relevant studies were identified by a preliminary search. After excluding 592 duplicate records, 1,025 articles were eliminated by reading titles and abstracts. Full-text evaluation was conducted in the remaining 33 studies, and finally, 20 studies (20, 21, 26, 29–45) that met the inclusion criteria were included (**Figure 1**).

TABLE 1 | Characteristics of 20 eligible studies.

Reference	Country	Study design	Sample	Age	Gender (M/ F)	Primary disease	Operation method	Fluorescence imaging system	ICG dose	Outcomes
Kudszus et al. (29)	Germany	PSM	I: 201 C: 201	I: 68 C: 69	I: 85/116 C: 85/116	Colorectal cancer	Colorectal resection	IC-View®, Pulsion Medical Systems AG, Munich, Germany	0.2–0.5 mg/kg	AL rate
Kin et al. (30)	USA	PSM	I: 173 C: 173	I: 58 C: 58	I: 93/80 C: 93/80	Malignant or benign disease	Colectomy or proctectomy	SPY Imaging System (Novadaq Technologies Inc, Bonita Springs, FL)	3ml	AL rate; Reoperation
Boni et al. (31)	Austria	PSM	I: 42 C: 38	I: 69 C: 67	I: 28/14 C: 22/16	Rectal cancer	Laparoscopic LAR	The Karl Storz image1 fluorescence system (Karl Storz, Tuttlingen, Germany)	0.2 mg/kg	AL rate; Reoperation; Postoperative morbidity; Mortality; Operative time; Postoperative hospital stay; No side effects or allergic reaction related to the injection of ICG.
Mizrahi et al. (32)	USA	PSM	I: 30 C: 30	I: 58 C: 58	I: 16/14 C: 18/12	Rectal cancer	Laparoscopic LAR	The PINPOINT^{TM} Endoscopic Fluorescence Imaging System (Novadaq, Toronto, Ontario, Canada)	0.1–0.3 mg/kg	AL rate; Postoperative morbidity; Mortality; Operative time; Conversion rates; No side effects or allergic reaction related to the injection of ICG
Pen et al. (33)	China	RCT	I: 63 C: 82	I: 61 C: 62	I: 36/27 C: 40/42	Colorectal cancer	Colorectal resection	Fluorescent laparoscopic system (Japan,Olympus Corporation)	NA	AL rate; Mortality; No side effects or allergic reaction related to the injection of ICG
Wada et al. (34)	Japan	PSM	I: 34 C: 34	I: 68 C: 67	I: 20/14 C: 24/10	Rectal cancer	Laparoscopic LAR	NIR camera system (PDE-neo System; Hamamatsu Photonics K.K., Hamamatsu, Japan)	5 mg	AL rate; Postoperative morbidity; Mortality; No adverse events related to ICG were observe.
Ishii et al. (35)	Japan	PSM	I: 87 C: 87	I: 64 C: 65	I: 49/38 C: 50/37	Colorectal cancer	Laparoscopic colorectal resection	NA	5 mg	AL rate; No adverse events related to ICG were observe.
Kojima et al. (36)	Japan	PSM	I: 27 C: 27	I: 72 C: 70	I: 15/12 C: 14/13	Colorectal cancer	Laparoscopic left-sided colorectal resection	The LSCI instrument (moorFLPI-2; Moor Instruments, Axminster, UK)	NA	AL rate; Postoperative morbidity; Mortality; Conversion rates; Postoperative hospital stay
Spinelli et al. (37)	Switzerland	PSM	I: 32 C: 32	I: 39 C: 46	I: 21/11 C: 22/10	Malignant or benign disease	LAR	PINPOINT endoscopic fluorescence imaging system (Stryker, Kalamazoo, Michigan, USA),	0.1–0.2 mg/kg	AL rate; Postoperative morbidity; Conversion rates; Operative time; Postoperative hospital stay; Reoperation

(Continued)

TABLE 1 | Continued

Reference	Country	Study design	Sample	Age	Gender (M/ F)	Primary disease	Operation method	Fluorescence imaging system	ICG dose	Outcomes
Watanabe et al. (45)	Japan	PSM	I: 211 C: 211	I: 66 C: 66	I: 128/83 C: 131/80	Rectal cancer	Laparoscopic LAR	Karl Storz (D-Light P; Tuttlingen, Germany) and the Stryker Corporation (1588 AIM Platform; Michigan, USA)	0.25 mg/kg	AL rate; Postoperative morbidity; Mortality; Operative time; Postoperative hospital stay; Reoperation; Blood loss
Losurdoet al. (39)	Italy	PSM	I: 75 C: 75	I: 71 C: 68	I: 41/34 C: 49/26	Rectal and left colon cancer	Rectal and left colon cancer surgery	A full HD camera system (Karl Storz Image 1-Professional Image Enhancement System-SPIESTtm, Karl Storz,Germany)	0.2 mg/kg	AL rate; Operative time
Alekseev et al. (40)	Russia	RCT	I: 187 C: 190	I: 63 C: 63	I: 92/95 C: 92/98	Malignant or benign sigmoid or rectal neoplasms	Sigmoid and rectal resection	Laparoscopic system (KARL STORZ GmbH &Co. KG, Tuttlingen, Germany) with light source (D-LIGHT P SCB, KARL STORZ)	0.2 mg/kg	AL rate; Postoperative morbidity; Mortality; Operative time; Postoperative hospital stay; Reoperation; Blood loss
De Nardi et al. (20)	Italy	RCT	I: 118 C: 122	I: 66 C: 65	I: 60/28 C: 66/56	Malignant or benign disease	Laparoscopic left-sided colon and rectal resection	Camera equipped with a xenon light source providing both NIR wavelength and standard light was employed (KARL STORZ GmbH & Co. KG, Tuttlin gen, Germany)	0.3 mg/kg	AL rate; Postoperative morbidity; Mortality; Reoperation; Operative time; Postoperative hospital stay; No adverse events related to ICG were observe
Foo et al. (26)	China	PSM	I: 253 C: 253	I: 67 C: 67	I: 166/87 C: 163/90	Malignant or benign disease	Left-sided colorectal resections	The SPY Elite System (Stryker, USA), Pinpoint System (Stryker, USA)	5–7.5 mg	AL rate; Operative time; Blood loss
Hasegawa et al. (38)	Japan	PSM	I: 141 C: 279	I: 63 C: 63	I: 99/42 C: 203/76	Rectal cancer	Laparoscopic LAR	The IMAGE1 S^{TM} system (Karl Storz SE & Co. KG, Tuttlingen, Germany), 1588 Advanced Imaging Modalities (AIM) Platform and SPY Fluorescence technology (Stryker, Kalamazoo, MI, USA), or HyperEye Medical System Handy (Mizuho Medical Co. Ltd., Tokyo, Japan)	5 mg	AL rate; Operative time; Blood loss; Mortality

(Continued)

TABLE 1 | Continued

Reference	Country	Study design	Sample	Age	Gender (M/ F)	Primary disease	Operation method	Fluorescence imaging system	ICG dose	Outcomes
Wojcik et al. (41)	France	PSM	I: 42 C: 42	I: 67 C: 69	I: 29/13 C: 29/13	Left-sided colonic or rectal cancer	Left colectomy or anterior resection	NIR light images (FLUOBEAM; Fluoptics, Grenoble, France) or on fusion images merging NIR and standard white light images (PINPOINT; Stryker, Kalamazoo, Michigan, USA)	0.1 mg/kg	AL rate; Postoperative morbidity; Mortality; Operative time; Postoperative hospital stay; Conversion rates
Jafari et al. (21)	USA	RCT	I: 178 C: 169	I: 57 C: 57	I: 104/74 C: 99/70	Rectal cancer	LAR	PINPOINT and/or SPY Elite near infrared range fluorescence imaging (Stryker, Kalamazoo, MI)	7.5 mg	AL rate; Postoperative morbidity; Mortality; Conversion rates
Watanabe et al. (42)	Japan	PSM	I: 370 C: 370	I: 72 C: 72	I: 187/183 C: 187/183	Colon Cancer	Colon cancer surgery	The Stryker Corporation (1588 AIM Platform; MI, USA), Olympus Medical Systems Corporation (VISERA ELITE II, Tokyo, Japan) and Karl Storz (D-Light P; Tuttlingen, Germany).	0.25 mg/kg	AL rate; Postoperative morbidity; Mortality; Operative time; Reoperation; Postoperative hospital stay; Blood loss
Guocong et al. (43)	China	RCT	I: 130 C: 130	I: 68 C: 67	I: 67/63 C: 71/59	Colorectal cancer	Laparoscopic colorectal resection	Fluoroscopy (optomedic-2100)	NA	AL rate; Mortality; Operative time; Postoperative hospital stay; Blood loss
Yanagita et al. (44)	Japan	PSM	I: 93 C: 93	I: N C: N	I: N C: N	Left-sided colon or rectal cancer	Left-sided colon or rectal cancer surgery	near-infrared excitation light (we used mainly Hyper Eye Medical Systems: Mizuho Medical Co., Ltd, Nagoya, Japan and/or IMAGE 1 SPIES^{TM}, KARL STORZ SE & Co. KG, Tuttlingen, Germany)	0.1 mg/kg	AL rate; Operative time; Blood loss; Conversion rates

AL, anastomotic leakage; C, control group; F, Female; I, intervention group; M, Male; LAR, low anterior resection; PSM, propensity-score matched study; N, not available; RCT, randomized controlled trial; USA, the United States of America.

TABLE 2 | Outcome of assessment of the quality of non-randomized studies using the Newcastle-Ottawa scale.

Reference	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not presented at the start		Assessment of outcome	Follow-up long enough	Adequacy of follow up	
Kudszus et al. (29)	*	-	*	*	**	*	-	-	6/9
Kin et al. (30)	*	-	*	*	**	*	*	*	8/9
Boni et al. (31)	*	-	*	*	**	*	-	-	6/9
Mizrahi et al. (32)	*	-	*	*	**	*	*	*	8/9
Wada, et al. (34)	*	-	*	*	**	*	-	*	7/9
Ishii et al. (35)	*	*	*	*	**	*	-	*	8/9
Kojima et al. (36)	*	-	*	*	**	*	-	*	7/9
Spinelli et al. (37)	*	-	*	*	**	*	*	*	8/9
Watanabe et al. (45)	*	*	*	*	**	*	-	*	8/9
Losurdo et al. (39)	*	-	*	*	**	*	-	*	7/9
Foo et al. (26)	*	-	*	*	**	*	*	*	8/9
Hasegawa et al. (38)	*	*	*	*	**	*	-	*	8/9
Wojcik et al. (41)	*	*	*	*	**	*	-	*	8/9
Watanabe et al. (42)	*	*	*	*	**	*	-	*	8/9
Yanagita et al. (44)	*	-	*	*	**	*	-	*	7/9

*A single asterisk (*) indicates 1 score, ** indicates 2 score, and dash (-) indicates 0 score.*

Study Characteristics

Twenty studies (20, 21, 26, 29–45), involving 5,125 participants from 9 countries (United States, Japan, Switzerland, Russia, Italy, France, China, Austria, and Germany), were included in our meta-analysis. Fifteen of the eligible studies (26, 29–32, 34–39, 41, 42, 44, 45) were PSM, while five were RCTs (20, 21, 33, 40, 43). The sample size varied from 54 to 740 subjects. Seven studies (21, 31, 32, 34, 37, 38, 45) performed low anterior resection and the remaining thirteen (20, 26, 29, 30, 33, 35, 36, 38–44) performed colorectal surgery. Follow-up ranged from 30 to 90 days. Most of the studies (21, 29, 31–36, 38, 39, 41–45) included patients only confined to malignant colorectal disease, whereas, five studies (20, 26, 30, 37, 40) included patients with both malignant and benign colorectal disease. Details of the 20 eligible studies (20, 21, 26, 29–45) are summarized in **Table 1**.

Quality Assessment

Fifteen trials were evaluated to be of good quality based on the NOS (**Table 2**) with scores of 6 and more. The risk of bias of RCTs is shown in **Figure 2**. The 5 RCTs were assessed to be of low risk.

Meta-Analysis

AL Rate

AL rate was reported in all 20 studies (20, 21, 26, 29–45). Compared with the control group, the incidence of AL was significantly reduced in the ICG group (OR, 0.46; 95% CI, 0.36, 0.59; $P < 0.00001$). No significant heterogeneity was observed ($P = 0.44$; $I^2 = 1\%$) (**Figure 3**). The results of subgroup analysis showed that ICG could effectively reduce the incidence of AL in both RCTs (20, 21, 33, 40, 43) (OR, 0.55; 95% CI, 0.34, 0.88; $P = 0.01$; $I^2 = 17\%$) (**Table 3**) and PSM studies (26, 29–32, 34–39, 41, 42, 44, 45) (OR, 0.41; 95% CI, 0.30, 0.56; $P < 0.00001$; $I^2 = 0\%$) (**Table 3**). When subgroups were performed according to surgical methods, ICG could effectively reduce the incidence of AL regardless of colorectal surgery (20, 26, 29, 30, 33, 35, 36, 38–44) (OR, 0.45; 95% CI, 0.34, 0.61; $P < 0.00001$; $I^2 = 0\%$) (**Table 3**) or low anterior resection (21, 31, 32, 34, 37, 38, 45) (OR, 0.45; 95% CI, 0.26, 0.78; $P = 0.004$; $I^2 = 21\%$) (**Table 3**).

Ten studies (20, 26, 31, 34, 36, 37, 39, 40, 44, 45) described the incidence of SAL. Data from RCTs and PSM studies showed that ICG was associated with a lower risk of SAL, with low heterogeneity between studies (OR, 0.48; 95% CI, 0.33, 0.71; $P = 0.0002$; $I^2 = 0\%$) (**Figure 4**).

Postoperative Complications

Postoperative complications were described in 11 studies (20, 21, 31, 32, 34, 36, 37, 40–42, 45). The total effect size indicated that intraoperative ICG fluorescence angiography did not reduce the incidence of total complications, with significant heterogeneity between studies (OR, 0.93; 95% CI, 0.64, 1.35; $P = 0.70$; $I^2 = 64\%$) (**Figure 5**). When subgroup analysis was performed by study

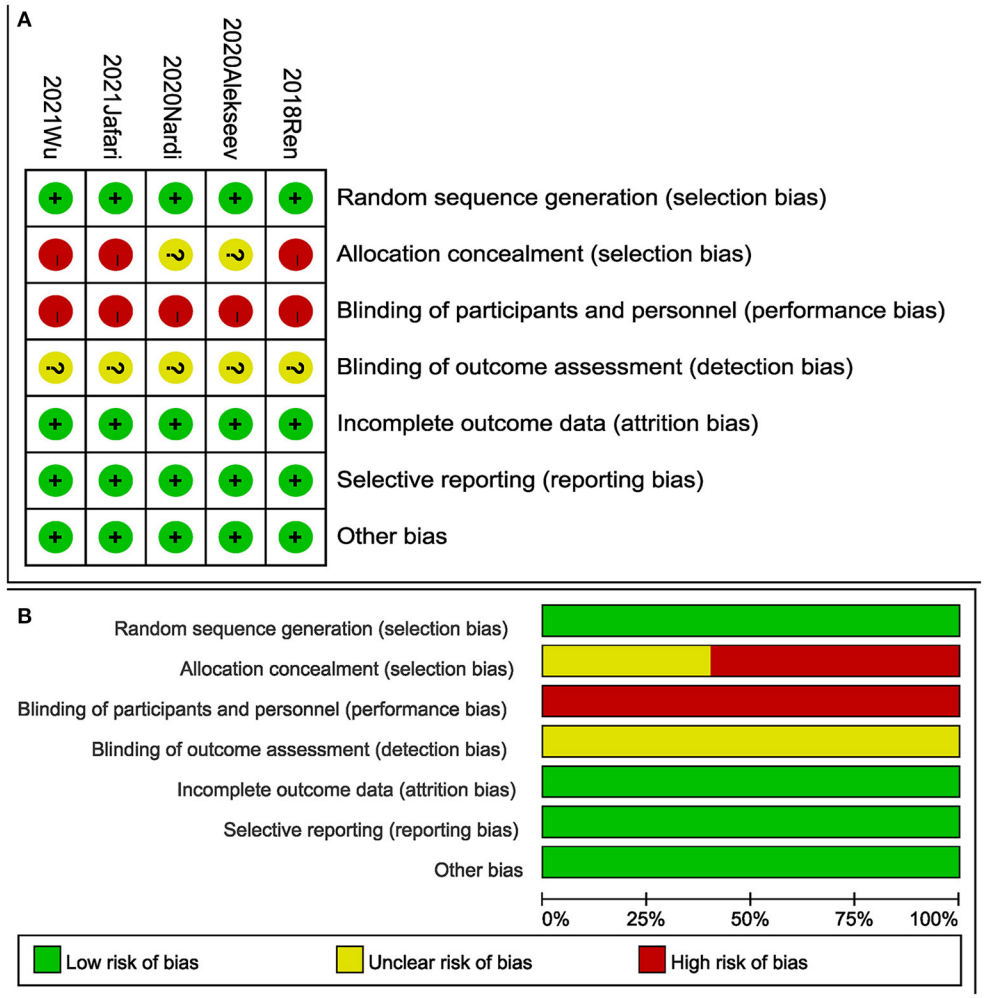

FIGURE 2 | Risk of bias for each included study. **(A)** Risk of bias summary. **(B)** Risk of bias graph.

type, the combined effect size of both RCTs (20, 21, 40) (OR, 0.74; 95% CI, 0.53, 1.02; $P = 0.06$) (**Table 3**) and PSM studies (31, 32, 34, 36, 37, 41, 42, 45) (OR, 1.10; 95% CI, 0.62, 1.95; $P = 0.75$) (**Table 3**) showed that ICG did not increase the incidence of total postoperative complications, and heterogeneity in the RCTs subgroup was significantly reduced ($P = 0.50$; $I^2 = 0\%$) (**Table 3**).

Postoperative Ileus

Evidence from a combination of 7 studies (20, 21, 31, 32, 34, 35, 40) suggests that ICG does not reduce the incidence of postoperative ileus, and no significant heterogeneity was observed between studies (OR, 1.26; 95% CI, 0.53, 2.97; $P = 0.60$; $I^2 = 41\%$) (**Figure 6A**). When subgroup analysis was based on study type, both RCTs (20, 21, 40) (OR, 1.06; 95% CI, 0.32, 3.54; $P = 0.93$; $I^2 = 58\%$) (**Table 3**) and PSM studies (31, 32, 34, 35) (OR, 1.93; 95% CI, 0.57, 6.50; $P = 0.29$; $I^2 = 7\%$) (**Table 3**) showed that ICG did not reduce the incidence of postoperative intestinal obstruction. There was no significant heterogeneity between subgroups ($P = 0.49$; $I^2 = 0\%$) (**Table 3**).

Wound Infection

Postoperative wound infection was reported in 8 studies (20, 31, 32, 34, 36, 40, 42, 45) (2 RCTs, 6 PSM studies), ICG did not reduce the risk of postoperative wound infection, and there was no significant heterogeneity between studies (OR, 0.76; 95% CI, 0.44, 1.32; $P = 0.33$; $I^2 = 0\%$) (**Figure 6B**). Both RCTs (20, 40) (OR, 0.52; 95% CI, 0.15, 1.89; $P = 0.32$; $I^2 = 16\%$) (**Table 3**) and PSM studies (31, 32, 34, 36, 42, 45) (OR, 0.84; 95% CI, 0.45, 1.57; $P = 0.58$; $I^2 = 0\%$) (**Table 3**) showed that ICG does not reduce the incidence of postoperative wound infection. Subgroup analysis showed that ICG did not reduce the incidence of postoperative wound infection during colorectal surgery (20, 36, 40, 42) (OR, 0.60; 95% CI, 0.32, 1.15; $P = 0.13$; $I^2 = 0\%$) (**Table 3**) or low anterior resection (31, 32, 34, 45) (OR, 1.38; 95% CI, 0.49, 3.89; $P = 0.55$; $I^2 = 0\%$) (**Table 3**).

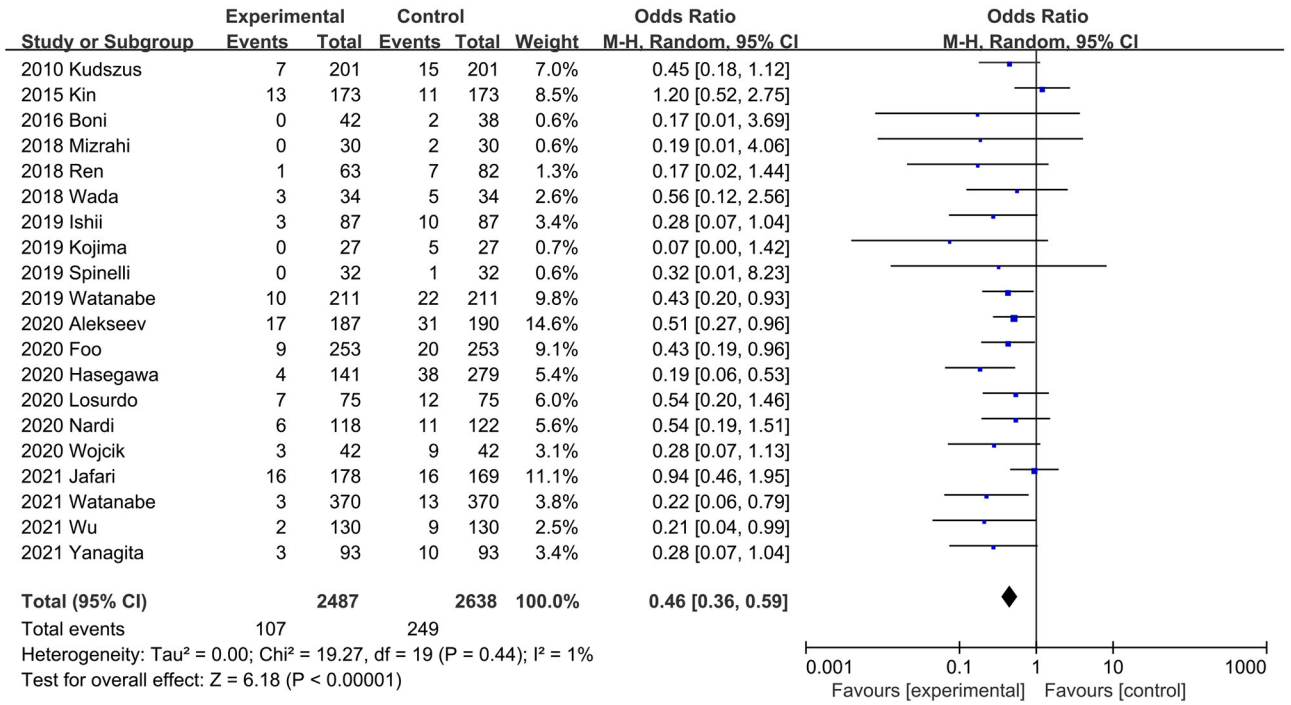

FIGURE 3 | Effect of indocyanine green on anastomotic leakage rate.

Urinary Tract Infection

Three studies (20, 31, 34) reported the urinary tract infections of both groups, and the difference between the ICG group and control group was not statistically significant (OR, 0.87; 95% CI, 0.30, 2.59; $P = 0.81$) (**Figure 6C**). No significant heterogeneity was observed ($P = 0.60$; $I^2 = 0\%$) (**Figure 6C**).

Pulmonary Infection

Pulmonary infection was reported in two studies (20, 34). Results of the meta-analysis showed that ICG did not reduce the incidence of pulmonary infection (OR, 0.23; 95% CI, 0.04, 1.45; $P = 0.12$) (**Figure 6D**), and there was no significant heterogeneity between studies ($P = 0.68$; $I^2 = 0\%$) (**Figure 6D**).

Urinary Retention

A combined dataset of 517 participants from three studies (31, 32, 40) showed that ICG did not reduce the risk of postoperative urinary retention (OR, 1.08; 95% CI, 0.23, 5.04; $P = 0.92$) (**Figure 7A**). No significant heterogeneity was observed ($P = 0.26$; $I^2 = 25\%$) (**Figure 7A**).

Anastomotic Bleeding

Four studies (20, 34, 42, 45) reported the rate of anastomotic bleeding. Intraoperative ICG fluorescence angiography did not reduce (OR, 1.53; 95% CI, 0.27, 8.60; $P = 0.63$) (**Figure 7B**) the incidence of anastomotic bleeding, and there was no significant heterogeneity ($P = 0.15$; $I^2 = 43\%$) (**Figure 7B**) between studies.

Anastomotic Stricture

Two trials (20, 26) reported the Incidence of anastomotic stricture. There was no significant difference in the Incidence of anastomotic stricture between the ICG and the control groups (OR, 0.74; 95% CI, 0.24, 2.29; $P = 0.61$) (**Figure 7C**). No significant heterogeneity ($P = 0.61$; $I^2 = 0\%$) (**Figure 7C**) was observed.

Reoperation Rates

Eight studies (20, 29–31, 37, 40, 42, 45) assessed the effect of ICG on postoperative reoperation rates. The combined effect size showed a lower reoperation rate in the ICG group than in the control group, but the difference was not statistically significant (OR, 0.71; 95% CI, 0.38, 1.30; $P = 0.26$; $I^2 = 39\%$) (**Figure 8A**). Subgroup analysis showed that ICG did not reduce reoperation rate in both RCTs (20, 40) (OR, 1.29; 95% CI, 0.59, 2.84; $P = 0.52$; $I^2 = 0\%$) (**Table 3**) and PSM studies (29–31, 37, 42, 45) (OR, 0.52; 95% CI, 0.26, 1.07; $P = 0.08$; $I^2 = 32\%$) (**Table 3**).

Conversion Rates

Six studies (21, 32, 36, 37, 41, 44) mentioned conversion rates. ICG did not increase conversion rates during surgery compared with the control group (OR, 1.34; 95% CI, 0.65, 2.78; $P = 0.42$) (**Figure 8B**), with no significant heterogeneity between studies ($P = 0.69$; $I^2 = 0\%$) (**Figure 8B**).

TABLE 3 | Summary of results from all subgroup analyses.

Outcome	Subgrouped by	The number of studies	Effect size	95%CI	I^2 (%)	P for between subgroup heterogeneity
AL	Surgery type	-	-	-	-	0.27
	Colorectal resection	13	0.45	0.34, 0.61	0	-
	Low anterior resection	7	0.45	0.26, 0.78	21	-
	Study type	-	-	-	-	0.32
	PSM	15	0.41	0.30, 0.56	0	-
	RCT	5	0.55	0.34, 0.88	17	-
SAL	Surgery type	-	-	-	-	0.66
	Colorectal resection	6	0.51	0.32, 0.82	4	-
	Low anterior resection	4	0.43	0.22, 0.82	0	-
	Study type	-	-	-	-	0.08
	PSM	8	0.39	0.25, 0.61	0	-
	RCT	2	0.81	0.41, 1.61	0	-
Postoperative morbidity	Surgery type	-	-	-	-	0.16
	Colorectal resection	5	0.77	0.56, 1.05	10	-
	Low anterior resection	6	1.31	0.66, 2.61	78	-
	Study type	-	-	-	-	0.23
	PSM	8	1.10	0.62, 1.95	73	-
	RCT	3	0.74	0.53, 1.02	0	-
Postoperative ileus	Surgery type	-	-	-	-	0.46
	Colorectal resection	3	1.82	0.65, 5.11	0	-
	Low anterior resection	4	1.00	0.29, 3.44	51	-
	Study type	-	-	-	-	0.49
	PSM	4	1.93	0.57, 6.50	7	-
	RCT	3	1.06	0.32, 3.54	58	-
Wound infection	Surgery type	-	-	-	-	0.19
	Colorectal resection	4	0.60	0.32, 1.15	0	-
	Low anterior resection	4	1.38	0.49, 3.89	0	-
	Study type	-	-	-	-	0.52
	PSM	6	0.84	0.45, 1.57	0	-
	RCT	2	0.52	0.15, 1.89	16	-
Anastomotic bleeding	Surgery type	-	-	-	-	0.36
	Colorectal resection	2	0.59	0.02, 19.75	73	-
	Low anterior resection	2	3.72	0.60, 22.96	0	-
Reoperation	Surgery type	-	-	-	-	0.30
	Colorectal resection	5	0.82	0.42, 1.58	47	-
	Low anterior resection	3	0.35	0.08, 1.51	14	-
	Study type	-	-	-	-	0.10
	PSM	6	0.52	0.26, 1.07	32	-
	RCT	2	1.29	0.59, 2.84	0	-
Conversion rates	Surgery type	-	-	-	-	0.98
	Colorectal resection	3	1.35	0.16, 11.78	21	-
	Low anterior resection	3	1.32	0.60, 2.91	0	-
Mortality	Surgery type	-	-	-	-	0.48
	Colorectal resection	4	0.36	0.07, 1.77	0	-
	Low anterior resection	2	0.98	0.10, 9.54	0	-
	Study type	-	-	-	-	0.54
	PSM	3	0.75	0.12, 4.84	0	-
	RCT	3	0.33	0.05, 2.10	0	-

(Continued)

TABLE 3 | Continued

Outcome	Subgrouped by	The number of studies	Effect size	95%CI	I^2 (%)	P for between subgroup heterogeneity
Operative time	Surgery type	-	-	-	-	0.03
	Colorectal resection	7	1.78	−2.48, 6.03	23	-
	Low anterior resection	5	−24.18	−47.85,−0.52	91	-
	Study type	-	-	-	-	0.09
	PSM	9	−14.45	−31.52, 2.62	91	-
	RCT	3	0.94	−4.06, 5.95	23	-
Blood loss	Surgery type	-	-	-	-	0.68
	Colorectal resection	4	−3.87	−7.54,−0.21	54	-
	Low anterior resection	2	−18.60	−89.49, 52.29	86	-
	Study type	-	-	-	-	0.63
	PSM	4	−10.20	−43.38, 22.99	90	-
	RCT	2	−1.97	−4.81, 0.87	0	-
Postoperative hospital stay	Surgery type	-	-	-	-	0.49
	Colorectal resection	7	−1.10	−2.05,−0.16	86	-
	Low anterior resection	2	−1.78	−3.46,−0.10	0	-
	Study type	-	-	-	-	0.32
	PSM	6	−1.67	−2.90,−0.43	65	-
	RCT	3	−0.61	−2.28, 1.05	87	-

AL, anastomotic leakage; LAR, low anterior resection; PSM, propensity-score matched study; RCT, randomized controlled trial; SAL, Symptomatic anastomotic leakage.

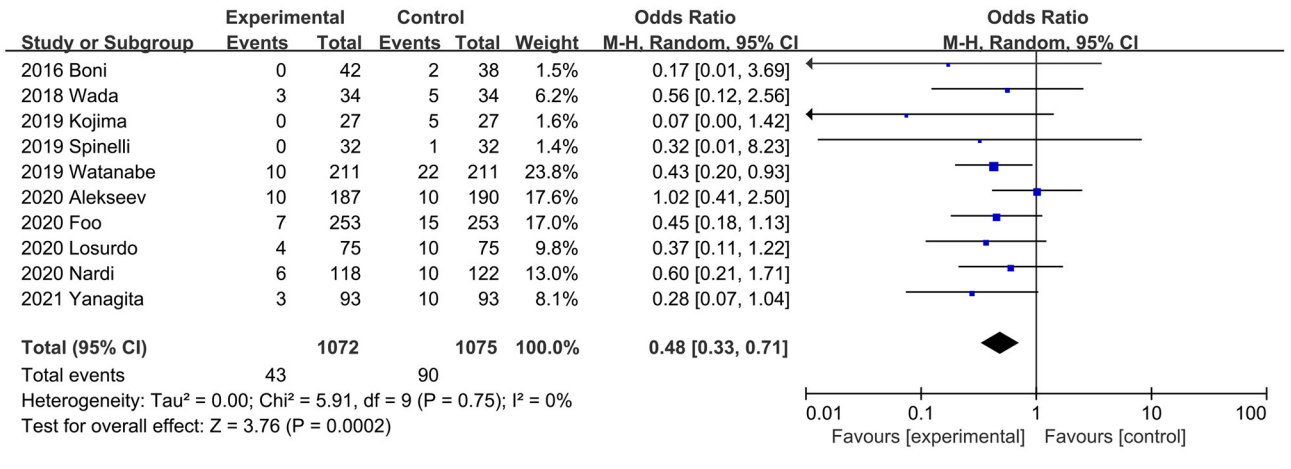

FIGURE 4 | Effect of indocyanine green on symptomatic anastomotic leakage rate.

Mortality

Postoperative mortality was reported in 11 studies (20, 21, 31–34, 36, 38, 42, 43, 45). There was no significant difference in perioperative mortality (OR, 0.50; 95% CI, 0.13, 1.85; $P = 0.30$) (**Figure 8C**) between the ICG group and the control group, and no significant heterogeneity ($P = 0.91$; $I^2 = 0\%$) (**Figure 8C**) was observed between studies.

Operative Time

Twelve studies (20, 26, 31, 32, 37–43, 45) compared the operative time between the ICG group and the control group. The total effect size showed that intraoperative ICG fluorescein angiography did not increase the operative time (MD,−9.64; 95% CI,−20.28, 1.01; $P = 0.08$) (**Figure 9A**), and significant heterogeneity was observed between studies ($P < 0.00001$; $I^2 = 90\%$) (**Figure 9A**). Subgroup analysis based on study type found that heterogeneity significantly decreased between RCTs (20, 40, 43) ($P = 0.27$; $I^2 = 23\%$) (**Table 3**), and heterogeneity was significant ($P = 0.09$; $I^2 = 65.2\%$) (**Table 3**) between subgroups.

Blood Loss

Six studies (26, 38, 40, 42, 43, 45) reported the blood loss during surgery. ICG can effectively reduce the blood loss during surgery (MD,−9.13; 95% CI,−17.52,−0.74; $P = 0.03$)

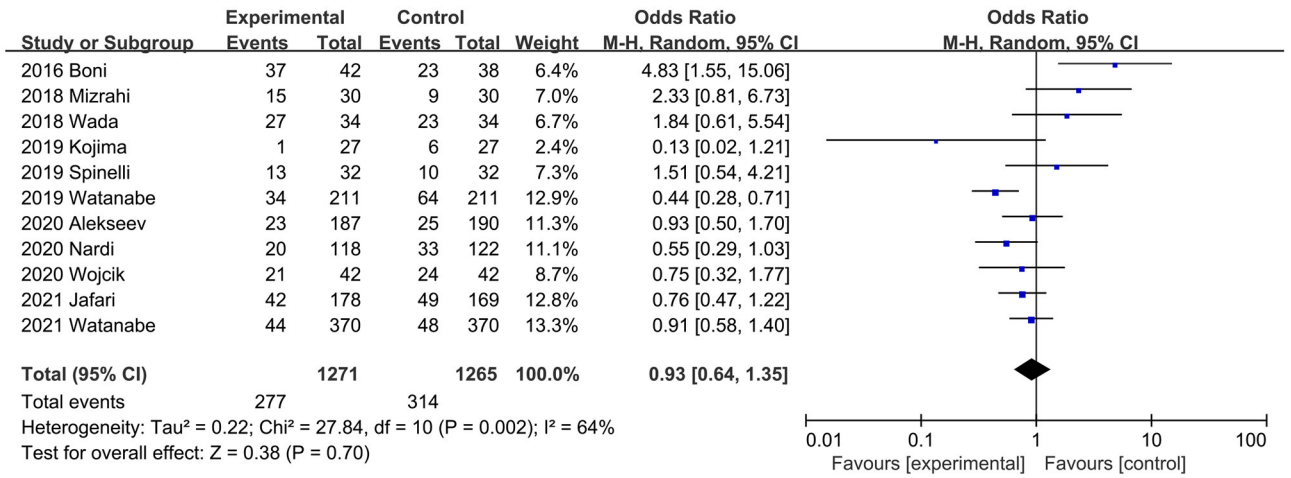

FIGURE 5 | Effect of indocyanine green on total postoperative complications rate.

(**Figure 9B**). Significant heterogeneity ($P < 0.00001$; $I^2 = 81\%$) (**Figure 9B**) was observed between these studies. When subgroup analysis was performed by type of surgery, intraoperative ICG fluorescein angiography did not reduce the amount of blood loss during low anterior resection (38, 45) (MD,−18.60; 95% CI,−89.49, 52.29; $P = 0.61$; $I^2 = 86\%$) (**Table 3**), but it did reduce the blood loss during colorectal surgery (26, 40, 42, 43) (MD,−3.87; 95% CI,−7.54,−0.21; $P = 0.04$; $I^2 = 54\%$) (**Table 3**).

Length of Postoperative Hospital Stay

Nine studies (20, 31, 36, 37, 40–43, 45) reported length of postoperative hospital stay. Meta-analysis showed that intraoperative ICG fluorescence angiography could effectively shorten postoperative hospital stay (MD,−1.21; 95% CI,−2.06,−0.35; $P = 0.06$) (**Figure 9C**), with significant heterogeneity among 9 studies ($P < 0.00001$; $I^2 = 82\%$) (**Figure 9C**). When subgroup analysis was performed based on study type, benefits of ICG for shorter length of hospital stay were observed only in the PSM studies (31, 36, 37, 41, 42, 45) (MD,−1.67; 95% CI,−2.90,−0.43; $P = 0.008$; $I^2 = 65\%$) (**Table 3**).

Sensitivity Analysis

The results of the sensitivity analysis showed that no single trial could affect the total effect size of AL rate, SAL rate, postoperative complications, postoperative ileus, wound infection, urinary tract infection, pulmonary infection, urinary retention, anastomotic bleeding, anastomotic stricture, conversion rates, reoperation rate, length of postoperative hospital stay, mortality and operative time. The study of Watanabe et al. (42) (MD,−4.90; 95% CI,−33.76, 23.97; $P = 0.74$; $I^2 = 88\%$) and the study of Zhang et al. (8) (MD,−6.55; 95% CI,−33.83, 20.72; $P = 0.64$; $I^2 = 87\%$) significantly affected the effect size of blood loss during surgery.

Publication Bias

The funnel plot of AL rate, SAL rate, postoperative complications and blood loss during surgery reveals a roughly symmetrical distribution of studies (**Figure 10**).

DISCUSSION

AL has increased the medical burden of patients and caused destructive results (4), so it is necessary to find effective strategies to reduce the risk of AL after colorectal surgery. In 2010, Kudszus et al. (29) first reported that ICG reduced the occurrence of AL after colorectal surgery by 4%. Skrovina et al. (18) also confirmed that ICG fluorescence angiography may be a potential strategy for preventing AL. Impellizzeri et al. (16) found that ICG fuorescence angiography is associated with a lower risk of AL after colorectal cancer surgery. The evidence from the above clinical studies well supports our conclusions. However, in Dinallo et al. study (46), the incidence of AL after colorectal surgery was 1.3% in both the ICG group and the non-ICG group. The low incidence of AL in the study may mask the true effect of ICG. In addition, almost all recent meta-analyses (4, 8, 22, 23) on this topic showed that intraoperative ICG fluorescence angiography could reduce the incidence of postoperative AL.

Our meta-analysis showed that ICG can effectively reduce the AL rate, SAL rate, blood loss, and hospital stays, without prolonging the operation time or increasing postoperative complications in colorectal surgery. The results of subgroup analysis indicated that both evidence from RCTs and PSM studies evidence indicated that ICG fluorescence angiography was an effective strategy for reducing postoperative AL. Although the incidence of asymptomatic AL is as high as 14%, the use of contrast agents to detect asymptomatic AL in post-colorectal surgery patients is not a routine strategy in clinical practice (4). Asymptomatic AL has little damage to the prognosis of patients, and almost all asymptomatic AL do not need intervention. In

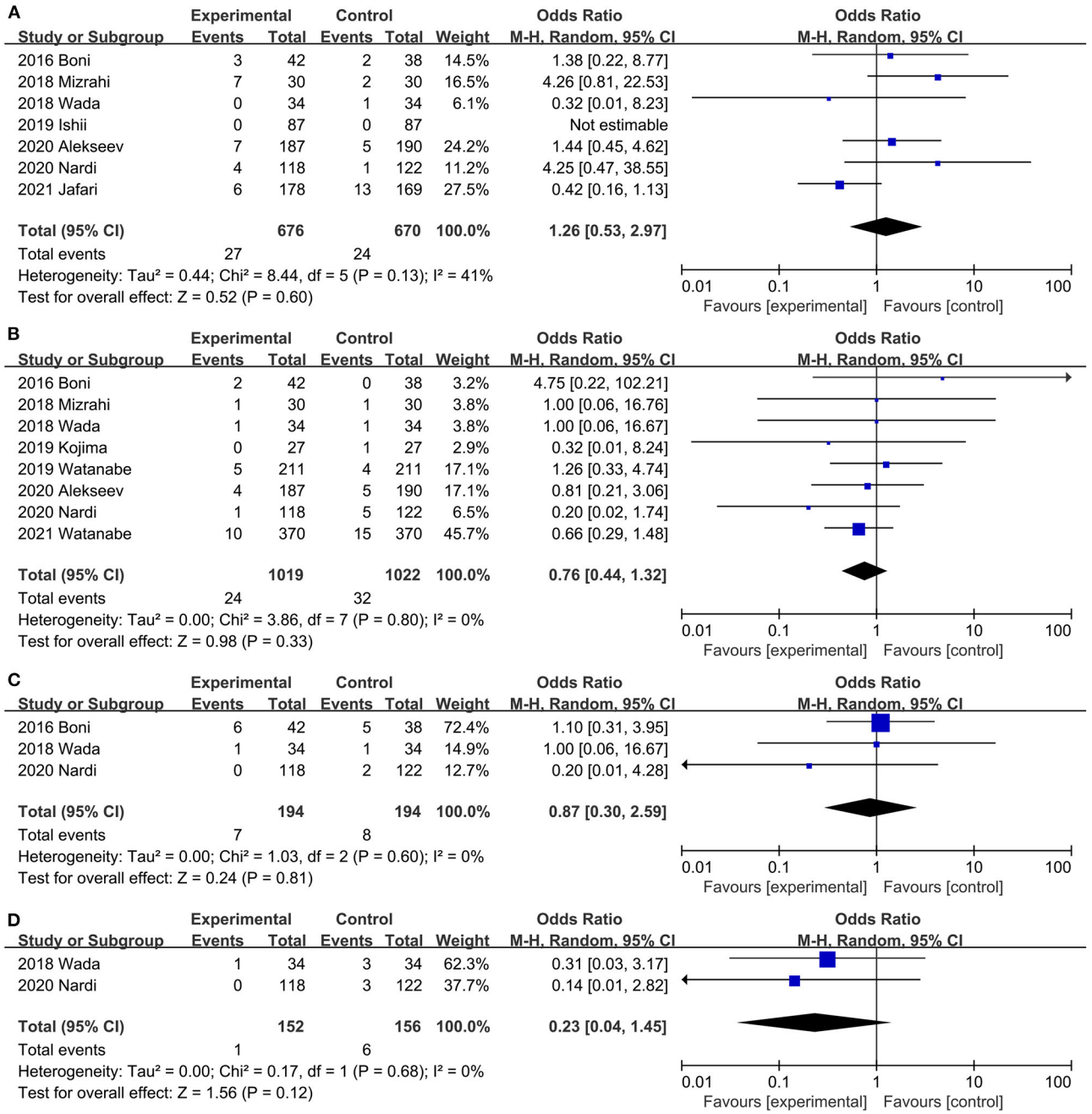

FIGURE 6 | Effect of indocyanine green on **(A)** Postoperative ileus rate. **(B)** Wound infection rate **(C)** Anastomotic stricture rate. **(D)** Pulmonary infection rate.

contrast, SAL was associated with poor short-and long-term outcomes of colorectal surgery (4). Therefore, we evaluated the preventive effect of ICG on SAL separately. We found that ICG use was associated with a reduced incidence of SAL. Previous studies have shown that the incidence of AL is related to the position of the anastomotic, and the lower the position, the higher the risk of AL (23, 47). Therefore, the trial of low anterior resection was used as a subgroup in this study, and the results of subgroup analysis showed that ICG could effectively reduce the incidence of AL in this high-risk population. Similarly, a retrospective study by Jafari et al. (15) found that the risk of AL in robot-assisted rectal surgery was reduced to 6% in the ICG group, compared with 18% in the control group. In a meta-analysis that included 27 studies, Emile et al. (48) found that ICG was associated with a significant reduction in the incidence of AL, whether in a subgroup analysis based on RCTs or in a subgroup analysis based on studies that included rectal cancer only. AL could lead to prolonged hospital stay (49). The results of this

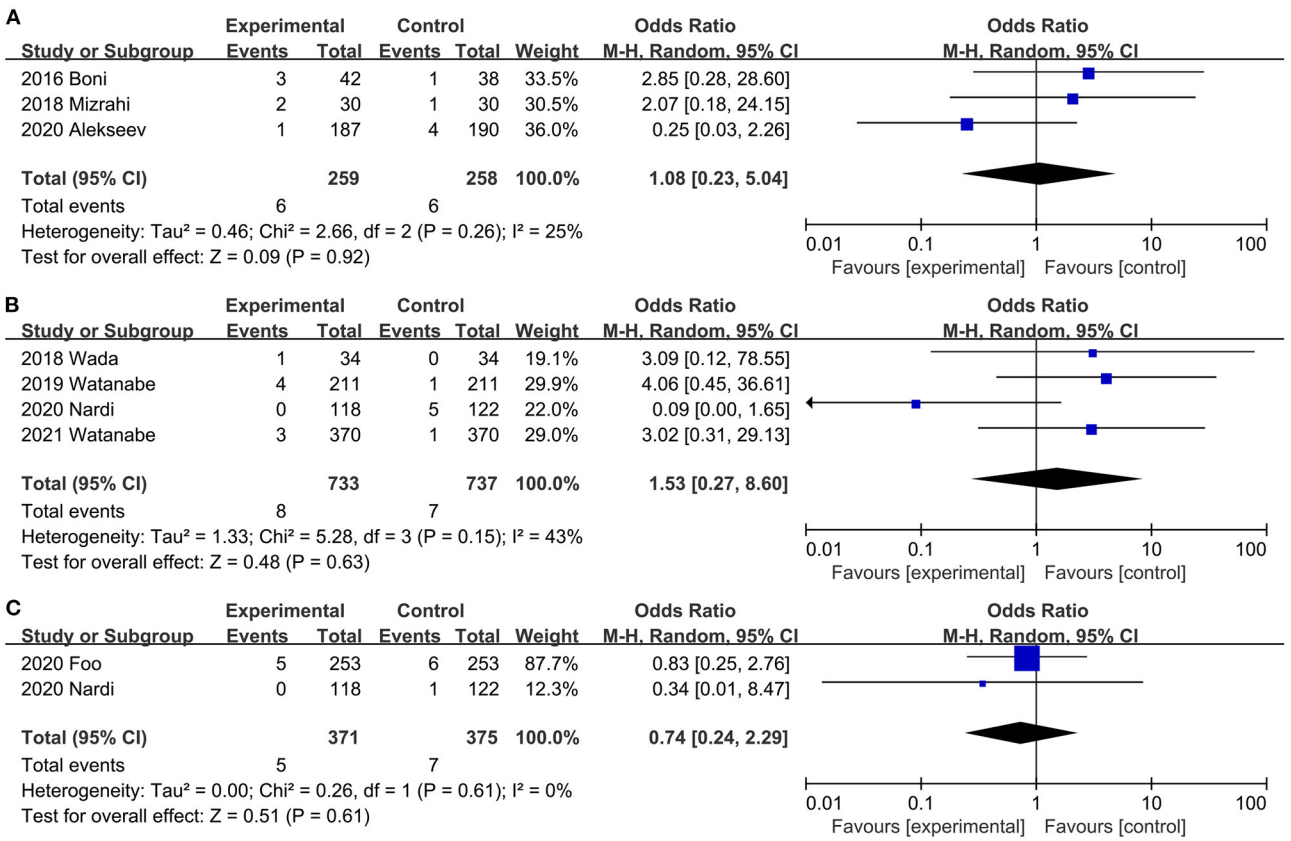

FIGURE 7 | Effect of indocyanine green on **(A)** Urinary retention rate. **(B)** Anastomotic bleeding rate **(C)** Urinary tract infection rate.

study showed that ICG could shorten the hospital stay of patients, which may be related to the reduction of the occurrence of AL. Grade C AL often requires surgical intervention, and the study of Liu et al. (22) showed that ICG could reduce the reoperation rate. However, no benefit of ICG in reducing reoperation rates was observed in this study. This may be related to the fact that few studies reported relevant outcome measures, with only eight of the included studies describing reoperation rates. In addition, our results suggest that ICG does not reduce postoperative mortality, which may be related to the low incidence of perioperative mortality and the small sample size of some of the included studies. Future prospective studies with a larger sample size should be conducted to investigate whether ICG fluorescein reduces the risk of perioperative mortality in colorectal surgery.

ICG is a safe dye, and its adverse reactions are rarely reported (50, 51). In a study of 1,226 participants, adverse events were observed in only eight subjects after intravenous ICG administration of 1 to 5 mg/kg, with only one severe adverse event and no deaths reported (52). Su et al. (50) found that no adverse reactions or allergic reactions associated with ICG were observed in colon cancer patients injected with 15 mg ICG. The doses used in the trials included in this study ranged from 0.1 to 0.5 mg/kg, and no adverse reactions were reported. In colorectal cancer surgery, Manen et al. (53) recommended intravenous injection of low-dose (2.5 mg) ICG to prevent AL, because 2.5 mg ICG can clearly observe the situation of colorectal anastomosis. Three studies (30, 34, 37) included in this study using 5mg of ICG showed that 5mg of ICG was effective in reducing the incidence of AL associated with perfusion. Although low-dose ICG may be an effective strategy to reduce AL, it is not clear whether low-dose ICG and high-dose ICG are equally effective in preventing AL. Our study showed that intraoperative ICG fluorescence angiography did not increase the incidence of total postoperative complications. Compared with the control group, ICG did not increase the risk of postoperative intestinal obstruction, wound infection, pulmonary infection, urinary retention, anastomotic bleeding, and anastomotic stenosis. A recent meta-analysis by Zhang et al. (8) showed that ICG fluorography did not increase wound infection, pneumonia, urinary retention, mortality, or postoperative bleeding. In addition, the results of this study showed that intraoperative ICG angiography did not prolong the operative time, but rather reduced intraoperative blood loss compared with the control group. This may be due to the increased frequency with which ICG fluorescein angiography was used, resulting in surgeons becoming more proficient with the system (23). A meta-analysis of 23 studies also showed that ICG did not increase intraoperative blood loss or operative time (9).

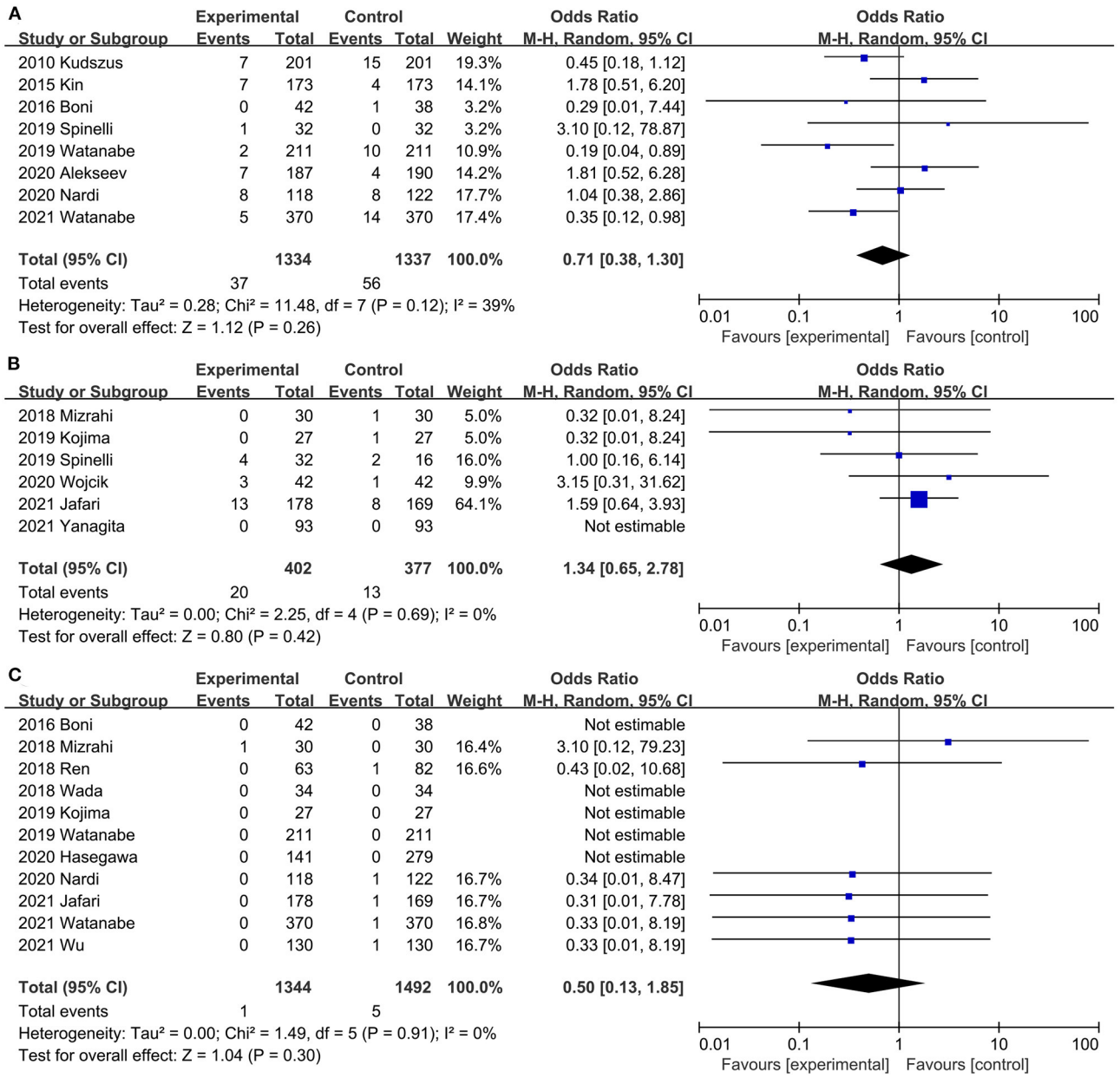

FIGURE 8 | Effect of indocyanine green on **(A)** Reoperation rate rate. **(B)** Conversion rate **(C)** Mortality.

This study has several strengths. First, in order to reduce potential bias, this study conducted a comprehensive literature search of several electronic databases (Embase, China National Knowledge Infrastructure, Web of Science, Scopus, PubMed, Cochrane Library, and VIP databases) without any language or time restrictions. Second, several recent important studies were included, which made our evidence more convincing. Third, different from previous meta-analyses, we only included PSM studies and RCTs, which made the experimental group and the control group more comparable and strengthened the reliability of our conclusions. Finally, advanced statistical methods (sensitivity analysis and subgroup analysis) were used to further confirm the robustness of our results.

There are several limitations in our meta-analysis. First, there was significant heterogeneity in some outcome measures of this study. This may be related to inconsistent follow-up times (from 30 to 90 days) and inconsistent definitions of AL used in the included studies. Moreover, five studies included patients with both malignant and benign colorectal disease. Inconsistent disease types may be one of the sources of heterogeneity. Second, a total of nine fluorescence imaging systems were used. It is not clear whether the effects of different fluorescence imaging

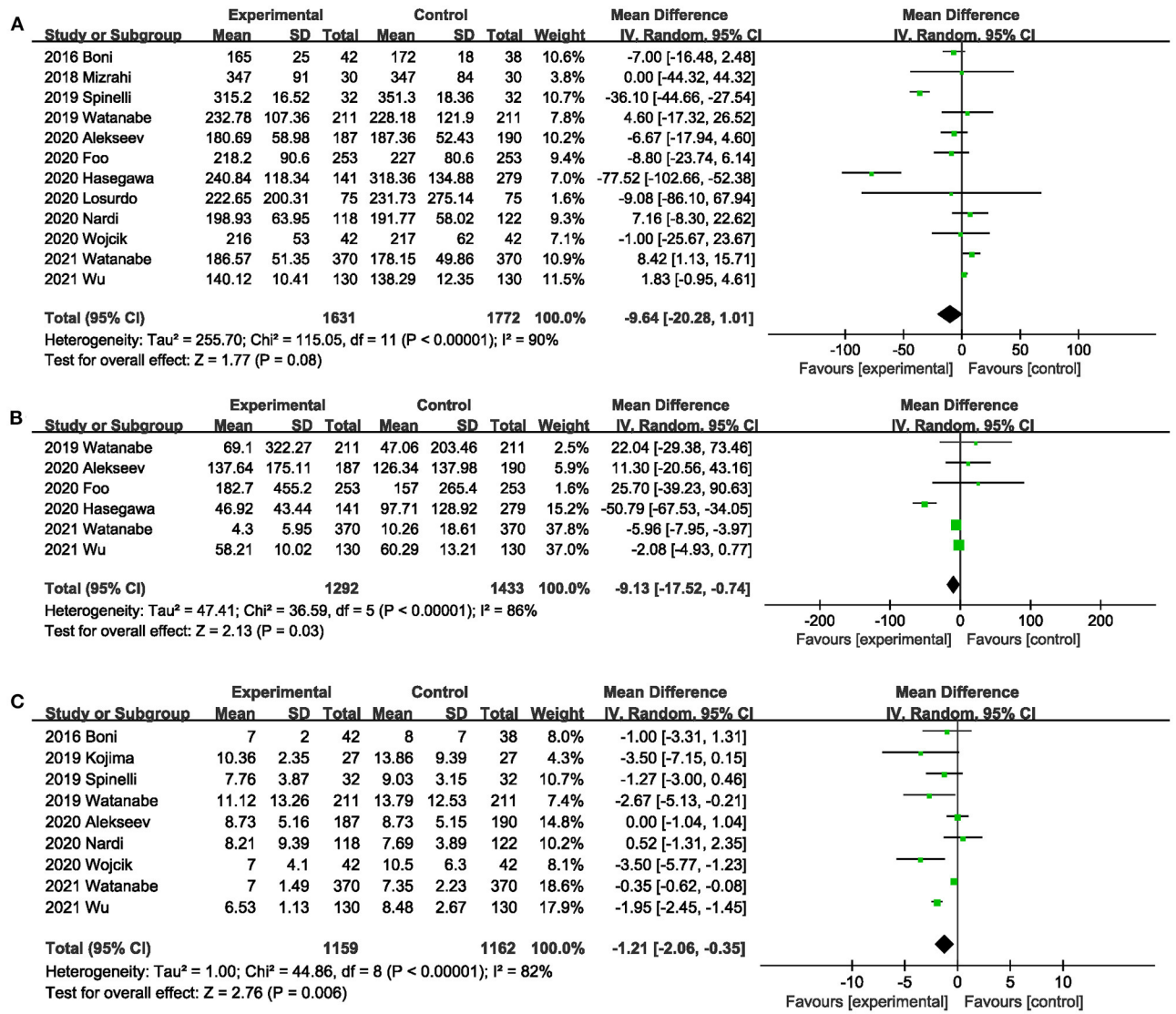

FIGURE 9 | Effect of indocyanine green on **(A)** Operative time. **(B)** Blood loss during surgery. **(C)** Length of postoperative hospital stay.

systems are consistent, which may need to be clarified in future studies. In the included studies, there were also differences in the dose of ICG injected intravenously. The influence of different doses on the study needs to be further explored, and finding the optimal dose may be the focus of future studies. These may also be sources of heterogeneity. Third, although this study showed that ICG may have potential benefits in reducing the incidence of AL after colorectal surgery, the fluorescence intensity in all the studies included in this meta-analysis was based on the subjective judgment of surgeons, lacking objective evaluation indicators (54). In addition, even if ICG fluorescence is displayed in the colorectal, intestinal ischemia may occur if blood flow is not meeting physiological demands (55). Therefore, the use of software to quantify the fluorescence parameters and find reliable parameters for predicting AL (54) may further confirm the benefits of ICG on AL in colorectal surgery. Cahill et al. (56) combined ICG fluorescence angiography and artificial intelligence to identify tumors by recognizing different perfusion modes. This technology can also be developed into real-time monitoring of anastomotic blood perfusion (57), so as to identify ischemic anastomotic sites. Finally, some of the outcome indicators (reoperation rate, conversion rate, postoperative ileus rate, wound infection rate, urinary tract infection rate, pulmonary infection rate, urinary retention rate, anastomotic bleeding rate and anastomotic stricture rate) in the included studies were based on evidence from a small number of studies, so it is not possible to determine whether ICG will bring more benefits, and more high-quality studies are needed to explore the impact of ICG on these outcomes.

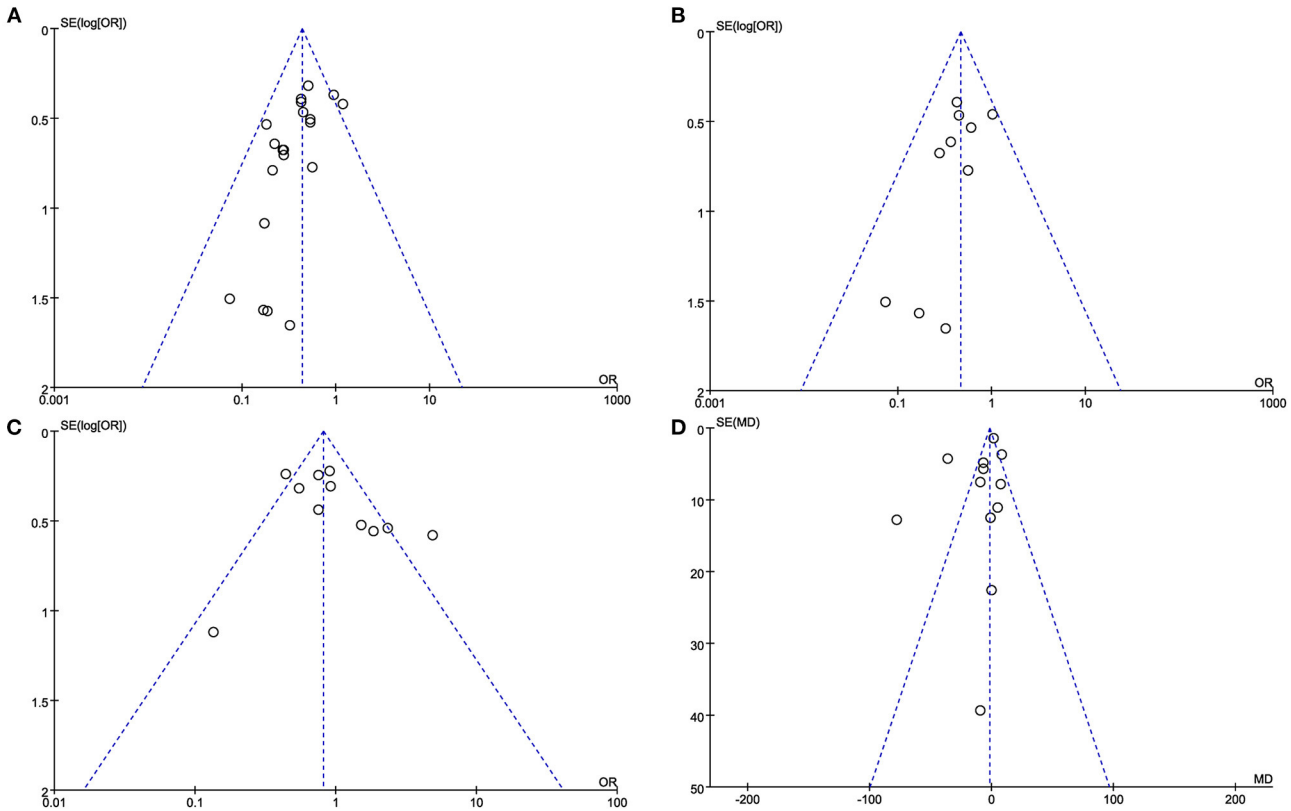

FIGURE 10 | The funnel plot of **(A)** AL rate. **(B)** SAL rate. **(C)** Postoperative complications. **(D)** Blood loss during surgery.

CONCLUSION

In conclusion, this meta-analysis demonstrated the value of ICG in patients undergoing colorectal surgery, as evidenced by the reduced AL rate, SAL rate, and blood loss. Further, hospital stays were shorter. ICG may be a potential strategy to prevent AL in colorectal surgery, and more high-quality large sample size RCTs are necessary to confirm the benefits of ICG in colorectal surgery.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

ZW, GT, JT, and DD: conceptualization and had primary responsibility for final content. JT, GT, and DD: data collection, analyses, and writing—original draft preparation. ZW, GT, and DD: writing—review and editing. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by Chongqing Joint Medical Scientific Research Project of Science and Health (No. 2018ZDXM007) and Chongqing Key Diseases Research and Application Demonstration Program (No. 2019ZX003).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.815753/full#supplementary-material

REFERENCES

1. Arezzo A, Bonino MA, Ris F, Boni L, Cassinotti E, Foo DCC, et al. Intraoperative use of fluorescence with indocyanine green reduces anastomotic leak rates in rectal cancer surgery: an individual participant data analysis. *Surg Endosc.* (2020) 34:4281–90. doi: 10.1007/s00464-020-07735-w
2. Yang J, Chen Q, Jindou L, Cheng Y. The influence of anastomotic leakage for rectal cancer oncologic outcome: a systematic review and meta-analysis. *J Surg Oncol.* (2020) 121:1283–97. doi: 10.1002/jso.25921

3. Kryzauskas M, Bausys A, Degutyte AE, Abeciunas V, Poskus E, Bausys R, et al. Risk factors for anastomotic leakage and its impact on long-term survival in left-sided colorectal cancer surgery. *World J Surg Oncol.* (2020) 18:205. doi: 10.1186/s12957-020-01968-8
4. Chan DKH, Lee SKF, Ang JJ. Indocyanine green fluorescence angiography decreases the risk of colorectal anastomotic leakage: systematic review and meta-analysis. *Surgery*. (2020) 168:1128–37. doi: 10.1016/j.surg.2020.08.024
5. Shen R, Zhang Y, Wang T. Indocyanine green fluorescence angiography and the incidence of anastomotic leak after colorectal resection for colorectal cancer: a meta-analysis. *Dis Colon Rectum.* (2018) 61:1228–34. doi: 10.1097/DCR.0000000000001123
6. Blanco-Colino R, Espin-Basany E. Intraoperative use of ICG fluorescence imaging to reduce the risk of anastomotic leakage in colorectal surgery: a systematic review and meta-analysis. *Tech Coloproctol.* (2018) 22:15–23. doi: 10.1007/s10151-017-1731-8
7. Sparreboom CL, van Groningen JT, Lingsma HF, Wouters M, Menon AG, Kleinrensink GJ, et al. Different risk factors for early and late colorectal anastomotic leakage in a nationwide audit. *Dis Colon Rectum.* (2018) 61:1258–66. doi: 10.1097/DCR.0000000000001202
8. Zhang W, Che X. Effect of indocyanine green fluorescence angiography on preventing anastomotic leakage after colorectal surgery: a meta-analysis. *Surg Today*. (2021) 51:1415–28. doi: 10.1007/s00595-020-02195-0
9. Li Z, Zhou Y, Tian G, Liu Y, Jiang Y, Li X, et al. Meta-analysis on the efficacy of indocyanine green fluorescence angiography for reduction of anastomotic leakage after rectal cancer surgery. *Am Surg.* (2020) 87:1910–9. doi: 10.1177/0003134820982848
10. Spinoglio G, Bertani E, Borin S, Piccioli A, Petz W. Green indocyanine fluorescence in robotic abdominal surgery. *Updates Surg.* (2018) 70:375–9. doi: 10.1007/s13304-018-0585-6
11. Egloff-Juras C, Bezdetnaya L, Dolivet G, Lassalle HP. NIR fluorescence-guided tumor surgery: new strategies for the use of indocyanine green. *Int J Nanomedicine.* (2019) 14:7823–38. doi: 10.2147/IJN.S207486
12. Weis F, Kilger E, Beiras-Fernandez A, Hinske CL, Nassau K, Adnan L, et al. Indocyanine green clearance as an outcome prediction tool in cardiac surgery: a prospective study. *J Crit Care.* (2014) 29:224–9. doi: 10.1016/j.jcrc.2013.10.023
13. Lee Z, Moore B, Giusto L, Eun DD. Use of indocyanine green during robot-assisted ureteral reconstructions. *Eur Urol.* (2015) 67:291–8. doi: 10.1016/j.eururo.2014.08.057
14. Yamamoto M, Orihashi K, Nishimori H, Wariishi S, Fukutomi T, Kondo N, et al. Indocyanine green angiography for intra-operative assessment in vascular surgery. *Eur J Vasc Endovasc Surg.* (2012) 43:426–32. doi: 10.1016/j.ejvs.2011.12.030
15. Jafari MD, Lee KH, Halabi WJ, Mills SD, Carmichael JC, Stamos MJ, et al. The use of indocyanine green fluorescence to assess anastomotic perfusion during robotic assisted laparoscopic rectal surgery. *Surg Endosc.* (2013) 27:3003–8. doi: 10.1007/s00464-013-2832-8
16. Impellizzeri HG, Pulvirenti A, Inama M, Bacchion M, Marrano E, Creciun M, et al. Near-infrared fluorescence angiography for colorectal surgery is associated with a reduction of anastomotic leak rate. *Updates Surg.* (2020) 72:991–8. doi: 10.1007/s13304-020-00758-x
17. Otero-Piñeiro AM, de Lacy FB, Van Laarhoven JJ, Martín-Perez B, Valverde S, Bravo R, et al. The impact of fluorescence angiography on anastomotic leak rate following transanal total mesorectal excision for rectal cancer: a comparative study. *Surg Endosc.* (2021) 35:754–62. doi: 10.1007/s00464-020-07442-6
18. Skrovina M, Bencurik V, Martinek L, Machackova M, Bartos J, Andel P, et al. The significance of intraoperative fluorescence angiography in miniinvasive low rectal resections. *Wideochir Inne Tech Maloinwazyjne.* (2020) 15:43–8. doi: 10.5114/wiitm.2019.84851
19. Kim JC, Lee JL, Kim CW, Lim SB, Alsaleem HA, Park SH. Mechanotechnical faults and particular issues of anastomotic complications following robot-assisted anterior resection in 968 rectal cancer patients. *J Surg Oncol.* (2019) 120:1436–45. doi: 10.1002/jso.25765
20. De Nardi P, Elmore U, Maggi G, Maggiore R, Boni L, Cassinotti E, et al. Intraoperative angiography with indocyanine green to assess anastomosis perfusion in patients undergoing laparoscopic colorectal resection: results of a multicenter randomized controlled trial. *Surg Endosc.* (2020) 34:53–60. doi: 10.1007/s00464-019-06730-0
21. Jafari MD, Pigazzi A, McLemore EC, Mutch MG, Haas E, Rasheid SH, et al. Perfusion assessment in left-sided/low anterior resection (PILLAR III): a randomized, controlled, parallel, multicenter study assessing perfusion outcomes with PINPOINT near-infrared fluorescence imaging in low anterior resection. *Dis Colon Rectum.* (2021) 64:995–1002. doi: 10.1097/DCR.0000000000002007
22. Liu D, Liang L, Liu L, Zhu Z. Does intraoperative indocyanine green fluorescence angiography decrease the incidence of anastomotic leakage in colorectal surgery? a systematic review and meta-analysis. *Int J Colorectal Dis.* (2021) 36:57–66. doi: 10.1007/s00384-020-03741-5
23. Lin J, Zheng B, Lin S, Chen Z, Chen S. The efficacy of intraoperative ICG fluorescence angiography on anastomotic leak after resection for colorectal cancer: a meta-analysis. *Int J Colorectal Dis.* (2021) 36:27–39. doi: 10.1007/s00384-020-03729-1
24. Syn NL, Kabir T, Koh YX, Tan HL, Wang LZ, Chin BZ, et al. Survival advantage of laparoscopic versus open resection for colorectal liver metastases: a meta-analysis of individual patient data from randomized trials and propensity-score matched studies. *Ann Surg.* (2020) 272:253–65. doi: 10.1097/SLA.0000000000003672
25. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* (2009) 339:b2535. doi: 10.1136/bmj.b2535
26. Foo CC, Ng KK, Tsang J, Wei R, Chow F, Chan TY, et al. Colonic perfusion assessment with indocyanine-green fluorescence imaging in anterior resections: a propensity score-matched analysis. *Tech Coloproctol.* (2020) 24:935–42. doi: 10.1007/s10151-020-02232-7
27. Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 The Cochrane Collaboration.* (2011). Available online at: www.cochrane-handbook org (accessed March 2011).
28. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* (2002) 21:1539–58. doi: 10.1002/sim.1186
29. Kudszus S, Roesel C, Schachtrupp A, Höer JJ. Intraoperative laser fluorescence angiography in colorectal surgery: a noninvasive analysis to reduce the rate of anastomotic leakage. *Langenbecks Arch Surg.* (2010) 395:1025–30. doi: 10.1007/s00423-010-0699-x
30. Kin C, Vo H, Welton L, Welton M. Equivocal effect of intraoperative fluorescence angiography on colorectal anastomotic leaks. *Dis Colon Rectum.* (2015) 58:582–7. doi: 10.1097/DCR.0000000000000320
31. Boni L, Fingerhut A, Marzorati A, Rausei S, Dionigi G, Cassinotti E. Indocyanine green fluorescence angiography during laparoscopic low anterior resection: results of a case-matched study. *Surg Endosc.* (2017) 31:1836–40. doi: 10.1007/s00464-016-5181-6
32. Mizrahi I, Abu-Gazala M, Rickles AS, Fernandez LM, Petrucci A, Wolf J, et al. Indocyanine green fluorescence angiography during low anterior resection for low rectal cancer: results of a comparative cohort study. *Tech Coloproctol.* (2018) 22:535–40. doi: 10.1007/s10151-018-1832-z
33. Peng R, Ye Z, Jianxin T, Renhui S, Tong W. Effect of indocyanine green imaging on decrease the anastomotic fistula after laparoscopic colorectal surgery. *J Clin Surg.* (2018) 26:754–6. doi: 10.3969/j.issn.1005 6483.2018.10.011
34. Wada T, Kawada K, Hoshino N, Inamoto S, Yoshitomi M, Hida K, et al. The effects of intraoperative ICG fluorescence angiography in laparoscopic low anterior resection: a propensity score-matched study. *Int J Clin Oncol.* (2019) 24:394–402. doi: 10.1007/s10147-018-1365-5
35. Ishii M, Hamabe A, Okita K, Nishidate T, Okuya K, Usui A, et al. Efficacy of indocyanine green fluorescence angiography in preventing anastomotic leakage after laparoscopic colorectal cancer surgery. *Int J Colorectal Dis.* (2020) 35:269–75. doi: 10.1007/s00384-019-03482-0
36. Kojima S, Sakamoto T, Matsui Y, Nambu K, Masamune K. Clinical efficacy of bowel perfusion assessment during laparoscopic colorectal resection using laser speckle contrast imaging: a matched case-control study. *Asian J Endosc Surg.* (2020) 13:329–35. doi: 10.1111/ases.12759
37. Spinelli A, Carvello M, Kotze PG, Maroli A, Montroni I, Montorsi M, et al. Ileal pouch-anal anastomosis with fluorescence angiography: a case-matched study. *Colorectal Dis.* (2019) 21:827–32. doi: 10.1111/codi.14611

38. Hasegawa H, Tsukada Y, Wakabayashi M, Nomura S, Sasaki T, Nishizawa Y, et al. Impact of intraoperative indocyanine green fluorescence angiography on anastomotic leakage after laparoscopic sphincter-sparing surgery for malignant rectal tumors. *Int J Colorectal Dis.* (2020) 35:471–80. doi: 10.1007/s00384-019-03490-0
39. Losurdo P, Mis TC, Cosola D, Bonadio L, Giudici F, Casagranda B, et al. Anastomosis leak: is there still a place for indocyanine green fluorescence imaging in colon-rectal surgery? a retrospective, propensity score-matched cohort study. *Surg Innov.* (2020).doi: 10.1177/1553350620975258. [Epub ahead of print].
40. Alekseev M, Rybakov E, Shelygin Y, Chernyshov S, Zarodnyuk I. A study investigating the perfusion of colorectal anastomoses using fluorescence angiography: results of the FLAG randomized trial. *Colorectal Dis.* (2020) 22:1147–53. doi: 10.1111/codi.15037
41. Wojcik M, Doussot A, Manfredelli S, Duclos C, Paquette B, Turco C, et al. Intra-operative fluorescence angiography is reproducible and reduces the rate of anastomotic leak after colorectal resection for cancer: a prospective case-matched study. *Colorectal Dis.* (2020) 22:1263–70. doi: 10.1111/codi.15076
42. Watanabe J, Ishibe A, Ohya H, Suwa Y, Suwa H, Kunisaki C, et al. Evaluating the effect of intraoperative near-infrared observation on anastomotic leakage after stapled side-to-side anastomosis in colon cancer surgery using propensity score matching. *Dis Colon Rectum.* (2021) 64:1542–50. doi: 10.1097/DCR.0000000000001960
43. Guocong W, Jun L, Wei X, Ce G, Fengming X. Application of indocyanine green imaging on preventing anastomotic leakage after laparoscopic colorectal cancer radical operation. *Med J West China.* (2021) 33:1035–8. doi: 10.3969/j.issn.1672-3511.2021.07.020
44. Yanagita T, Hara M, Osaga S, Nakai N, Maeda Y, Shiga K, et al. Efficacy of intraoperative ICG fluorescence imaging evaluation for preventing anastomotic leakage after left-sided colon or rectal cancer surgery: a propensity score-matched analysis. *Surg Endosc.* (2021) 35:2373–85. doi: 10.1007/s00464-020-08230-y
45. Watanabe J, Ishibe A, Suwa Y, Suwa H, Ota M, Kunisaki C, et al. Indocyanine green fluorescence imaging to reduce the risk of anastomotic leakage in laparoscopic low anterior resection for rectal cancer: a propensity score-matched cohort study. *Surg Endosc.* (2020) 34:202–8. doi: 10.1007/s00464-019-06751-9
46. Dinallo AM, Kolarsick P, Boyan WP, Protyniak B, James A, Dressner RM, et al. Does routine use of indocyanine green fluorescence angiography prevent anastomotic leaks? a retrospective cohort analysis. *Am J Surg.* (2019) 218:136–9. doi: 10.1016/j.amjsurg.2018.10.027
47. Ji WB, Kwak JM, Kim J, Um JW, Kim SH. Risk factors causing structural sequelae after anastomotic leakage in mid to low rectal cancer. *World J Gastroenterol.* (2015) 21:5910–7. doi: 10.3748/wjg.v21.i19.5910
48. Emile SH, Khan SM, Wexner SD. Impact of change in the surgical plan based on indocyanine green fluorescence angiography on the rates of colorectal anastomotic leak: a systematic review and meta-analysis. *Surg Endosc.* (2022). doi: 10.1007/s00464-021-08973-2. [Epub ahead of print].
49. Mok HT, Ong ZH, Yaow CYL, Ng CH, Buan BJL, Wong NW, et al. Indocyanine green fluorescent imaging on anastomotic leakage in colectomies: a network meta-analysis and systematic review. *Int J Colorectal Dis.* (2020) 35:2365–9. doi: 10.1007/s00384-020-03723-7
50. Su H, Wu H, Bao M, Luo S, Wang X, Zhao C, et al. Indocyanine green fluorescence imaging to assess bowel perfusion during totally laparoscopic surgery for colon cancer. *BMC Surg.* (2020) 20:102. doi: 10.1186/s12893-020-00745-4
51. Munechika T, Kajitani R, Matsumoto Y, Nagano H, Komono A, Aisu N, et al. Safety and effectiveness of high ligation of the inferior mesenteric artery for cancer of the descending colon under indocyanine green fluorescence imaging: a pilot study. *Surg Endosc.* (2021) 35:1696–702. doi: 10.1007/s00464-020-07556-x
52. Hope-Ross M, Yannuzzi LA, Gragoudas ES, Guyer DR, Slakter JS, Sorenson JA, et al. Adverse reactions due to indocyanine green. *Ophthalmology.* (1994) 101:529–33. doi: 10.1016/S0161-6420(94)31303-0
53. van Manen L, Handgraaf HJM, Diana M, Dijkstra J, Ishizawa T, Vahrmeijer AL, et al. A practical guide for the use of indocyanine green and methylene blue in fluorescence-guided abdominal surgery. *J Surg Oncol.* (2018) 118:283–300. doi: 10.1002/jso.25105
54. Gomez-Rosado JC, Valdes-Hernandez J, Cintas-Catena J, Cano-Matias A, Perez-Sanchez A, Del Rio-Lafuente FJ, et al. Feasibility of quantitative analysis of colonic perfusion using indocyanine green to prevent anastomotic leak in colorectal surgery. *Surg Endosc.* (2022) 36:1688–95. doi: 10.1007/s00464-021-08918-9
55. Son GM, Kwon MS, Kim Y, Kim J, Kim SH, Lee JW. Quantitative analysis of colon perfusion pattern using indocyanine green (ICG) angiography in laparoscopic colorectal surgery. *Surg Endosc.* (2019) 33:1640–9. doi: 10.1007/s00464-018-6439-y
56. Cahill RA, O'Shea DF, Khan MF, Khokhar HA, Epperlein JP, Mac Aonghusa PG, et al. Artificial intelligence indocyanine green (ICG) perfusion for colorectal cancer intra-operative tissue classification. *Br J Surg.* (2021) 108:5–9. doi: 10.1093/bjs/znaa004
57. Pampiglione T, Chand M. Enhancing colorectal anastomotic safety with indocyanine green fluorescence angiography: an update. *Surg Oncol.* (2021) 101545. doi: 10.1016/j.suronc.2021.101545. [Epub ahead of print].

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Surgery

ORIGINAL RESEARCH
published: 28 March 2022
doi: 10.3389/fsurg.2022.821509

Timing of Closure of a Protective Loop-Ileostomy Can Be Crucial for Restoration of a Functional Digestion

Jens M. Werner, Paul Kupke, Matthias Ertl, Sabine Opitz, Hans J. Schlitt and Matthias Hornung*

Department of Surgery, University Hospital Regensburg, Regensburg, Germany

Introduction: Protective loop-ileostomy is one of the most common interventions in abdominal surgery to provide an alternative intestinal outlet until sufficient healing of a distal anastomosis has occurred. However, closure of a loop-ileostomy is also associated with complications. Thus, knowledge of the optimal time interval between primary and secondary surgery is crucial.

Methods: Data from 409 patients were retrospectively analyzed regarding complications and risk factors in closure-associated morbidity and mortality. A modified Clavien-Dindo classification of surgical complications was used to evaluate the severity of complications.

Results: A total of 96 (23.5%) patients suffered from postoperative complications after the closure of the loop-ileostomy. Early closure within 150 days from enterostomy ($n = 229$) was associated with less complications ($p < 0.001$**). Looking at the severity of complications, there were significantly more ($p = 0.014$*) mild postoperative complications in the late closure group (>150 days). Dysfunctional digestive problems—either (sub-) ileus ($p = 0.004$*), diarrhea or stool incontinence ($p = 0.003$*)—were the most frequent complications associated with late closure. Finally, we could validate in a multivariate analysis that "time to closure" ($p = 0.002$*) is independently associated with the development of complications after closure of a protective loop-ileostomy.

Conclusion: Late closure (>150 days) of a loop-ileostomy is an independent risk factor in post-closure complications in a multivariate analysis. Nevertheless, circumstances of disease and therapy need to be considered when scheduling the closure procedure.

Keywords: protective loop-ileostomy, enterostomy, closure surgery, surgical complications, dysfunctional digestion

OPEN ACCESS

Edited by:
Sven Flemming, University Hospital of Wuerzburg, Germany

Reviewed by:
Ulf Gunnarsson, Umeå University, Sweden
Walter Brunner, Kantonsspital St. Gallen, Switzerland
Matthias Kelm, University Hospital Würzburg, Germany

****Correspondence:***
Jens M. Werner
jens.werner@ukr.de

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *24 November 2021*
Accepted: *28 February 2022*
Published: *28 March 2022*

Citation:
Werner JM, Kupke P, Ertl M, Opitz S, Schlitt HJ and Hornung M (2022) Timing of Closure of a Protective Loop-Ileostomy Can Be Crucial for Restoration of a Functional Digestion. Front. Surg. 9:821509. doi: 10.3389/fsurg.2022.821509

INTRODUCTION

Installation of an artificial bowel output (enterostomy) to circumvent an intestinal obstruction can be traced back to ancient times with first records of a surgical ileostomy, ranging back to 1879 (1). Today, many oncologic and non-oncologic diseases involving intra-abdominal organs demand the installation of an enterostomy during disease owed to complications, such as perforation, obstruction, compression, or infection of the intestine (1–3). Protective (loop-) ileostomy is one

of the most common interventions in abdominal surgery to provide—in conjunction with the attached stoma appliance—an alternative intestinal outlet (2).

Procedures of surgical enterostomy are principally reversible, and, especially, a protective loop-ileostomy is generally intended to be only temporary until sufficient healing of a distal anastomosis has occurred (2). However, not only the feasibility of stoma closure but also the timing is a relevant question that is a decisive factor influencing patient-related physical and psychological outcomes (4, 5). Until recently, abdominal surgeons have widely agreed upon a temporizing strategy when confronted with a decision toward or against early closure of a protective loop-ileostomy (6–8). However, current literature suggests that a belated closure of a protective loop-ileostomy—even though lacking a consistent and consensual critical cut-off—might be associated with higher morbidity and mortality, thus, suggesting some prognostic risk factors in post-closure complications (2–5, 9–12). In our hospital, we aim to perform the stoma reversal procedure within 3–6 months.

Because of the inconsistent and yet sparsely conducted research, this study wants to validate those recent observations and aims at confining the optimal time interval to ameliorate adverse outcomes after the closure of protective loop-ileostomy.

METHODS

In a retrospective analysis, 409 patients with the closure of a protective loop-ileostomy—as the only inclusion criterion—at the University of Regensburg medical center were included. The time of primary surgery covered a period from January 2000 to August 2012. Patient demographics, primary diagnosis, and indication for enterostomy as well as details of the circumstances of enterostomy creation and the primary surgery, and stoma-related complications during and after a hospital stay, as well as information about ileostomy closure and follow-up care, were recorded by means of a hospital-internal questionnaire.

The widely approved Clavien-Dindo classification of surgical complications was applied for the ranking of adverse perioperative outcomes (13, 14). Grade I represents mild complications and comprises any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, or radiological interventions. The present modification condensed Clavien-Dindo Grades II and III to the new category moderate complications that summarize those unwanted events that indicate any further intervention. Severe complications (Clavien-Dindo Grade IV) contain life-threatening conditions requiring ICU management and/or re-operation. Lethal outcomes correspond to Clavien-Dindo Grade V. Complication rates were operationalized as a proportion of patients with at least one adverse sequelae of the respective population.

Statistical analysis was conducted with IBM SPSS Statistics 20. Data were checked for normal distribution with the Kolmogorov-Smirnov-Test. Fisher's Exact test or Chi-Square test served for comparison of nominal values; risk factors were analyzed with univariate and multivariate logistic regression. When reaching a two-sided α-error level of $p < 0.05$, statistical significance was assumed.

This clinical research project was assessed and approved by the local Ethical Committee of the University of Regensburg medical center under reference No. 18-104-899.

RESULTS

Late Closure of a Protective Loop-Ileostomy Has a Higher Risk of Complications

In our study population, closure of a protective loop-ileostomy was feasible in 86.8% (data not shown). That means, at the same time, 13.2% of all cases failed to be reversed, and a temporarily intended enterostomy might have become a permanent one (death, $n = 39$; lost to follow-up, n=16; refused any further surgical intervention, $n = 4$). For the 409 patients included in our further analyses, the average time from the primary procedure to the closure of the protective loop ileostomy was 1,674 days (median = 136 days). A negative and unwanted post-closure outcome with postoperative complications affected nearly every fourth closure procedure (23.5%). We found that waiting more than 90 days ($p = 0.032^*$) or 120 days ($p = 0.012^*$) was already associated with a significantly higher rate of postoperative complications (data not shown). However, as shown in **Figure 1** and **Table 1**, especially scheduling the closure procedure after 150 days from the initial procedure, made a decisive difference concerning negative outcomes after loop-ileostomy closure (31.7 vs. 17.%; $p = 0.001^{**}$) compared to an early closure within 150 days. Furthermore, as shown in **Figure 2**, patients with a late closure procedure also had a significantly longer hospital stay (median, 6 vs. 6.5 days and IQR, 3 vs. 4.75 days; $p = 0.0087$).

Reasons for Late Closure of a Protective Loop-Ileostomy

Having established that timing of the closure of a protective loop-ileostomy had a significant impact on the rate of postoperative complications, we further analyzed potential reasons for a belated closure procedure to find any distribution bias between the early (<150 days) and late (>150 days) closure group. As shown in **Table 2**, the patients who received an early closure (mean = 57.5 years, SD = 14.6 years) were—on average—significantly younger than the patients whose enterostomy was closed after 150 days (mean = 60.3 years, SD = 11. years; $p = 0.028^*$). However, the ratio between young and old patients with enterostomy below or above 60 years of age was equally distributed between both groups ($p = 0.122$). Furthermore, there was no significant difference in the gender distribution between the early (men: 71.2%; women: 28.8%) and late (men: 73.3%; women: 26.7%) closure groups ($p = 0.630$).

Regarding the primary diagnosis, the patients with rectal cancer significantly more often (83.3%) underwent a late closure after 150 days from primary surgery compared to the patients with other diagnoses ($p < 0.001^{**}$), while the closure of protective

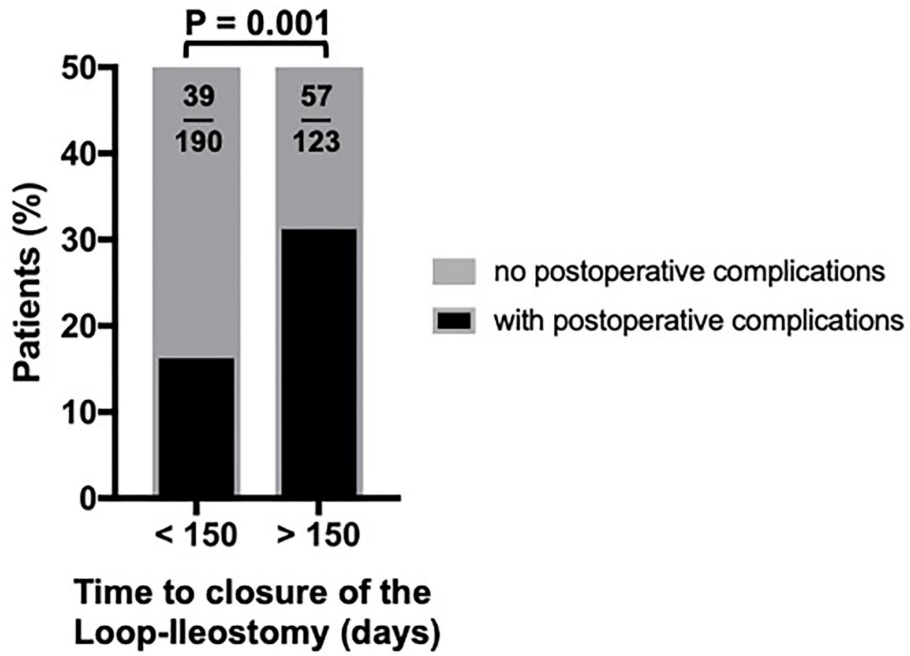

FIGURE 1 | Complications depending on the time to closure of the protective loop-ileostomy.

TABLE 1 | Complications after protective loop-ileostomy closure.

	Total [$n = 409$]	Closure < 150 days [$n = 229$]	Closure > 150 days [$n = 180$]	p-value
Complications [% (n)]	23.5 (96)	17.0 (39)	31.7 (57)	<0.001**
Quality of complications [% (n)]				
Anastomosis insufficiency	3.7 (15)	2.2 (5)	5.6 (10)	0.072 (ns)
(Sub-) Ileus	8.3 (34)	4.8 (11)	12.8 (23)	0.004*
Diarrheaorstoolincontinence	9.5 (39)	5.7 (13)	14.4 (26)	0.003*
Fistula orabscess	2.9 (12)	1.7 (4)	4.4 (8)	0.109 (ns)
Injury of other intraabdominal organs	0.7 (3)	1.3 (3)	–	0.123 (ns)
Impaired wound healing	4.2 (17)	3.9 (9)	4.4 (8)	0.796 (ns)
Hernia	0.7 (3)	0.9 (2)	0.6 (1)	0.708 (ns)
The severity of complications [% (n)]				
I° (mild)	11.2 (46)	7.9 (18)	15.6 (28)	0.014*
II° (moderate)	6.6 (27)	4.8 (11)	8.9 (16)	0.099 (ns)
III° (severe)	5.6 (23)	4.4 (10)	7.2 (13)	0.213 (ns)

*$p < 0.05$, **$p < 0.001$.

loop-ileostomy in the patients with ulcerative colitis (17.9%; $p = 0.002$*) or peritoneal carcinomatosis (10%; $p = 0.034$*) was significantly more frequently conducted early within 150 days after enterostomy. Only the patients with (sigmoid) colon cancer were equally distributed between the groups of early and late closure ($p = 0.508$).

The corresponding primary surgical interventions, however, did not significantly differ in the distribution between early or late closure ($p = 0.491$)—neither for (hemi-) colectomy and sigma resection ($p = 0.938$), nor for extraperitoneal rectum resection ($p = 0.236$) or low anterior rectum resection and proctocolectomy ($p = 0.447$). Furthermore, neither the reconstruction technique (end to end or side to side), nor the suture technique was significantly different between the two groups. However, the patients in the late closure group frequently received significantly adjuvant chemotherapy before the closure procedure was performed ($p = 0.0141$).

Late Closure of a Loop-Ileostomy Is Associated With Digestive Dysfunction

Next, we analyzed the severity of post-closure complications based on a slightly modified Clavien-Dindo classification. As shown in **Table 1**, digestive dysfunctions occurred significantly more often in the patients with a late closure (>150 days): (sub-) ileus (4.8 vs. 12.8%; $p = 0.004$*) or diarrhea and stool incontinence (5.7 vs. 14.4%; $p = 0.003$*) affected the patients with a belated closure more often. Other unwanted outcomes, such as formation of fistulas or abscesses (1.7 vs. 4.4%; $p = 0.109$), injury of other intra-abdominal organs (1.3 vs.0.0%; $p = 0.123$), insufficient wound healing (3.9 vs. 4.4%; $p = 0.796$) or development of an abdominal wall hernia (0.9 vs.0.6%; $p = 0.708$), were found with a similar contribution between both groups. Moreover, *the* severity of the post-closure complications was associated with the timing of the closure procedure. Early stoma closure within 150 days from primary surgery was associated with significantly less mild (7.9 vs. 15.6%; $p = 0.014$*) complications. The categories of moderate (4.8 vs. 8.9%; $p = 0.099$) or severe complications (4.4 vs. 7.2%; $p = 0.213$),

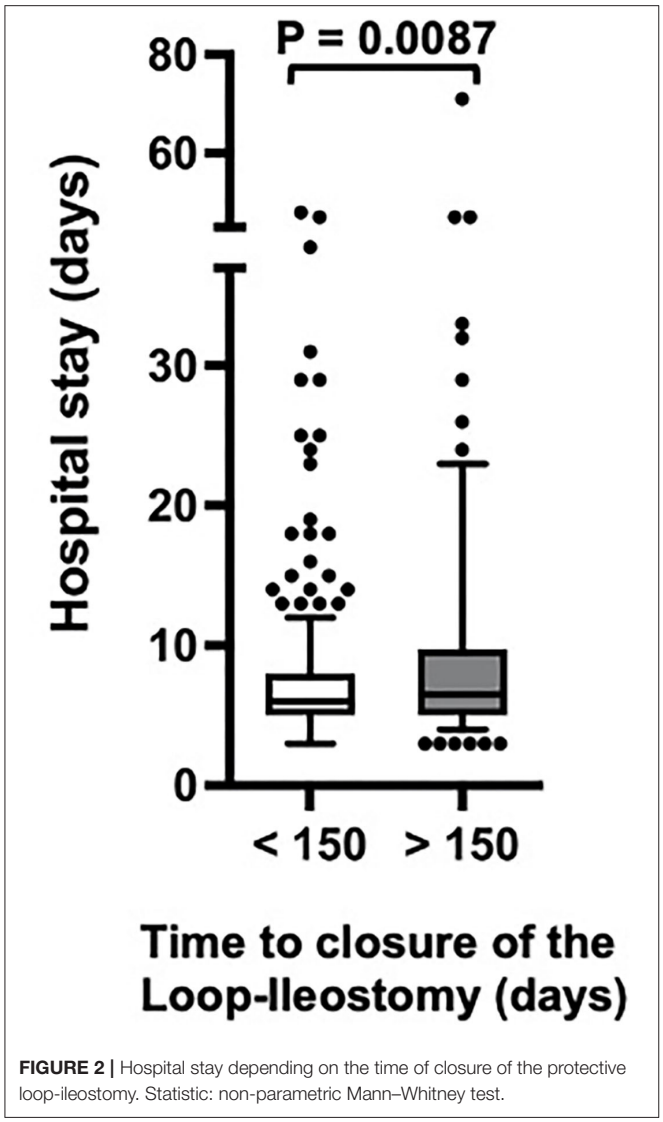

FIGURE 2 | Hospital stay depending on the time of closure of the protective loop-ileostomy. Statistic: non-parametric Mann–Whitney test.

however, resembled similar distribution between both groups without lethal complications.

Risk Factors in Post-closure Complications

In a final step, we wanted to link certain associated factors with post-closure complications. We found "time to clo" ($p < 0.001^{**}$) and "sex" ($p = 0.045^{*}$) as significant risk factors in the development of post-closure complications in a univariate logistic regression analysis as demonstrated in **Table 3**. Late closure of the protective loop-ileostomy after 150 days was associated with up to 12 times elevated risk for complications compared to early closure within 150 days from primary surgery (OR: 0.443; CI, 95%: 0.078–0.706) and the risk for men tripled that of women (OR: 0.566; CI, 95%: 0.324–0.988). Finally, we could substantiate that the timing of the closure is still a significant risk factor ($p = 0.002^{*}$), even when controlled for gender, in a multivariate logistic regression analysis as shown in **Table 4**.

TABLE 2 | Distribution of risk factors in the overall population and within the subgroups of early and late closure.

	Total [$n = 409$]	Closure < 150 days [$n = 229$]	Closure > 150 days [$n = 180$]	*p*-value
Age [M (SD)]	59.5 years (13.1 years)	57.5 years (14.6 years)	60.3 years (11.0 years)	0.028*
Age groups [% (*n*)]				0.122 (ns)
<60 years	45.97 (188)	49.34 (113)	41.67 (75)	
>60 years	54.03 (221)	50.66 (116)	58.33 (105)	
Sex [% (*n*)]				0.630 (ns)
Men	72.13 (295)	71.18 (163)	73.33 (132)	
Women	27.87 (114)	28.82 (66)	26.67 (48)	
Primary diagnosis[% (*n*)]				0.001**
Rectal cancer	73.35 (300)	65.50 (150)	83.33 (150)	<0.001**
Ulcerative colitis	13.20 (54)	17.90 (41)	7.22 (13)	0.002*
Peritoneal carcinomatosis	7.58 (31)	10.04 (23)	4.44 (8)	0.034*
Sigmoid (colon) cancer	5.87 (24)	6.55 (15)	5.00 (9)	0.508 (ns)
Primary surgery[% (*n*)]				0.491 (ns)
Colectomy, hemicolectomy, sigma resection	7.34 (30)	7.42 (17)	7.22 (13)	0.938 (ns)
Extraperitoneal rectum resection (cytoreductive surgery)	3.42 (14)	4.37 (10)	2.22 (4)	0.236 (ns)
Low anterior rectum resection, proctocolectomy	89.24 (365)	88.21 (202)	90.56 (163)	0.447 (ns)
Reconstruction[% (*n*)][†]				0.277 (ns)
End to end	84.60 (346)	88.65 (203)	79.44 (143)	
Side to side	11.25 (48)	10.04 (24)	12.78 (24)	
Suture technique[% (*n*)][†]				0.359 (ns)
Running suture	91.93 (376)	94.76 (217)	88.33 (159)	
Single stitches	2.44 (10)	3.06 (7)	1.67 (3)	
Stapler	0.49 (2)	0.87 (2)	0 (0)	
Adjuvant chemotherapy [% (*n*)]	49.88 (204)	28.33 (97)	59.44 (107)	0.014*

[†] *Missing documentation about surgical reconstruction; *p < 0.05, **p < 0.001.*

DISCUSSION

The best timing of the closure of a protective loop-ileostomy is yet a quite inconclusive issue with many considerations being insufficiently addressed. Finding the "sweet spot" is further aggravated, because either a hasty or a delayed closure is accompanied by a tremendous risk of post-closure complications (5, 6, 15), amounting to 23.5% in total in the present study. Here, the number of adverse outcomes after protective loop-ileostomy closure was strongly associated with the time interval between primary surgery and closure of the enterostomy. When bowel continuity was restored within 150 days, complications occurred in 17%.

TABLE 3 | Univariate analysis of risk factors in complications after closure of the protective loop-ileostomy.

	OR	CI 95%	*p*-value
Time to closure			0.001**
<150 days	0.443	0.078-0.706	
>150 days	1		
Age groups			0.231 (ns)
<60 years	0.753	0.474–1.197	
>60 years	1		
Sex			0.045*
Men	1		
Women	0.566	0.324–0.988	
Primary diagnosis			0.131 (ns)
Rectal cancer	1		
Ulcerative colitis	0.636	0.305–1.323	0.226 (ns)
Peritoneal carcinomatosis	0.300	0.089–1.013	0.053 (ns)
Sigmoid (colon) cancer	0.559	0.186–1.687	0.302 (ns)
Primary surgery			0.645 (ns)
Colectomy, hemicolectomy, sigma resection	0.630	0.234–1.694	0.359 (ns)
Extraperitoneal rectum resection (cytoreductive surgery)	858	0.234–3.147	0.818 (ns)
Low anterior rectum resection, proctocolectomy	1		

TABLE 4 | Multivariate analysis of risk factors in complications after closure of the protective loop-ileostomy.

	OR	CI 95%	*p*-value
Time to closure			0.002*
<150 days	0.468	0.289–0.757	
>150 days	1		
Age groups			0.562 (ns)
<60 years	0.859	0.514–1.436	
>60 years	1		
Sex			0.121 (ns)
Men	1		
Women	0.632	0.353–1.129	
Primary diagnosis			0.981 (ns)
Rectal cancer	1		
Ulcerative colitis	0.932	0.397–2.187	0.872 (ns)
Peritoneal carcinomatosis	0.000	0.000	0.998 (ns)
Sigmoid (colon) cancer	0.712	0.146–3.480	0.675 (ns)
Primary surgery			0.962 (ns)
Colectomy, hemicolectomy, sigma resection	0.814	0.191–3.472	0.780 (ns)
Extraperitoneal rectum resection (cytoreductive surgery)	0.000	0.000	0.998 (ns)
Low anterior rectum resection, Proctocolectomy	1		

Waiting more than 150 days for the closure procedure was associated with complications in almost every third case (31.7%).

The time between installation and closure of a protective loop-ileostomy is often substantially longer than initially planned. Completion of adjuvant chemotherapy is usually the leading argument against the closure of an enterostomy (7, 8). But waiting too long might result in medical, surgical, and psychological impairments (2, 3): Electrolyte derangements, dehydration, and malnutrition such as parastomal skin irritations can be found frequently in patients with a protective loop-ileostomy, and problems such as parastomal herniation, obstruction, or ileus may require surgical intervention (1, 16). Besides, an artificial bowel output disturbs activities of daily living, often leading to a diminution of health-related quality of life, and it changes the self-concept, which, in turn, could lower the patient's self-esteem (17, 18).

As we could demonstrate, dysfunctional complications such as either (sub-) ileus or diarrhea and stool incontinence might not only occur due to a prolonged loop-ileostomy but also as a result of a belated closure. Even though the severity of post-closure complications was relatively low and did not differ between groups in the categories of moderate and severe negative outcomes, mild complications were found significantly more frequent in patients with a late closure of a protective loop-ileostomy. Our data are in line with reports from Abdalla and Scarpinata (19) as well as Hughes et al. (20), who accounted for the negative impact of a delayed closure more than 6 months after index surgery on the rate of post-closure complications in a small cohort, whereas Zhen et al. (21) could not substantiate the inferiority of a late closure operation. The authors observed a comparable number of adverse outcomes for patients with a closure beyond 6 months from primary surgery, but this study group actually received more adjuvant chemotherapy cycles and might, thus, even have a better prognosis than patients with an early closure. Li and Ozuner (22) investigated a time interval of more or <3 months between enterostomy and stoma closure. Findings revealed no relevant intergroup differences.

Closure of a protective loop-ileostomy has to be acknowledged as an independent intervention unaffected by primary indication or surgery and with an often-underestimated risk for post-closure morbidity and mortality (15, 23–25). Although a vast spectrum of gastrointestinal diseases demanding an enterostomy and corresponding diverse enteric resections was included in the analysis, no negative impact of those substantial factors could be proved as relevant for the closure operation in our study. However, rectal cancer and the usual correspondingly low anterior rectum resection seem to negatively influence the post-closure outcome when waiting more than 150 days until the closure of protective loop-ileostomy. Yet, another bias must be critically considered: The closure of a protective loop-ileostomy in patients with rectal cancer is significantly more often postponed and, hence, has proportionately more cases with closure after 150 days from enterostomy.

So far, it was a silent agreement that a closure procedure should not be performed 60–90 days after installation of an enterostomy. This consensus was based on a clinical experience of patient recovery and owed to the circumstance that intra-abdominal adhesions are more manageable after about 2 months from primary surgery, and inflammation, as well as edema of the

loop-ileostoma, has usually been resolved. (4, 6) Nevertheless, recent reports have even intended to curtail the time to enterostomy closure to a minimum of only a few weeks (4, 26–30). Farang et al. (29) found that early closure of loop-ileostomy within 2 weeks of index surgery of distal colorectal resection was feasible with outcomes comparable to delayed closure. Robertson et al. (30) came to the same conclusion but pointed out that further investigations are warranted with a special focus on sensitive selection strategies to identify those patients that might profit from this non-standard fast-track approach (27).

However, there are also limitations to our study that need to be considered when interpreting the results. The included number of patients ($n = 409$) is relatively small, especially when calculating the outcomes for subgroups. A retrospective analysis of clinical data, *per se,* has some limitations since the assessment of outcomes relies on others for accurate record-keeping, and because the retrospective aspect may introduce selection bias. Furthermore, the data were collected only in a single center and in a health care system with no influence of insufficient resources. This needs to be considered when our data are compared to other settings, where the closure of a protective ileostomy might be delayed due to insufficient health care resources or high costs for the patients.

In our study population, closure of a protective loop-ileostomy was feasible in 86.8% (data not shown). That means, at the same time, 13.2% of all cases failed to be reversed, and a temporarily intended enterostomy became a permanent one. Literature designates relevant risk factors that include advanced age, anastomotic leakage, metastasis, and adjuvant radiochemotherapy (4, 5, 7, 31–34). Consequently, a circumspect consideration of those predictors for non-closure, in conjunction with an overall benefit/risk analysis, is required to achieve the best outcome for each patient when deciding upon a temporary or a permanent stoma in advance of enterostomy (35, 36). Predictive tools like the nomogram, developed by Abe et al. (37), might help to identify patients with a high risk of stoma non-reversal.

CONCLUSION

Protective loop-ileostomy is one of the most common interventions in abdominal surgery. Late closure (>150 days) of a protective loop-ileostomy is associated with a significantly higher rate of postoperative complications. Dysfunctional digestive problems, such as ileus, diarrhea, or stool incontinence, were the most frequent complications associated with late closure. Hence, early restitution of enteric continuity might be considered under a careful selection of patients, a thorough pre-operative assessment, and an evaluation of feasibility.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the University of Regensburg medical center under the reference number 18-104-899. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MH and JW: conception and design of the study. PK, ME, and SO: data acquisition. PK, ME, SO, MH, and JW: analysis and interpretation of the data. JW: drafting of the manuscript. HS, MH, and JW: revision of the manuscript. All authors had access to the study data and critically reviewed and approved the final version of the manuscript.

REFERENCES

1. Martin ST, Vogel JD. Intestinal stomas. *Adv Surg.* (2012) 46:19–49. doi: 10.1016/j.yasu.2012.04.005
2. Ambe PC, Kurz NR, Nitschke C, Odeh SF, Moslein G, Zirngibl H. Intestinal ostomy. *Dtsch Arztebl Int.* (2018) 115:182–7. doi: 10.3238/arztebl.2018.0182
3. Shabbir J, Britton DC. Stoma complications: a literatureoverview. *Color Dis.* (2010) 12:958–64. doi: 10.1111/j.1463-1318.2009.02006.x
4. Sherman KL, Wexner SD. Considerations in stoma reversal. *Clin Colon Rectal Surg.* (2017) 30:172–7. doi: 10.1055/s-0037-1598157
5. Gessler B, Haglind E, Angenete E. Loop ileostomies in colorectal cancer patients–morbidity and risk factors for nonreversal. *J Surg Res.* (2012) 178:708–14. doi: 10.1016/j.jss.2012.08.018
6. Perez RO, Habr-Gama A, Seid VE, Proscurshim I, Sousa A, Kiss D, et al. Loop ileostomy morbidity: timing of closure matters. *Dis Colon Rectum.* (2006) 49:1539–45. doi: 10.1007/s10350-006-0645-8
7. Sier MF, van Gelder L, Ubbink DT, Bemelman WA, Oostenbroek RJ. Factors affecting timing of closureand non-reversal of temporaryileostomies. *Int J Colorectal Dis.* (2015) 30:1185–92. doi: 10.1007/s00384-015-2253-3
8. Bakx R, Busch ORC, Bemelman WA, Veldink GJ, Slors JFM, van Lanschot JJB. Morbidity of temporary loop ileostomies. *Dig Surg.* (2004) 21:277–81. doi: 10.1159/000080201
9. Jimenez-Rodriguez RM, Segura-Sampedro JJ, Rivero-Belenchon I, Diaz Pavon J, Garcia Cabrera A, Vazquez Monchul J, et al. Is the interval from surgery to ileostomy closure a risk factor for low anterior resection syndrome? *Colorectal Dis.* (2017) 19:485–90. doi: 10.1111/codi.13524
10. Saito Y, Takakura Y, Hinoi T, Egi H, Tashiro H, Ohdan H. Body mass index as a predictor of postoperative complications in loop ileostomy closure after rectal resection in Japanese patients. *Hiroshima J Med Sci.* (2014) 63:33–8.
11. Man VCM, Choi HK, Law WL, Foo DCC. Morbidities after closure of ileostomy: analysis of risk factors. *Int J Colorectal Dis.* (2016) 31:51–7. doi: 10.1007/s00384-015-2327-2
12. Pokorny H, Herkner H, Jakesz R, Herbst F. Mortality and complications after stoma closure. *Arch Surg.* (2005) 140:956–60; discussion 960. doi: 10.1001/archsurg.140.10.956
13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* (2004) 240:205–13. doi: 10.1097/01.sla.0000133083.54934.ae

14. Clavien PA, Barkun J, de Oliveira ML, Vauthey J, Dindo D, Schulick R, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg.* (2009) 250:187–96. doi: 10.1097/SLA.0b013e3181b13ca2
15. Sharma A, Deeb A-P, Rickles AS, Iannuzzi JC, Monson JRT, Fleming FJ. Closure of defunctioning loop ileostomy is associated with considerable morbidity. *Colorectal Dis.* (2013) 15:458–62. doi: 10.1111/codi.12029
16. Caricato M, Ausania F, Ripetti V, Bartolozzi F, Campoli G, Coppola R. Retrospective analysis of long-term defunctioning stoma complications after colorectal surgery. *Color Dis.* (2007) 9:559–61. doi: 10.1111/j.1463-1318.2006.01187.x
17. Tsunoda A, Tsunoda Y, Narita K, Watanabe M, Nakao K, Kusano M. Quality of life after low anterior resection and temporary loop ileostomy. *Dis Colon Rectum.* (2008) 51:218–22. doi: 10.1007/s10350-007-9101-7
18. O'Leary DP, Fide CJ, Foy C, Lucarotti ME. Quality of life after low anterior resection with total mesorectal excision and temporary loop ileostomy for rectal carcinoma. *Br J Surg.* (2001) 88:1216–20. doi: 10.1046/j.0007-1323.2001.01862.x
19. Abdalla S, Scarpinata R. Early and late closure of loop ileostomies: a retrospective comparative outcomes analysis. *Ostomy Wound Manage.* (2018) 64:30–5. doi: 10.25270/owm.2018.12.3035
20. Hughes DL, Cornish J, Morris C. Functional outcome following rectal surgery-predisposing factors for low anterior resection syndrome. *Int J Colorectal Dis.* (2017) 32:691–7. doi: 10.1007/s00384-017-2765-0
21. Zhen L, Wang Y, Zhang Z, Wu T, Liu R, Li T, et al. Effectiveness between early and late temporary ileostomy closure in patients with rectal cancer: a prospective study. *CurrProbl Cancer.* (2017) 41:231–40. doi: 10.1016/j.currproblcancer.2017.02.007
22. Li W, Ozuner G. Does the timing of loop ileostomy closure affect outcome: a case-matched study. *Int J Surg.* (2017) 43:52–55. doi: 10.1016/j.ijsu.2017.05.039
23. Chow A, Tilney HS, Paraskeva P, Jeyarajah S, Zacharakis E, Purkayastha S. The morbidity surrounding reversal of defunctioning ileostomies: a systematic review of 48 studies including 6,107 cases. *Int J Colorectal Dis.* (2009) 24:711–23. doi: 10.1007/s00384-009-0660-z
24. Abegg RM, Brokelman W, van Bebber IP, Bosscha K, Prins HA, Lips DJ. Results of construction of protective loop ileostomies and reversal surgery for colorectal surgery. *Eur Surg Res.* (2014) 52:63–72. doi: 10.1159/000357053
25. Mengual-Ballester M, García-Marín JA, Pellicer-Franco E, Guillén-Paredes M, García-García M, Cases-Baldó M, et al. Protective ileostomy: complications and mortality associated with its closure. *Rev Esp Enferm Dig.* (2012) 104:350–4. doi: 10.4321/S1130-01082012000700003
26. Lee KH, Kim HO, Kim JS, Kim JY. Prospective study on the safety and feasibility of early ileostomy closure 2 weeks after lower anterior resection for rectal cancer. *Ann Surg Treat Res.* (2019) 96:41–6. doi: 10.4174/astr.2019.96.1.41
27. Menahem B, Lubrano J, Vallois A, Alves A. Early closure of defunctioning loop ileostomy: is it beneficial for the patient? A meta-analysis. *World J Surg.* (2018) 42:3171–8. doi: 10.1007/s00268-018-4603-0
28. Danielsen AK, Park J, Jansen JE, Bock D, Skullman S, Wedin A, et al. Early closure of a temporary ileostomy in patients with rectal cancer: a multicenter randomized controlled trial. *Ann Surg.* (2017) 265:284–90. doi: 10.1097/SLA.0000000000001829
29. Farag S, Rehman S, Sains P, Baig MK, Sajid MS. Early vs delayed closure of loop defunctioning ileostomy in patients undergoing distal colorectal resections: an integrated systematic review and meta-analysis of published randomized controlled trials. *Colorectal Dis.* (2017) 19:1050–7. doi: 10.1111/codi.13922
30. Robertson JP, Puckett J, Vather R, Jaung R, Bissett I. Early closure of temporary loop ileostomies: a systematic review. *Ostomy Wound Manage.* (2015) 61:50–7.
31. da-Fonseca LM, Buzatti KC de LR, Castro LL, Lacerda Filho A, Correia MITD, da-Silva RG. Factors preventing restoration of bowel continuity in patients with rectal cancer submitted to anterior rectal resection and protective ileostomy. *Rev Col Bras Cir.* (2019) 45:e1998. doi: 10.1590/0100-6991e-20181998
32. Chiu A, Chan HT, Brown CJ, Raval MJ, Phang PT. Failing to reverse a diverting stoma after lower anterior resection of rectal cancer. *Am J Surg.* (2014) 207:708–11; discussion 711. doi: 10.1016/j.amjsurg.2013.12.016
33. Lindgren R, Hallbook O, Rutegard J, Sjodahl R, Matthiessen P. What is the risk for a permanent stoma after low anterior resection of the rectum for cancer? A six-year follow-up of a multicenter trial. *Dis Colon Rectum.* (2011) 54:41–7. doi: 10.1007/DCR.0b013e3181fd2948
34. David GG, Slavin JP, Willmott S, Corless DJ, Khan AU, Selvasekar CR. Loop ileostomy following anterior resection: is it really temporary? *Colorectal Dis.* (2010) 12:428–32. doi: 10.1111/j.1463-1318.2009.01815.x
35. Gustafsson CP, Gunnarsson U, Dahlstrand U, Lindforss U. Loop-ileostomy reversal-patient-related characteristics influencing time to closure. *Int J Colorectal Dis.* (2018) 33:593–600. doi: 10.1007/s00384-018-2994-x
36. Cipe G, Erkek B, Kuzu A, Gecim E. Morbidity and mortality after the closure of a protective loop ileostomy: analysis of possible predictors. *Hepatogastroenterology.* (2012) 59:2168–72. doi: 10.5754/hge12115
37. Abe S, Kawai K, Nozawa H, Hata K, Kiyomatsu T, Tanaka T, et al. Use of a nomogram to predict the closure rate of diverting ileostomy after low anterior resection: a retrospective cohort study. *Int J Surg.* (2017) 47:83–8. doi: 10.1016/j.ijsu.2017.09.057

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Surgery

ORIGINAL RESEARCH
published: 08 April 2022
doi: 10.3389/fsurg.2022.821827

Intraoperative Colonic Irrigation for Low Rectal Resections With Primary Anastomosis: A Fail-Safe Surgical Model

Jonas Herzberg[1]*, *Shahram Khadem*[1], *Salman Yousuf Guraya*[2], *Tim Strate*[1] and *Human Honarpisheh*[1]

[1] Department of Surgery—Krankenhaus Reinbek St. Adolf-Stift, Reinbek, Germany, [2] Department of Clinical Sciences, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates

Aim: Regardless the technological developments in surgery, the anastomotic leakage (AL) rate of low rectal anastomosis remains high. Though various perioperative protocols have been tested to reduce the risk for AL, there is no standard peri-operative management approach in rectal surgery. We aim to assess the short-term outcome of a multidisciplinary approach to reduce the rates of ALs using a fail-safe-model using preoperative and intraoperative colonic irrigation in low rectal resections with primary anastomosis.

Methods: Between January 2015 and December 2020, 92 patients received low rectal resections for rectal cancer with primary anastomosis and diverting ileostomy. All these patients received pre-operative mechanical bowel preparation (MBP) without antibiotics as well as intraoperative colonic irrigation. The intraoperative colonic irrigation was performed *via* the efferent loop of the ileostomy. All data were analyzed by SPSS for descriptive and inferential analyses.

Results: In the study period, 1.987 colorectal surgical procedures were performed. This study reports AL in 3 (3.3%) of 92 recruited patients. Other postoperative complications (Dindo-Clavien I-IV) were reported in 25 patients (27.2%), which occurred mainly due to non-surgical reasons such as renal dysfunction and sepsis. According to the fail-safe model, AL was treated by endoscopic or re-do surgery. The median postoperative length of hospitalization was 8 days (4–45) days.

Conclusion: This study validates the effectiveness of a multi-disciplinary fail-safe model with a pre-operative MBP and an intraoperative colonic irrigation in reducing AL rates. Intraoperative colonic irrigation is a feasible approach that lowers the AL rates by reducing fecal load and by decontamination of the colon and anastomotic region. Our study does not recommend a pre-operative administration of oral antibiotics for colorectal decontamination.

Keywords: rectal resection, anastomotic leakage, colonic irrigation, mechanical bowel preparation, rectal cancer

OPEN ACCESS

Edited by:
Hans Martin Schardey, Agatharied Hospital GmbH, Germany

Reviewed by:
Walter Brunner, Kantonsspital St. Gallen, Switzerland
Ulf Gunnarsson, Umeå University, Sweden

***Correspondence:**
Jonas Herzberg
jonas.herzberg@Krankenhaus-Reinbek.de

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *24 November 2021*
Accepted: *22 February 2022*
Published: *08 April 2022*

Citation:
Herzberg J, Khadem S, Guraya SY, Strate T and Honarpisheh H (2022) Intraoperative Colonic Irrigation for Low Rectal Resections With Primary Anastomosis: A Fail-Safe Surgical Model. Front. Surg. 9:821827. doi: 10.3389/fsurg.2022.821827

INTRODUCTION

Anastomotic leakage (AL) after colorectal surgery is a feared complication due to its high morbidity and mortality rates (1, 2). Though there is no consensus about a standard definition of AL, the "International Multispecialty Anastomotic Leak Global Improvement Exchange" has elaborated AL as "a defect of the integrity in a surgical join between two hollow viscera with communication between the intraluminal and extraluminal compartments" (3). In colorectal surgery, the reported incidence of ALs significantly varies according to the location of the anastomosis (4). Literature has reported a wide range of AL rates of 1 to 20% for all colonic locations; from 0 to 2% after colocolonic and 0.02 to 4% after enteroenteric and ileocolonic anastomoses (5). In the low rectal anastomoses, much higher ALs rates of up to 28% have been reported (6).

Besides the surgical volumes and surgeon's experience, which are decisive for surgical outcomes (7), additional factors such as mechanical bowel preparation (MBP) potentially influence short-term surgical outcomes and AL rates (8). Significant colonization of lower GI tract with aerobic and anaerobic microbes leads to infectious complications with resultant increased concentrations of collagenases and matrix metalloproteinases (9). This adversely affects stromal regeneration and leads to an early degradation of collagen at the anastomotic sites (10, 11). The purpose of MBP is to reduce the rate of surgical side infection (SSI) and AL by reducing fecal load and bacterial count in the colon (12). Using pre-operative oral antibiotics and MBP, the National Surgical Quality Improvement Program by the American College of Surgeons has shown an approximately 50% reduction of AL rates and superficial surgical site infections (SSIs) and better rates of 30-day mortality (13). Several other researchers have also endorsed the use of non-absorbable oral antibiotics and MBP in reducing the SSIs and ALs rates in colorectal surgery (14, 15).

Regrettably, controversy prevails about the impact of pre-operative MBP in colorectal surgery (16–18). In their multi-center randomized trial, Si-Oen et al. could not find significant difference in the outcome variables between patients with and without MBP in elective open colonic surgery (19). The authors argued that MPB may be discontinued in open colon surgery. Similarly, other researchers have discouraged the routine pre-operative use of MBP in colonic surgery (20, 21). In addition to the controversial role of MBP, some investigators have coined the possibility of intra-operative colonic irrigation for reducing AL rates in planned colorectal surgery (22, 23). The combination of pre-operative MBP and intra-operative colonic irrigation following a multidisciplinary approach may be an alternative that has not been rigorously investigated in the literature so far.

In our study, we aimed to evaluate the short-term outcomes after open and laparoscopic low rectal resections and primary anastomosis for rectal cancers using a multidisciplinary standardized fail-safe approach in colorectal surgery. This fail-safe approach, was first used in the engineering discipline and has now been widely adopted in the bioengineering field (24). According to this model, every potential error is secured by an additional safety net, so the magnitude of possible hazards is minimized. We adopted these safety nets for colorectal surgery including a wide range of pre-, peri- and postoperative steps. We measured surgical outcomes in terms of post-operative complications, particularly ALs, and report the effectiveness of the fail-safe model using pre-operative MBP and intraoperative colonic irrigation in rectal surgery.

METHODS AND MATERIAL

Patients' Cohort and Study Design

We recruited all consecutive patients with resectable rectal cancer undergoing elective surgical resections with primary anastomosis and protective ileostomy from January 2015 till December 2020 at Reinbek Hospital St. Adolf-Stift Germany (**Figure 1**). All patients were managed by a standard multidisciplinary approach of a fail-safe-mode as outlined in **Table 1**. We excluded all patients with benign rectal lesions, emergency rectal surgeries, patients with terminal stoma without anastomosis and patients without perioperative colonic irrigation or ileostomy. The patients with cancer of the middle (>6–12 cm from the anal verge) or lower third of the rectum (<6 cm from the anal verge) received a neo-adjuvant therapy if staged IIA (according to AJCC/UICC-classification) or higher (25) using a neoadjuvant chemoradiation following the multidisciplinary tumor board decision. Patients with lesions in the upper rectum (>12 cm from the anal verge) were included, if they were treated with low anterior resection due to tumor extension or if localized in the middle rectum preoperatively. We recorded the patients' demographics, body mass index (BMI), the American Society of Anesthesiologists (ASA) classification of physical health, tumor localization, open or laparoscopic surgical procedure, laparoscopic conversion to open surgery, length of hospital stay, complications according to Dindo-Clavien's classification (26) and 30-days-mortality.

MBP was performed one day before surgery using 2l of Endofalk® (Dr. Falk Pharma GmbH®, Freiburg, Germany). No oral antibiotic was applied to the patients' cohort in our study. A peri-operative single shot antibiotic using 500mg metronidazole and 1,500 mg cefuroxime was given to all patients, half an hour before the incision, and was repeated at 4 h during surgery. The primary endpoint of the surgical therapy using the fail-safe model was the estimation of the rate of AL. We used endoscopy for the diagnosis of AL followed by a CT scan instead of a primary CT scan. The characteristics for AL were defined by the grading system proposed by Rahbari et al. (2). Postoperative morbidity was defined as complication occurring within 30 days after surgery, or during the same hospital stay.

Surgical Procedure

For rectal cancer resections with low rectal anastomosis, a full mobilization of the left hemicolon was routinely performed. During the laparoscopic rectal resection, first a nerve preserving total mesorectal excision (TME) was done. Then the dissection and resection of the rectum below the tumor about 1–3 cm from the anal verge with a linear stapler (45 mm EndoGIA™, Medtronic, Dublin, Ireland) was performed. In case of large specimen, additional stapling catridges were used. In case of an open procedure, the transection of the rectal specimen was done using an Echelon CONTOUR™

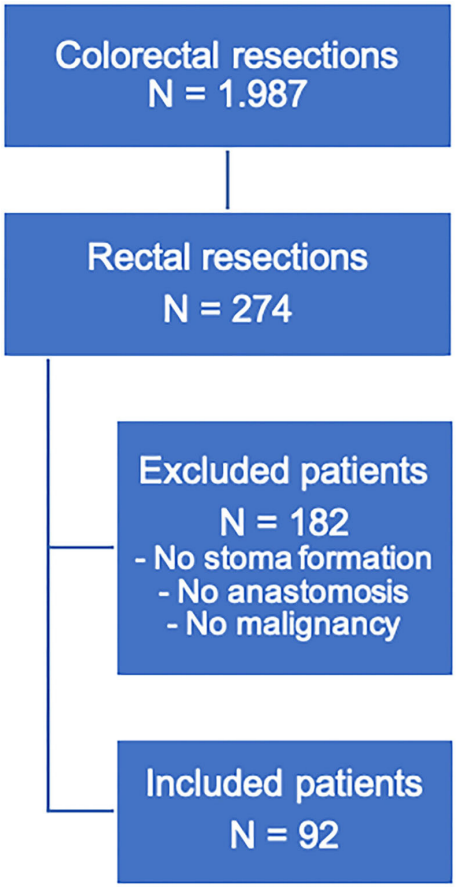

FIGURE 1 | Flowchart for the selection of patients with rectal resections in this study. Patients with rectal resections for benign lesions, abdominoperineal extirpation, or no stoma formation (due to preoperative stoma or upper rectal resection) were excluded.

TABLE 1 | Fail-safe protocol for laparoscopic elective rectal resections in this study.

Preoperative settings	
Mechanical bowel preparation with 2l Endofalk®	O
Preoperative intravenous single-shot antibiotics	O
Operative approach/technical aspects	
Multidisciplinary team lead by an experienced colorectal surgeon	O
Complete mobilization of the hemicolon for tensions free anastomosis	O
Bleeding / perfusion test at the edge of resection margin	O
End-to-end anastomosis	O
– Mesentery is in one line with resection margin	O
– Do not free endings from fatty tissue	O
– Avoid sharp-angled edges	O
– Stretching of anal sphincter muscle for 3 minutes	O
– Spine of the stapling-device in direct contact with stapled line	O
– After joining ends, compression for at least 1 minute before release	O
– Anastomotic assessment using sigmoidoscope (air test + intraluminal inspection)	O
– Diverting stoma for low rectal anastomosis	O
– On-table-lavage over efferent loop of ileostomy with 5l of NaCl	O
– Place a drainage tube near the anastomosis	O
Postoperative protocol	
3 days liquid low-volume high-calorie nutrition (except patients with diverting stoma)	O
Full meals from 4th POD onwards	O
Endoscopic control of colorectal-/coloanal anastomosis on 4th POD	O
In case of insufficiency consideration of OTSC ® application	O

device (Ethicon, Raritan USA). The proximal division was performed extracorporially through a Pfannenstiel incision. Before performing the anastomosis, the sphincter muscle was manually stretched. The anastomosis was performed intracorporially using a transanally introduced circular stapling device (28 mm circular stapling device, Metronic, Dubin, Ireland) with the spine in contact to the linear stapling line (27). Before performing the anastomosis, a compression for at least 60 s was done to reduce the tissue edema. An air-leakage test was routinely performed afterwards. A protective ileostomy was conducted for all low rectal anastomosis at the terminal ileum loop. An additional intraoperative colonic irrigation was installed with 5 liters of warm saline *via* efferent loop of the ileostomy. For this procedure, a urinary catheter was inserted into the efferent loop that was blocked by manual control with 5 ml of sterile water to prevent a massive retrograde discharge (**Figure 2**). To secure the anastomosis, a second surgeon would manually stretch the anal orifice to ensure a seamless outflow. The outflow was visually examined for persisting fecal load by the second surgeon and the procedure was continued until the outflow was clear and without any visible fecal load. Afterwards, a soft drainage tube was placed intracorporeally near the site of anastomosis (**Table 1**). On the 4th postoperative day, an endoscopy was performed to confirm the anastomotic integrity and then the soft drainage tube was removed.

AL was defined as "a defect of the intestinal wall integrity at the ileocolic, colorectal or coloanal anastomotic site (including suture and staple lines of neorectal reservoirs) leading to a communication between the intra- and extraluminal compartments" (2). A pelvic abscess close to the anastomosis was also considered as anastomotic leakage (2). AL was graded according to the standard classification into grade A, B or C.

Statistics and Ethics

Statistical analyses were performed using IBM SPSS Statistics Version 25 (IBM Co., Armonk, NY, USA). All variables were listed as means with standard deviation. Categorical variables were arranged as numbers with percentages.

This study was conducted in accordance with the declaration of Helsinki (28). Ethical approval was waived by the local Ethics Committee of the Medical Association Schleswig-Holstein as this

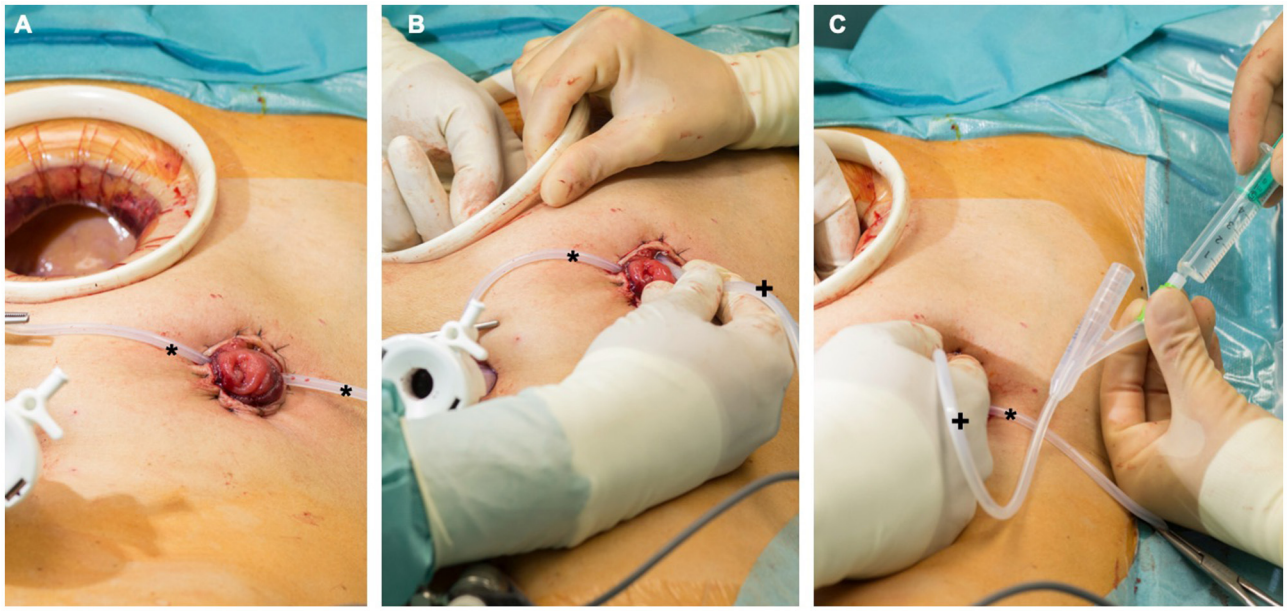

FIGURE 2 | (A) Protective ileostomy after rectal resection. The Pfannenstiel incision is still protected by a wound retractor. A loop (*) is stabilizing the stoma during manipulation. **(B)** A urinary catheter (+) is placed in the efferent loop. **(C)** The catheter (+) is blocked under manual control with 5 ml before starting the antegrade colonic irrigation. The intestine can be checked within the procedure by one surgeon to prevent dislocation of the catheter or accidental perforation.

is a retrospective study and all the procedures being performed were part of the routine care.

RESULTS

Between January 2015 and December 2020 1,987 colorectal surgical procedures were performed in the study center. This included a total of 274 (13.8%) rectal resections including Hartmann procedures or abdominoperineal extirpations. 92 patients were treated for rectal cancer and underwent therefor low rectal resections with primary anastomosis and protective ileostomy using the fail-safe model including an intraoperative colonic irrigation.

Of the 92 patients, 61 (66.3%) were men and 31 (33.7%) were women, with a mean overall age of 64.40 years (range 37–86 years). In 88 (95.7%) patients, a laparoscopic approach was used, while four patients were treated by laparotomies (4.3%). The patients' characteristics in this study are listed in **Table 2**.

An anastomotic leakage occurred in 3 (3.3%) cases. Two case of type B rectal insufficiency according to the classification by Rahbari et al. were diagnosed via endoscopic assessment, and they were treated by endoscopic vacuum therapy. One patient needed a re-operation due to an extended wall deficit.

Post-operative complications were reported in 25 (27.2%) patients that were grouped according to the Dindo-Clavien's classification; 7 (7.6%) grade I, 6 (6.5%) grade II, 0 (0%) grade IIIa, 7 (7.6%) grade IIIb and 5 (5.4%) grade IV cases were reported. There was no mortality during hospital stay and within first 30 days after surgery. **Table 3** provides an overview of the short-term postoperative outcomes and complications. Of the cases with grade IIIb complications, one patient had prolonged paralysis, two cases had postoperative subcutaneous hematoma, which needed evacuation, two AL treated by endoscopy, one by re-operation and one perioperative perforation of the ileum. The median postoperative length of hospitalization was 8 (4–45) days.

DISCUSSION

In our study, using a standardized fail-safe approach including a pre-operative MBP and peri-operative colonic irrigation, we report an over-all complication rate of 27.2% with AL rate of 3.3%. The fail-safe approach includes pre- and intra-operative colonic irrigation as a core component of the multi-step peri-operative management plan for low rectal resections.

The use of colonic irrigation before and during surgery provides a foundation for a safe anastomosis by reducing intracolonic pressure, fecal load, and bacterial count in the vicinity of anastomosis (29, 30).

Preoperative Mechanical Bowel Preparation

As first reported by Nichols and Condon in 1971, MBP is associated with a reduced complication rate following colorectal surgery (31). In contrast, some large data sets have shown that pre-operative MBP alone has no influence on post-operative complications such as SSI or AL (16, 32, 33). However, the combination of non-absorbable oral antibiotics with pre-operative MBP was shown to be beneficial in preventing and reducing SSI and AL (18, 34, 35). Currently, this combination of pre-operative antibiotics and MBP is frequently used worldwide

TABLE 2 | Characteristics of the study cohort ($n = 92$).

Age, years (mean ± SD)	64.4 ± 11.66
Body Mass Index (mean ± SD)	27.15 ± 4.84
Sex (%)	
Male	61 (66.3)
Female	31 (33.7)
UICC/AJCC (%)	
0	5 (5.4)
I	36 (37.1)
II	17 (18.5)
IIIA	13 (14.4)
IIIB	12 (13.1)
IIIC	4 (4.3)
IV	5 (5.4)
ASA classification (%)	
ASA 1	4 (4.3)
ASA 2	69 (75.0)
ASA 3	19 (20.7)
ASA 4	0 (0)
Tumor localization (%)	
Lower rectum (<6 cm)	34 (37.0)
Middle rectum (6–12 cm)	47 (51.1)
Upper rectum (12–16 cm)	11 (12.0)
Approach (%)	
Open	4 (4.3)
Laparoscopic	88 (95.7)
Number of used stapling devices, mean (Range)	2.3 (1–4)
Neoadjuvant treatment (%)	47 (51.1)
Comorbidity (%)	
Arterial Hypertension	43 (46.7)
Smoking	11 (12.0)
Diabetes mellitus	12 (12.0)

TABLE 3 | Outcome after intraoperative colonic irrigation ($n = 92$).

Outcome	***n* (%)**
Anastomotic leakage	3 (3.3)
Prolonged paralysis	5 (7.1)
Kidney failure	4 (5.7)
Pneumonia	2 (2.9)
Surgical side infection	1 (1.4)
Other	8 (11.4)
Postoperative bleeding	2 (2.2)
Length of hospital stay after surgery [days] (mean ± SD)	10 ± 6.55

Some postoperative complications occurs in the same patient.
SD, standard deviation.

with success. A recently published large retrospective registry study including more than 20,000 patients showed a significantly lower SSI and AL rates after combined MPB with oral antibiotics, whereas the research did not report benefit of MBP when used alone (36).

MBP has not been widely adopted by the European colorectal surgeons. The reasons for this reluctance are multifactorial, but the trend toward enhanced recovery after surgery (ERAS) protocols that excludes routine MBP is probably a significant contributor (37). According to the fail-safe model used in our study and, in contrast to some randomized controlled trials, we used MPB without oral antibiotics but with an intra-operative colonic irrigation in rectal surgery. This approach resulted in lower AL rates than those reported by Klinger et al. (36). In their study on a total of 27,804 patients, 5,471 patients underwent surgery without pre-operative preparation, 7,617 received MBP alone, 1,374 were given antibiotic bowel preparation (ABP) alone, while 8,885 patients received both ABP and MBP. The patients with dual preparation showed less rates of SSIs and ALs (OR = 0.53, $p < 0.001$). The study has recommended a routine use of ABP and MBP in elective colorectal resections. In contrast, we used MBP and peri-operative colonic irrigation with even better results. In 2017, Ji et al. have a large single-center data on more than 1,300 rectal cancer resections. The authors have shown that AL rate did not significantly differ with or without MPB but remained substantially high with 7.81% vs. 9.27%, respectively (38). Nevertheless, until recently, the published data has shown AL rates of higher than 5% regardless of ABP or MBP alone or in combination. Of course, our data with a leakage rate of 3.3% comes from a retrospective single center cohort study and has to be carefully compared with the results of randomized controlled trials mentioned earlier. Nevertheless, an AL-rate below 5% in rectal cancer surgery is promising and needs further evaluation.

Intraoperative Colonic Irrigation

Even after meticulous pre-operative bowel preparation, the colon is usually not completely mechanically cleaned and fecal particles and ingested roughage are still left in the colon. In our study, beside pre-operative bowel preparation, diverting ileostomy and intra-operative colonic irrigation were performed *via* efferent loop of the ileostomy. These two additional measures were taken in order to decontaminate the colon and thus mitigating the risk of AL. Intra-operative colonic irrigation was first introduced by Muir et al. (39), and was modified by Dudley and co-workers proposing antegrade on-table colonic irrigation with primary anastomosis (22, 29). Interestingly, various authors have argued that intraoperative colonic irrigation with primary anastomosis was feasible for left sided resections (40–42). The intra-operative colonic preparation would be more valuable in unprepared or inadequately prepared bowels in emergency situations and in tumorous stenosis. There is also enthusiasm for the on-table colonic irrigation with an additional on-table colonoscopy especially when a pre-operative colonoscopy is not feasible due to emergency or tumor stenosis (42).

Several studies have shown that performing colonic irrigation intraoperatively can potentially reduce the rate of Hartman's procedures (22, 43). However, there is no reported data that can establish the effectiveness of routine pre-operative MBP in combination with on-table colonic irrigation as demonstrated by the fail-safe model in our study. Such approach offers another opportunity of cleansing the colon as well as the rectal anastomosis for better oncological surgical outcomes.

Fail-Safe-Protocol

The key elements of our fail-safe model for lower rectal resections include MBP, intraoperative colonic irrigation with drainage near anastomosis, proximal ileostomy and a routinely performed endoscopic assessment on the 4th postoperative day. Using this protocol, our study showed a low rate of AL (3.3%). Such encouraging results are often attributed to the surgeon's experience, which is truly vital. However, over a span of more than 5 years and in the presence of different operating surgeons with various levels of experience in a teaching hospital, higher complication rates could be expected. Following our fail-safe-protocol, standardized steps are elaborated not only for pre- and post-operative course but also during surgery. Especially in the phase of reconstruction the elaborated steps are clearly defined. This means a routinely perfusion test exactly at the resection margin and the preservation of fatty tissue from one or the other end to reduce perfusion deficiency. The anastomosis in the rectal resections were routinely performed using a circular stapling devices and end-to-end reconstruction. Before performing the anastomosis, a routinely stretching of the sphincter muscle was done. Then, the spine of the device would pierce in direct contact to the stapling line and a slow close approximation was followed by a compression for at least 1 min. This reduces tissue edema to ensure a safe staple-line. The functional outcomes after reconstruction in rectal surgery is a key element and the German Guidelines of Colorectal Cancer favor a non-straight anastomosis, as this strategy has shown better functional results, especially in the early postoperative period (44, 45). A retrospective analysis of the postoperative functional outcome following the fail-safe-approach showed a reduced AL rate without adverse functional outcomes or quality of life (27).

From a different perspective, intraoperative colonic irrigation might be beneficial if an AL occurs because of the reduced fecal load. Historically, the treatment of choice for a leaking colorectal or coloanal anastomosis had been a resection of the anastomosis followed by a Hartmann's procedure. Pelvic abscesses are often drained percutaneously under a CT-guided approach. Our study demonstrates that the incidence of pelvic abscess or peritonitis and especially the scale of complications resulting from AL can be avoided by intraoperative colonic irrigation integrated into a multidisciplinary fail-safe protocol.

Study Limitations

Our study results are drawn from a small sample size in a single center setting with a heterogenous study cohort. Due to several reasons, including explicit inclusion criteria for rectal cancers, not all patients with rectal surgery could be included in this analysis. In addition, the retrospective design of this study indicates possible selection bias. Lastly, an absence of a control group due to its retrospective design did not allow us to report a case-control study. Though our results are promising, larger clinical trials in multi-center settings using a randomization are needed to help establish the effectiveness of our fail-safe model including the described intraoperative colonic irrigation.

CONCLUSION

This study concludes that a low rate of AL in elective low rectal resections is feasible. This can be achieved by adopting a standardized fail-safe model peri-operative protocol. In the study center, this includes a pre-operative MBP, an intra-operative colonic irrigation to reduce fecal load at anastomotic site, a covering protective ileostomy and endoscopic evaluation on the 4th postoperative day. Even not all the peri-operative steps are evidence based, the presented AL rate is promising. A low rate of AL potentially reduces the concomitant complications of pelvic abscess, peritonitis, paralytic ileus and SSIs. As this is a retrospective cohort study reporting a single-center experience, further studies are essential, especially including emergency and training procedures, that can potentially validate our fail-safe-model using intra-operative colonic irrigation.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JH collected and analyzed the data and drafted the manuscript. SK developed the fail-safe-concept and drafted the manuscript. SG performed a scientific enrichment, linguistics manuscript drafting, and statistical analysis. TS reviewed the manuscript and supervised the implementation of the new concept. HH reviewed the manuscript and made an impact on discussion. All authors read and approved the final manuscript.

REFERENCES

1. Rullier E, Laurent C, Garrelon JL, Michel P, Saric J, Parneix M. Risk factors for anastomotic leakage after resection of rectal cancer. *Br J Surg.* (1998) 85:355–8. doi: 10.1046/j.1365-2168.1998.00615.x
2. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery.* (2010) 147:339–51. doi: 10.1016/j.surg.2009.10.012
3. Tsai Y, Chen WT. Management of Anastomotic Leakage After Rectal Surgery: A Review Article. *J Gastrointest Oncol.* (2019) 10:1229–37. doi: 10.21037/jgo.2019.07.07
4. Chadi SA, Fingerhut A, Berho M, DeMeester SR, Fleshman JW, Hyman NH, et al. Emerging Trends in the Etiology, Prevention, and Treatment of

Gastrointestinal Anastomotic Leakage. *J Gastrointest Surg.* (2016) 20:2035–51 doi: 10.1007/s11605-016-3255-3
5. Phitayakorn R, Delaney CP, Reynolds HL, Champagne BJ, Heriot AG, Neary P, et al. Standardized algorithms for management of anastomotic leaks and related abdominal and pelvic abscesses after colorectal surgery. *World J Surg.* (2008) 32:1147–56. doi: 10.1007/s00268-008-9468-1
6. Swellengrebel HAM, Marijnen CAM, Verwaal VJ, Vincent A, Heuff G, Gerhards MF, et al. Toxicity and complications of preoperative chemoradiotherapy for locally advanced rectal cancer. *Br J Surg.* (2011) 98:418–26. doi: 10.1002/bjs.7315
7. Marinello FG, Baguena G, Lucas E, Frasson M, Hervás D, Flor-Lorente B, et al. Anastomotic leakage after colon cancer resection: does the individual surgeon matter? *Color Dis.* (2016) 18:562–9. doi: 10.1111/codi.13212
8. Espín E, Ciga MA, Pera M, Ortiz H. Spanish rectal cancer project. Oncological outcome following anastomotic leak in rectal surgery. *Br J Surg.* (2015) 102:416–22. doi: 10.1002/bjs.9748
9. Shogan BD, Carlisle EM, Alverdy JC, Umanskiy K. Do we really know why colorectal anastomoses leak? *J Gastrointest Surg.* (2013) 17:1698–707. doi: 10.1007/s11605-013-2227-0
10. Guraya SY, Murshid KR. Malignant duodenocolic fistula. Various therapeutic surgical modalities. *Saudi Med J.* (2004) 25:1111–4. Available online at: http://www.ncbi.nlm.nih.gov/pubmed/15322610 (accessed May 2, 2020).
11. Lundy J. A Primer on wound healing in colorectal surgery in the age of bioprosthetic materials. *Clin Colon Rectal Surg.* (2014) 27:125–33. doi: 10.1055/s-0034-1394086
12. Biondo S, Parés D, Kreisler E, Ragué JM, Fraccalvieri D, Ruiz AG, et al. Anastomotic dehiscence after resection and primary anastomosis in left-sided colonic emergencies. *Dis Colon Rectum.* (2005) 48:2272–80. doi: 10.1007/s10350-005-0159-9
13. Kiran RP, Murray ACA, Chiuzan C, Estrada D, Forde K. Combined preoperative mechanical bowel preparation with oral antibiotics significantly reduces surgical site infection, anastomotic leak, and ileus after colorectal surgery. *Ann Surg.* (2015) 262:416–25. doi: 10.1097/SLA.0000000000001416
14. Shogan BD, Belogortseva N, Luong PM, Zaborin A, Lax S, Bethel C, et al. Collagen degradation and MMP9 activation by Enterococcus faecalis contribute to intestinal anastomotic leak. *Sci Transl Med.* (2015) 7:286ra68. doi: 10.1126/scitranslmed.3010658
15. Scarborough JE, Mantyh CR, Sun Z, Migaly J. Combined mechanical and oral antibiotic bowel preparation reduces incisional surgical site infection and anastomotic leak rates after elective colorectal resection: an analysis of colectomy-targeted ACS NSQIP. *Ann Surg.* (2015) 262:331–7. doi: 10.1097/SLA.0000000000001041
16. Koller SE, Bauer KW, Egleston BL, Smith R, Philp MM, Ross HM, et al. Comparative effectiveness and risks of bowel preparation before elective colorectal surgery. *Ann Surg.* (2018) 267:734–42. doi: 10.1097/SLA.0000000000002159
17. Cunningham C, Leong K, Clark S, Plumb A, Taylor S, Geh I, et al. Association of Coloproctology of Great Britain & Ireland (ACPGBI): guidelines for the management of cancer of the colon, rectum and anus (2017)—diagnosis, investigations and screening. *Color Dis.* (2017) 19:9–17. doi: 10.1111/codi.13703
18. Murray ACA, Kiran RP. Benefit of mechanical bowel preparation prior to elective colorectal surgery: current insights. *Langenbeck's Arch Surg.* (2016) 401:573–80. doi: 10.1007/s00423-016-1461-9
19. Fa-Si-Oen P, Roumen R, Buitenweg J, van de Velde C, van Geldere D, Putter H, et al. Mechanical bowel preparation or not? Outcome of a multicenter, randomized trial in elective open colon surgery. *Dis Colon Rectum.* (2005) 48:1509–16. doi: 10.1007/s10350-005-0068-y
20. Contant CM, Hop WC. van 't Sant HP, Oostvogel HJ, Smeets HJ, Stassen LP, et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. *Lancet.* (2007) 370:2112–7. doi: 10.1016/S0140-6736(07)61905-9
21. Zmora O, Mahajna A, Bar-Zakai B, Rosin D, Hershko D, Shabtai M, et al. Colon and Rectal Surgery Without Mechanical Bowel Preparation. *Ann Surg.* (2003) 237:363–7. doi: 10.1097/01.SLA.0000055222.90581.59
22. Hong Y, Nam S, Kang JG. The usefulness of intraoperative colonic irrigation and primary anastomosis in patients requiring a left colon resection. *Orig Artic Ann Coloproctol.* (2017) 33:106–11. doi: 10.3393/ac.2017.33.3.106
23. Simmerman EL, King RS, Ham PB, Hooks VH. Feasibility and Safety of Intraoperative Colonoscopy after Segmental Colectomy and Primary Anastomosis. *Am Surg.* (2018) 84:1175–1179. doi: 10.1177/000313481808400733
24. Lemay J-F, Bachand F. Fail-safe transcription termination: Because one is never enough. *RNA Biol.* (2015) 12:927–32. doi: 10.1080/15476286.2015.1073433
25. Vaccaro CA, Bonadeo FA, Benati ML, Quintana GMO, Rubinstein F, Mullen E, et al. Colorectal cancer staging: reappraisal of N/PN classification. *Dis Colon Rectum.* (2004) 47:66–9. doi: 10.1007/s10350-003-0004-y
26. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* (2004) 240:205–13. doi: 10.1097/01.sla.0000133083.54934.ae
27. Herzberg J, Khadem S, Begemann V, Strate T, Honarpisheh H, Guraya SY. Quality of life in patients with rectal resections and end-to-end primary anastomosis using a standardized perioperative pathway. *Front Surg.* (2022) 8:705. doi: 10.3389/fsurg.2021.789251
28. The World Medical Association. *WMA Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects*. Available online at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (accessed August 27, 2021).
29. Dudley HAF, Radcliffe AG, McGeehan D. Intraoperative irrigation of the colon to permit primary anastomosis. *Br J Surg.* (1980) 67:80–1. doi: 10.1002/bjs.1800670203
30. Forloni B, Reduzzi R, Paludetti A, Colpani L, Cavallari G, Frosali D. Intraoperative colonic lavage in emergency surgical treatment of left-sided colonic obstruction. *Dis Colon Rectum.* (1998) 41:23–7. doi: 10.1007/BF02236891
31. Nichols RL, Condon RE. Preoperative preparation of the colon. *Surg Gynecol Obstet*. (1971) 132:323–37. Available online at: http://www.ncbi.nlm.nih.gov/pubmed/4929735 (Accessed December 29, 2019).
32. Slim K, Vicaut E, Panis Y, Chipponi J. Meta-analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation. *Br J Surg.* (2004) 91:1125–30. doi: 10.1002/bjs.4651
33. Slim K, Vicaut E, Launay-Savary M-V, Contant C, Chipponi J. Updated systematic review and meta-analysis of randomized clinical trials on the role of mechanical bowel preparation before colorectal surgery. *Ann Surg.* (2009) 249:203–9. doi: 10.1097/SLA.0b013e318193425a
34. Chen M, Song X, Chen L, Lin Z, Zhang X. Comparing mechanical bowel preparation with both oral and systemic antibiotics versus mechanical bowel preparation and systemic antibiotics alone for the prevention of surgical site infection after elective colorectal surgery. *Dis Colon Rectum.* (2016) 59:70–8. doi: 10.1097/DCR.0000000000000524
35. Morris MS, Graham LA, Chu DI, Cannon JA, Hawn MT. Oral antibiotic bowel preparation significantly reduces surgical site infection rates and readmission rates in elective colorectal surgery. *Ann Surg.* (2015) 261:1034–40. doi: 10.1097/SLA.0000000000001125
36. Klinger AL, Green H, Monlezun DJ, Beck D, Kann B, Vargas HD, et al. The role of bowel preparation in colorectal surgery. *Ann Surg.* (2019) 269:671–7. doi: 10.1097/SLA.0000000000002568
37. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery. *JAMA Surg.* (2017) 152:292. doi: 10.1001/jamasurg.2016.4952
38. Ji WB, Hahn KY, Kwak JM, Kang DW, Baek SJ, Kim J, et al. Mechanical bowel preparation does not affect clinical severity of anastomotic leakage in rectal cancer surgery. *World J Surg.* (2017) 41:1366–74. doi: 10.1007/s00268-016-3839-9
39. Muir EG. Safety in colinic resection. *Proc R Soc Med.* (1968) 61:401–8. Available online at: http://www.ncbi.nlm.nih.gov/pubmed/5654002 (accessed December 29, 2019).
40. Pollock A V, Playforth MJ, Evans M. Peroperative lavage of the obstructed left colon to allow safe primary anastomosis. *Dis Colon Rectum.* (1987) 30:171–3. doi: 10.1007/BF02554331
41. Otsuka S, Kaneoka Y, Maeda A, Takayama Y, Fukami Y, Isogai M. One-stage colectomy with intraoperative colonic irrigation for acute left-sided malignant colonic obstruction. *World J Surg.* (2015) 39:2336–42. doi: 10.1007/s00268-015-3078-5

42. Sasaki K, Kazama S, Sunami E, Tsuno NH, Nozawa H, Nagawa H, et al. One-stage segmental colectomy and primary anastomosis after intraoperative colonic irrigation and total colonoscopy for patients with obstruction due to left-sided colorectal cancer. *Dis Colon Rectum.* (2012) 55:72–8. doi: 10.1097/DCR.0b013e318239be5e
43. Regenet N, Pessaux P, Hennekinne S, Lermite E, Tuech JJ, Brehant O, et al. Primary anastomosis after intraoperative colonic lavage vs. Hartmann's procedure in generalized peritonitis complicating diverticular disease of the colon. *Int J Colorectal Dis.* (2003) 18:503–7. doi: 10.1007/s00384-003-0512-1
44. Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF. *German Guideline for Colorectal Cancer*. (2019). Available online at: https://www.awmf.org/uploads/tx_szleitlinien/021-007OLl_S3_Kolorektales-Karzinom-KRK_2019-01.pdf (accessed September 29, 2020).
45. Brown CJ, Fenech DS, McLeod RS. Reconstructive techniques after rectal resection for rectal cancer. *Cochrane database Syst Rev*. (2008) CD006040. doi: 10.1002/14651858.CD006040.pub2

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Surgery

SYSTEMATIC REVIEW
published: 22 April 2022
doi: 10.3389/fsurg.2022.882173

Coating of Intestinal Anastomoses for Prevention of Postoperative Leakage: A Systematic Review and Meta-Analysis

Kamacay Cira[1], Felix Stocker[1], Stefan Reischl[2†], Andreas Obermeier[3], Helmut Friess[1], Rainer Burgkart[3] and Philipp-Alexander Neumann[1†]*

[1]Department of Surgery, School of Medicine, Klinikum rechts der Isar, Technical University of Munich, Munich, Bavaria, Germany, [2]Institute of Diagnostic and Interventional Radiology, School of Medicine, Klinikum rechts der Isar, Technical University of Munich, Munich, Bavaria, Germany, [3]Department of Orthopaedics and Sports Orthopaedics, School of Medicine, Klinikum rechts der Isar, Technical University of Munich, Munich, Bavaria, Germany

OPEN ACCESS

Edited by:
Sven Flemming, University Hospital of Wuerzburg, Germany

Reviewed by:
Michael Meir, University Hospital Würzburg, Germany
Ulf Gunnarsson, Umeå University, Sweden

***Correspondence:**
Kamacay Cira
kamacay.cira@tum.de

†ORCID:
Philipp-Alexander Neumann
orcid.org/0000-0001-8361-3934
Stefan Reischl
orcid.org/0000-0001-7341-4296

Speciality section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *23 February 2022*
Accepted: *05 April 2022*
Published: *22 April 2022*

Citation:
Cira K, Stocker F, Reischl S, Obermeier A, Friess H, Burgkart R and Neumann P-A (2022) Coating of Intestinal Anastomoses for Prevention of Postoperative Leakage: A Systematic Review and Meta-Analysis. Front. Surg. 9:882173. doi: 10.3389/fsurg.2022.882173

Background: For several decades, scientific efforts have been taken to develop strategies and medical aids for the reduction of anastomotic complications after intestinal surgery. Still, anastomotic leakage (AL) represents a frequently occurring postoperative complication with serious consequences on health, quality of life, and economic aspects. Approaches using collagen and/or fibrin-based sealants to cover intestinal anastomoses have shown promising effects toward leak reduction; however, they have not reached routine use yet. To assess the effects of covering intestinal anastomoses with collagen and/or fibrin-based sealants on postoperative leakage, a systematic review and meta-analysis were conducted.

Method: PubMed, Web of Science, Cochrane Library, and Scopus (01/01/1964 to 17/01/2022) were searched to identify studies investigating the effects of coating any intestinal anastomoses with collagen and/or fibrin-based sealants on postoperative AL, reoperation rates, Clavien–Dindo major complication, mortality, and hospitalization length. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

Results: Overall, 15 studies (five randomized controlled trials, three nonrandomized intervention studies, six observational cohort studies) examining 1,387 patients in the intervention group and 2,243 in the control group were included. Using fixed-effects meta-analysis ($I^2 < 50\%$), patients with coated intestinal anastomoses presented significantly lower AL rates (OR = 0.37; 95% CI 0.27–0.52; $p < 0.00001$), reoperation rates (OR, 0.21; 95% CI, 0.10–0.47; $p = 0.0001$), and Clavien–Dindo major complication rates (OR, 0.54; 95% CI, 0.35–0.84; $p = 0.006$) in comparison to controls, with results remaining stable in sensitivity and subgroup analyses (stratified by study design, age group, intervention used, location of anastomoses, and indication for surgery). The length of hospitalization was significantly shorter in the intervention group (weighted mean difference (WMD), −1.96; 95% CI, −3.21, −0.71; $p = 0.002$)

using random-effects meta-analysis ($I^2 \geq 50\%$), especially for patients with surgery of upper gastrointestinal malignancy (WMD, −4.94; 95% CI, −7.98, −1.90; $p = 0.001$).

Conclusion: The application of collagen-based laminar biomaterials or fibrin sealants on intestinal anastomoses can significantly reduce postoperative rates of AL and its sequelae. Coating of intestinal anastomoses could be a step toward effective and sustainable leak prevention. To assess the validity and robustness of these findings, further clinical studies need to be conducted.

Keywords: intestinal anastomoses, coated collagen patch, fibrin sealant, fibrin glue (FG), anastomotic leakage (AL)

INTRODUCTION

In the field of visceral surgery, both patients and surgeons are still challenged with a very common and potentially devastating postoperative complication, namely, anastomotic leakage (AL). Whether the intestinal anastomoses were performed in the upper or lower gastrointestinal tract (GIT), postoperative AL accompanies a significant proportion of intestinal surgical procedures (1–10). Colorectal procedures, for instance, present with AL rates of up to 25.6% (4, 8, 9), and esophageal or esophagogastric procedures present with AL rates as high as 19.5% (6, 7). AL rates among patients with malignancies are even associated with local (11) and distant (12) tumor recurrences. Furthermore, AL has been shown to increase the total clinical and economic burden by 0.6–1.9 times for patients undergoing intestinal surgery for colorectal cancer (13).

In this context, it is not surprising that substantial scientific efforts have been invested now for over half a century to develop strategies and medical aids to reduce or even prevent the development of postoperative AL. The first approach toward covering and hereby mechanically strengthening the newly built intestinal anastomosis was to apply cyanoacrylate preparations, better known as surgical glues initially tested on skin wounds in military settings. Their rapid formation of a stable but flexible connection with intestinal tissue was considered advantageous (14, 15). Other experimental approaches utilized sterile polyethylene plastic sheets (16), fibrin adhesives (17, 18), and collagen fleeces (17) to additionally support the anastomoses. The most promising adhesives, however, are fibrin sealants, as these have been acknowledged across various surgical specialties and were approved in their liquid form by the FDA in 1998 (19).

Biodegenerable and absorbable fibrin sealants consist of two components: sealer protein solution (human fibrinogen, factor XIII, and protease inhibitor aprotinin) and thrombin solution (human thrombin and calcium chloride). Upon application of the sealant to the site of anastomosis, thrombin transforms fibrinogen into insoluble fibrin monomers, which are then polymerized in the presence of factor XIII to a stable fibrin network within minutes. Protease inhibitor aprotinin protects this network from plasmin-mediated proteolysis. Simulating the last step of the coagulation cascade, fibrin sealants are used to initiate hemostasis, seal tissue, and promote the healing processes (20).

With the 2010 FDA approval of a fibrin sealant-coated equine collagen matrix (21) used primarily for hemostatic purposes, experimental approaches studying its potentially beneficial effect on anastomotic healing were initiated. Within the last decade, mainly animal studies were conducted, revealing promising effects on reducing postoperative AL and mortality rates upon using either fibrin sealants or collagen-based laminar biomaterials (22–33). For many years, just a small number of experimental trials have been available, examining the effect of these sealants on human populations (34–40). Until now, no meta-analysis has been conducted examining the effect of externally covering intestinal anastomoses with collagen-based laminar biomaterials or fibrin sealants on postoperative AL and its consequences within a human population.

Therefore, the aim of this study was to systematically evaluate the efficacy of externally coating intestinal anastomoses of the upper and lower GIT, regardless of location or underlying disease, with collagen-based laminar biomaterials and/or fibrin sealants in reducing postoperative AL rates and its accompanying complications. A systematic review and meta-analysis of existing human studies was conducted, comparing the summary effect size, calculating the pooled odds ratios (ORs) with 95% confidence intervals (CIs), and performing subgroup analyses stratified by study design, coating utilized, age group, indication for surgery, and location of anastomoses.

METHODS

This systematic review and meta-analysis was conducted and reported according to the recommendations in the *Cochrane Handbook for Reviews of Interventions* (41) and the *Preferred Reporting Items for Systematic Review and Meta-Analyses* (*PRISMA*) *Statement 2020* (42).

Eligibility Criteria

For this study, all observational studies (prospective or retrospective comparative cohort or case–control studies), nested case–control studies, randomized controlled trials (RCTs), nonrandomized controlled trials, and cross-sectional studies were included based on the following criteria: examined a human population—regardless of age, sex, or underlying condition; published only in English, German, or Spanish language; available as either abstract or full-text article in the medical databases between 01/01/1964 and 17/01/2022; included humans undergoing any intestinal surgical procedure

with the formation of any kind of intestinal anastomoses with focus on the upper and lower GIT; the intervention group included patients who received an intestinal anastomosis (regardless of anastomotic technique) coated or reinforced with either a collagen-based laminar biomaterial or a fibrin sealant (synthetic or animal derived, with or without additional substances embedded, regardless of the manufacturer); control group included patients who received an intestinal anastomosis (regardless of anastomotic technique) not coated or reinforced with any product; and depicted postoperative clinical outcomes, including but not restricted to, AL, reoperation and mortality rates, major complication rates (grades III–V) according to the Clavien–Dindo classification of surgical complications (43) (C-DMC), and length of hospital stay.

Exclusion criteria comprised studies representing reviews or meta-analyses, case reports or case series, animal studies, *ex vivo* or *in vitro* studies; gastrointestinal surgical procedures without the formation of an intestinal anastomosis; hepatobiliary anastomoses (e.g., pancreaticointestinal anastomoses, biliodigestive anastomoses); closure of transmural and nontransmural intestinal defects; intestinal stumps or pouches; coating of anastomosis in an operative revision, secondary to AL or fistula formation; and any kind of anastomotic coatings or sealants not based on collagen and/or fibrin.

Search Strategy

We conducted a comprehensive systematic literature search for studies published in the electronic medical databases PubMed (MEDLINE), Web of Science, Scopus, and Cochrane Library using predefined search items, further specified in **Supplementary Table S1**.

To ensure that potentially relevant studies were not missed, reference lists of reviews and included studies were examined manually, and additional web search was conducted. In case of ambiguous or inadequate data presentation, we contacted these studies' authors to provide the required information. The final search was conducted on 17/01/2022.

Selection Process

Study selection was performed by two investigators (surgical residents: K.C. and F.S.) independently. All studies identified in the search process were exported to the reference management tool EndNote X9 (The EndNote Team, Clarivate 2013, Philadelphia, PA, USA).

Duplicates were removed by computer-based methods, followed by a secondary manual exclusion. Titles and abstracts were assessed manually and excluded in accordance with our predefined eligibility criteria. Abstracts and full-text articles correlating with these criteria were retrieved and further evaluated for eligibility. Disagreements concerning eligibility were discussed and resolved in consensus with a third investigator (surgical specialist: P-A.N.), who independently assessed the accuracy of the search results.

Data Collection Process

Two investigators (K.C. and F.S.) independently performed data collection and analysis onto a Microsoft Excel spreadsheet (Home and Student 2019 edition; Microsoft, Redmond, WA, USA), and a third investigator (radiology resident: S.R.) independently assessed the accuracy of the extracted data. In case of any discrepancies, the extracted data were discussed and resolved in consensus with the fourth investigator (P-A.N.) acting as an arbitrator.

Data Extraction

For each study, we collected the following data, if available: author, year, and country of publication; study design and inclusion period; ethical approval and funding; inclusion and exclusion criteria; number of patients in the intervention and control group; baseline characteristics such as age, sex, and body mass index; surgical characteristics: indication for surgery, surgical intervention and technique, and anastomoses (number, location, and technique); collagen-based biomaterial or fibrin sealant used in the intervention group; and any additional intervention. Study and patients' characteristics are presented in **Table 1**, and surgical characteristics are given in **Table 2**.

To provide an implication on and utilization in surgical practice, data on postoperative AL, reoperation, C-DMC, mortality rate, and the length of hospitalization were collected (**Table 3**).

Risk of Bias Assessment

The quality of the included studies was assessed by two investigators (K.C. and F.S.) independently. Systematic assessment of the risk of bias for randomized controlled studies and nonrandomized studies of interventions was conducted using the Risk of Bias 2 (RoB 2) tool (44) and the Risk Of Bias In Nonrandomized Studies of Interventions (ROBINS-I) tool (45), according to the recommendations in the Cochrane Handbook for Reviews of Interventions (41). The Newcastle–Ottawa Scale (NOS) for cohort studies (46), a commonly used and established tool, was used to evaluate the quality of included observational studies. We defined any study with an NOS score of >7 as high quality, 5–7 as moderate, and <5 as low quality. Any disagreements were resolved in consensus with the third investigator (S.R.).

Synthesis Method

All statistical analyses in this review were carried out using Review Manager software version 5.3. (Nordic Cochrane Centre, Copenhagen, Denmark) and the JASP Team (2021; JASP, version 0.16). Results with a p-value of <0.05 are considered significant. Values given in the unit "median (interquaratile range)" or "median (range: minimum – maximum)" were converted using the Box–Cox method of McGrath et al. (47) to estimate the sample mean and standard deviation. Heterogeneity across studies was analyzed using the statistical I^2 test, considering $I^2 \geq 50\%$ as substantial heterogeneity (48). In case of substantial heterogeneity ($I^2 \geq 50\%$), the random-effects model was used to conduct the meta-analyses; for $I^2 < 50\%$, the fixed-effects model was utilized.

TABLE 1 | Study and patient characteristics.

Author	Year	Country	Study design	Age group	Number of patients, *n*		Anastomotic coating (intervention group)	Indication for surgery
					I	C		
Brehant et al. (50)	2013	France	RCS	Adult	202	404	Collatamp Sponge (C-BLB)	Colorectal cancer; Benign lesions
Marano et al. (54)	2016	Italy	RCS	Adult	28	34	TachoSil (C-BLB)	Gastric cancer; Esophagogastric junction cancer
Torres-Melero et al. (58)	2016	Spain	NRS	Adult	22	27	Fibrin-coated collagen sponge (C-BLB)	Peritoneal carcinomatosis (colorectal cancer)
Fernandez et al. (34)	1996	Spain	RCT	Adult	42	44	Tissucol (FS)	Gastric adenocarcinoma
Grieder et al. (51)[a]	2010	Switzerland	Pilot-study	Adult	118	113	Fibrin Glue (FS)	Colorectal cancer
Huang et al. (52)	2021	China	RCS	Adult	86	141	Bioseal (FS)	Squamous cell or adenocarcinoma of the thoracic or esophagogastric junction
Huh et al. (36)	2010	Korea	PCS	Adult	104	119	Tissucol or Greenplast (FS)	Rectal cancer
Kim et al. (53)	2013	Korea	RCS	Adult	414	734	Tissucol or Greenplast (FS)	Rectal cancer
Liu et al. (37)	2003	United States	NRS	Adult	120	360	Tisseel (FS)	Obesity (bariatric surgery)
Oliver et al. (55)	2012	Spain	RCT	Adult	52	52	Tissucol Duo (FS)	Different conditions (high-risk anastomoses)
Saldaña-Cortés et al. (38)	2009	Mexico	NRS	Pediatric	14	24	Quixil (FS)	Caustic esophageal injury
Sdralis et al. (56)	2019	Greece	RCT	Adult	35	22	Tisseel (FS)	Adenocarcinoma of the distal esophagus or esophagogastric junction
Sieda et al. (57)	2015	Egypt	PCS	Adult	35	35	Commercial Fibrin Sealant	Malignant colonic obstruction; Nonmalignant colonic obstruction
Silecchia et al. (39)	2006	Italy	RCT	Adult	93	111	Tissucol (FS)	Obesity (bariatric surgery)
Upadhyaya et al. (40)	2007	India	RCT	Pediatric	22	23	Tisseel (FS)	Esophageal atresia with tracheoesophageal fistula

RCS, Retrospective cohort study; PCS, prospective cohort study; RCT, randomized controlled trial; NRS, nonrandomized study; *I, Intervention group (coated or reinforced anastomoses); C, control group*; *C-BLB, collagen-based laminar biomaterial; FS, fibrin sealant; Benign lesions*, *diverticulitis, inflammatory bowel disease, or other lesions; nonmalignant colonic obstruction*, *perforated diverticulum, inflammatory bowel disease, volvulus, fecal fistula, bands.*
[a]*Abstract.*

Potential publication bias was examined using Egger's test (49) for funnel plot asymmetry for outcomes including ≥10 studies, as it is not recommended to conduct the test in the case of fewer studies included (41). To evaluate the stability of our outcomes, we conducted a sensitivity analysis by evaluating the impact of excluding one study at a time on the pooled OR, regardless of the observed heterogeneity. Subgroup analyses were planned *a priori* to assess potential risk factors on studied postoperative outcomes and patient groups at higher risk for complications. The predefined subgroups, assessed in secondary analysis, were stratified by study design, intervention used (collagen-based laminar biomaterials and/or fibrin sealants), age group (adult or pediatric), location of anastomoses (esophagus, stomach, small intestine, colon, and/or rectum), and indication for surgery. Differences in the outcomes across these subgroups were assessed and reported using the test for subgroup differences (TSD).

In subject to the calculated I^2 percentage, either the random-effects model ($I^2 \geq 50\%$) or the fixed-effects model ($I^2 < 50\%$) was used to summarize and depict pooled ORs with 95% CIs in a forest plot.

RESULTS

In summary, we identified 1,581 studies through electronic database search and 11 studies through citation and website search, out of which 382 duplicates were removed. Title and abstracts of 1,199 studies were screened manually, and 1,142 studies lacking eligibility were excluded. Of 57 eligible studies thus-acquired for full-text analysis, 35 could not be retrieved, leaving 22 studies originating from the database search and 11 studies identified by other methods. After full-text analysis, 10 of 22 studies were excluded: five studies without a control group, four studies using other interventions, and one study with an irrelevant endpoint. Of the 11 studies identified through citation and website search, eight studies without the formation of an anastomosis were excluded. Finally, 15 studies (34, 36–40, 50–58) were analyzed quantitatively and qualitatively for this systematic review and included in our meta-analyses (**Figure 1**).

Study Characteristics

This systematic review and meta-analysis evaluates five RCTs (34, 39, 40, 55, 56), three nonrandomized intervention studies (NRSs)

TABLE 2 | Surgical characteristics.

Author	Year	Open/ laparoscopic[b]	Surgical intervention	Site and technique of anastomosis	
				I[c]/C[c]	Anastomotic covering/ reinforcement (I[c])
Brehant et al. (50)	2013	✓/✓	Colon or colorectal resection	Intestinal anastomosis	Collatamp (10 × 10 cm)
Marano et al. (54)	2016	✓/—	Total or distal gastric resection; Distal esophagectomy and total gastrectomy	Mechanical end-to-side esophagojejunal anastomosis (25 mm anvil head circular stapler); mechanical side-to-end gastrojejunal anastomosis (28 mm anvil head circular stapler)	TachoSil (9.5 × 4.8 × 0.5 cm with two seromuscular stitches)
Torres-Melero et al. (58)	2016	N/A	Debulking colon resection	Mechanical intestinal anastomosis	Fibrin-coated collagen sponge (9.5 × 4.8 cm)
Fernandez et al. (34)	1996	N/A	Curative R_2 or extended gastrectomy	Mechanical end-to-side esophagojejunal anastomosis (Roux-en-Y jejunal loop used; tobacco pouch formed manually)	Tissucol (applied on both surfaces during approximation of anvil to the Stapler Cartridge)
Grieder et al. (51)[a]	2010	✓/✓	Colorectal resection	Mechanical intestinal anastomosis (approximately 10 cm above anal verge)	Fibrin glue (1 mL; applied between pressure plates of stapler, fired after 2–3 min)
Huang et al. (52)	2021	✓/✓	McKeown esophagectomy	Mechanical end-to-side esophagogastric anastomosis (inverted; circular stapler: EEA 21 or 25 mm)	Bioseal (2.5 mL)
Huh et al. (36)	2010	—/✓	Low anterior rectal resection	Double-stapled colorectal anastomosis	Tissucol or Greenplast (1–2 mL)
Kim et al. (53)	2013	✓/✓	Low anterior rectal resection with total mesorectal excision	Double-stapled colorectal anastomosis	Tissucol or Greenplast (1–2 mL)
Liu et al. (37)	2003	✓/✓	Roux-en-Y-gastric bypass	Hand-sewn gastrojejunal anastomosis	Tisseel (5 mL; perivisceral fat pad glued to anterolateral part of anastomosis)
Oliver et al. (55)	2012	N/A	Esophageal resection; Roux-en-Y-gastric bypass; gastrectomy; rectal resection; intestinal resection of obstructed segment	Intestinal anastomosis (according to procedure)	Tissucol
Saldaña-Cortés et al. (38)	2009	✓/–	Colon interposition for esophageal reconstruction	Hand-sewn, single layer, end-to-side cervicocolic anastomosis covered (4-0 Vicryl)	Quixil (3–4 mL)
Sdralis et al. (56)	2019	✓/✓	Two-stage esophagectomy—Ivor-Lewis procedure	Intrathoracic mechanical end-to-side esophagogastric anastomosis (circular stapler: CDH 25 OR 29 mm)	Tisseel
Sieda et al. (57)	2015	✓/—	Enterocolic resection or colectomy	Hand-sewn, single layer, enterocolic or colocolic anastomosis (continuous suture, 3-0 Vicryl)	Fibrin sealant
Silecchia et al. (39)	2006	✓/—	Roux-en-Y-gastric bypass	Mechanical or hand-sewn gastrojejunal anastomosis (Gagner technique with circular stapler 25 EEA; linear stapler; two-layer continuous suture); jejunal anastomosis	Tissucol (2- or 5-mL)
Upadhyaya et al. (40)	2007	✓/—	Esophageal reconstruction	Hand-sewn, single layer, end-to-side esophageal anastomosis (5-0 Vicryl)	Tisseel

N/A, Not available; mm, millimeter; cm, centimeter; mL, milliliter; ✓, yes; –, no; I, intervention group (coated or reinforced anastomoses); C = Control Group.
[a]*Abstract.*

(37, 38, 58), four retrospective cohort studies (RCSs) (50, 52–54), two prospective cohort studies (PCS) (36, 57), and one abstract (51). These studies were published between 1996 and 2021 and were conducted in China (52), Egypt (57), France (50), Greece (56), India (40), Italy (39, 54), Korea (36, 53), Mexico (38), Spain (34, 55, 58), Switzerland (51), and the USA (37).

Of 3,630 patients included in 15 studies, 1,387 patients received an intervention, while 2,243 served as a control. To

TABLE 3 | Postoperative outcomes.

Author	Year	Anastomotic leakage, *n* (%)		Reoperation, *n* (%)		Clavien-Dindo major complications (43), *n* (%)		Length of hospitalization, mean (SD)[b]; in Days		Mortality, *n* (%)	
		I[c]	C[c]	I[c]	C[c]	I[c]	C[c]	I[c]	C[c]	I[c]	C[c]
Brehant et al. (50)	2013	N/A	N/A	N/A	N/A	**↓18 (9)**	**↑67 (16.6)**	↓	↑	N/A	N/A
Marano et al. (54)	2016	0 (0)	4 (11.8)	N/A	N/A	N/A	N/A	**↓ 14.7 ± 4.3**	**↑ 19.9 ± 5.6**	0 (0)	0 (0)
Torres-Melero et al. (58)	2016	0 (0)	3 (11.1)	1 (4.6)	3 (11.1)	N/A	N/A	N/A	N/A	N/A	N/A
Fernandez et al. (34)	1996	0 (0)	4 (9)	0 (0)	0 (0)	N/A	N/A	N/A	N/A	0 (0)	0 (0)
Grieder et al. (51)[a]	2010	5 (4.2)	9 (8)	3 (2.5)	9 (8)	N/A	N/A	N/A	N/A	N/A	N/A
Huang et al. (52)	2021	**↓4 (4.7)**	**↑28 (19.4)**	N/A	N/A	12 (14)	28 (20)	**↓12.11 ± 3.86**	**↑15.51 ± 9.54**	0 (0)	2 (1.4)
Huh et al. (36)	2010	6 (5.8)	13 (11)	N/A	N/A	N/A	N/A	9.46 ± 2.37	9.81 ± 3.03	N/A	N/A
Kim et al. (53)	2013	**↓17 (4.1)**	**↑59 (8)**	0 (0)	7 (1)	N/A	N/A	N/A	N/A	N/A	N/A
Liu et al. (37)	2003	**↓0 (0)**	**↑8 (2.2)**	**↓3 (2.5)**	**↑12 (3.3)**	N/A	N/A	N/A	N/A	N/A	N/A
Oliver et al. (55)	2012	**↓7 (13.5)**	**↑15 (28.9)**	N/A	N/A	N/A	N/A	N/A	N/A	3 (5.8)	4 (7.7)
Saldaña-Cortés et al. (38)	2009	4 (28.6)	12 (50)	N/A	N/A	N/A	N/A	12.6 ± 2.6	12.9 ± 2.6	1 (7.1)	1 (4.1)
Sdralis et al. (56)	2019	5 (14.3)	3 (13.7)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sieda et al. (57)	2015	3 (8.6)	7 (20)	N/A	N/A	N/A	N/A	5 ± 1.7	7 ± 2.3	N/A	N/A
Silecchia et al. (39)	2006	0 (0)	2 (1.8)	**↓0 (0)**	**↑8 (7.2)**	N/A	N/A	7.0 ± 1.6	7.0 ± 1.8	0 (0)	0 (0)
Upadhyaya et al. (40)	2007	**↓2 (9.1)**	**↑10 (43.5)**	N/A	N/A	N/A	N/A	N/A	N/A	2 (9.1)	6 (26)

N/A, Not available; ↓, significantly lower; ↑, significantly higher.

I, Intervention group (coated or reinforced anastomoses); and C, control group.

[a]*Abstract.*

[b]*If given in "median (interquaratile range)" or "median (range: minimum – maximum", values were converted using the Box–Cox (BC) method of McGrath et al. 2020 (47) to estimate the sample mean and standard deviation.*

The bold indicates significant outcomes.

cover the anastomoses, collagen-based laminar biomaterials were utilized in 252 patients (50, 54, 58), and fibrin sealants were utilized in 1,135 cases (34, 37–40, 51–53, 55–57). The majority of studies examined adult patients (34, 36, 37, 39, 50–58) undergoing intestinal surgery for malignant tumors (34, 36, 50–54, 56–58), benign lesions (such as diverticulitis, inflammatory bowel disease, or any kind of nonmalignant intestinal obstruction) (50, 55, 57), or bariatric surgery due to morbid obesity (37, 39). Pediatric patients were examined in two studies (38, 40); indications for surgery were either congenital esophageal atresia with tracheoesophageal fistula (40) or caustic esophageal injury (38) (**Table 1**).

In all cases, regardless of the anastomotic location or technique, intestinal anastomoses of patients in the intervention group were either reinforced or covered externally with either collagen-based laminar biomaterials (Collatamp or TachoSil) (50, 54, 58) or fibrin sealants (Tisseel, Tissucol, Greenplast, Bioseal or Quixil) (34, 36–40, 51–53, 55–57). Patients in the control group received the same surgical procedure as the intervention group but without covering the anastomoses with any substance. Detailed surgical characteristics, including surgical intervention and anastomotic technique, are depicted in **Table 2**.

Postoperative AL was assessed in 14 studies (34, 36–40, 51–58), out of which five (37, 40, 52, 53, 55) found a significantly lower AL rate within the intervention group. Reoperation and C-DMC rates were found to occur significantly less common in patients with sealed anastomoses in two (37, 39) out of six and one (50) out of two studies, respectively. Two out of six studies (52, 54) reported significantly longer hospitalizations for patients in the control group. Differences between the study groups in regard to mortality rates could not be detected in seven studies (34, 38–40, 52, 54, 55) (**Table 3**).

Risk of Bias Assessment

Risk of bias assessment was performed for all but one study (51), representing an abstract instead of a full-text article (**Supplementary Table S2**).

To assess the risk of bias for included RCTs (34, 39, 40, 55, 56), the RoB 2 tool (44) was utilized, and for nonrandomized studies (37, 38, 58), the ROBINS-I tool (45) was applied, according to the recommendations in the *Cochrane Handbook for Reviews of Interventions* (41). All of these studies presented either some concerns (RCT) (34, 39, 40, 55, 56) or moderate risk of bias (NRS) (37, 38, 58).

The NOS for cohort studies (46) was used to assess the quality of the six included observational studies (36, 50, 52–54, 57). The risk of bias based on this quality assessment presented the majority of studies (36, 50, 52–54) as being of moderate quality ($n = 5$; NOS score 6–7), while one study (57) appeared to be low in quality (NOS < 5).

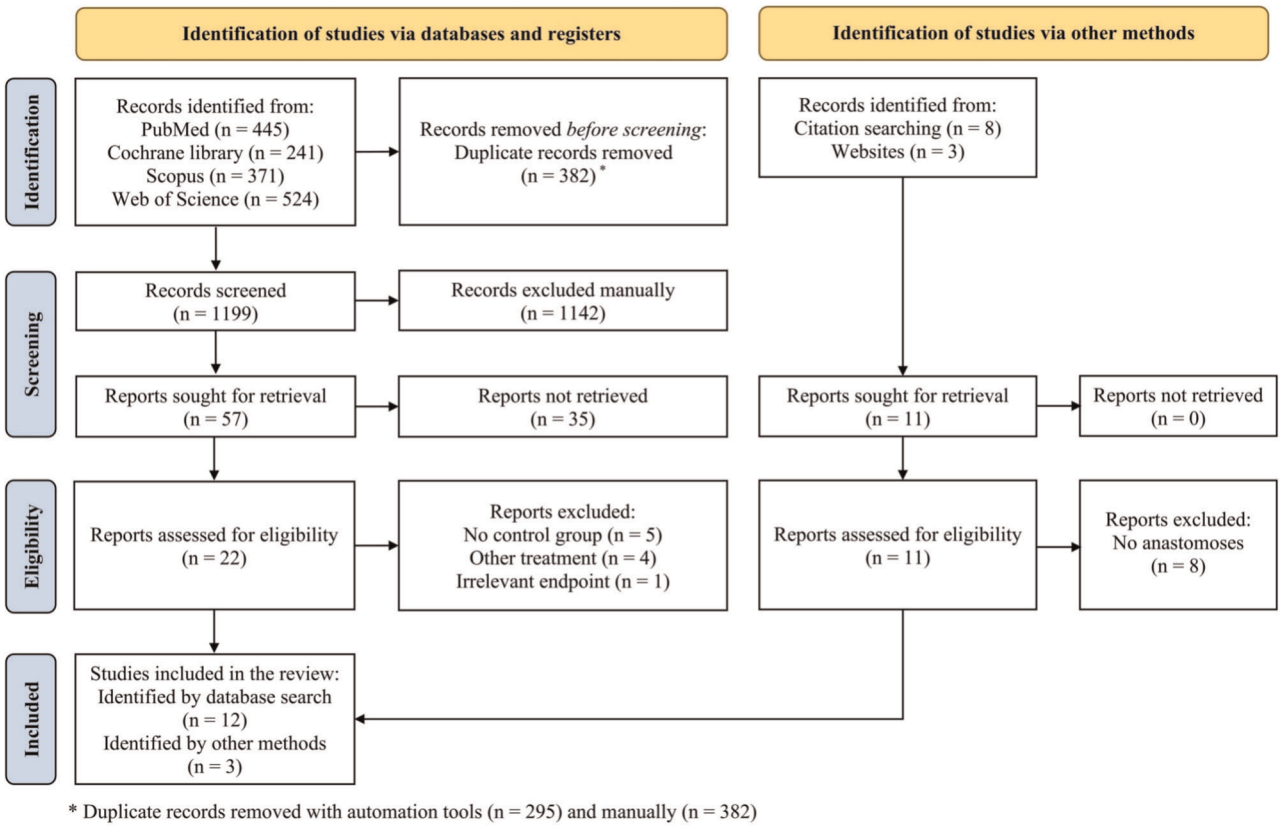

FIGURE 1 | Study flow diagram according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Statement 2020 (42).

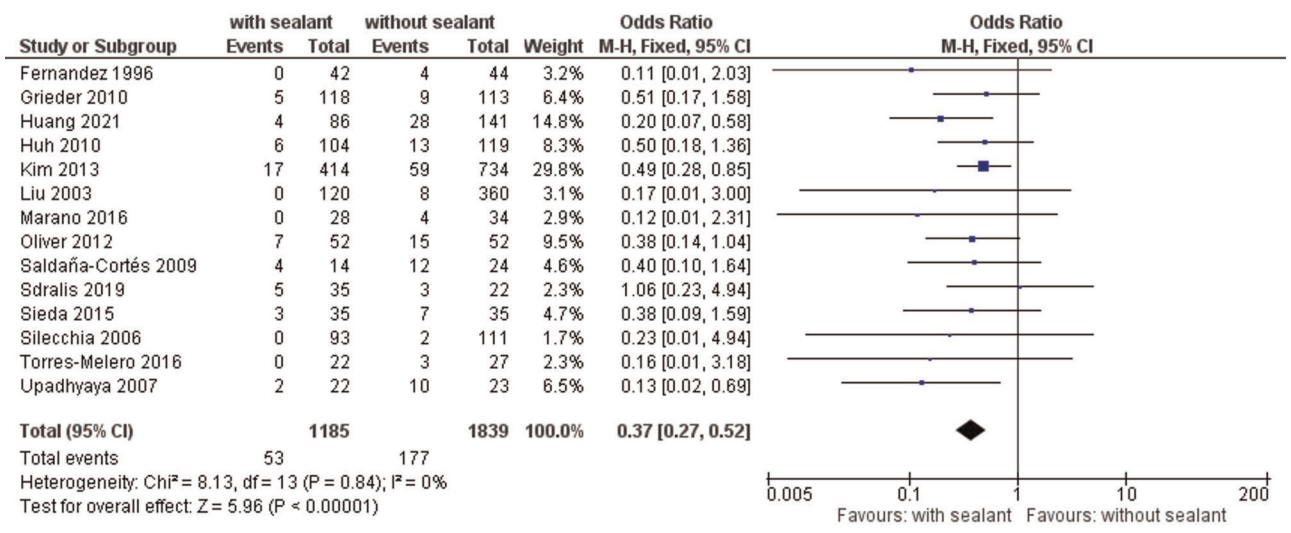

FIGURE 2 | Fixed-effects meta-analysis for the postoperative anastomotic leakage rate in the intervention (coated or reinforced anastomoses) and control group. The forest plot of all studies is included.

TABLE 4 | Fixed-effects meta-analysis for postoperative anastomotic leakage in the intervention and control group.

Postoperative anastomotic leakage	Odds ratio (OR): fixed-effects model	Heterogeneity	Eggers test
Overall	OR, 0.37; 95% CI, 0.27–0.52; **$p < 0.00001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.84$	$p = 0.227$
Sensitivity analyses			
Excluded study	**OR: fixed-effects model**	**Heterogeneity**	
Fernandez et al. (34)	OR, 0.38; 95% CI, 0.28–0.53; **$p < 0.00001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.83$	
Grieder et al. (51)	OR, 0.36; 95% CI, 0.26–0.51; **$p < 0.00001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.79$	
Huang et al. (52)	OR, 0.40; 95% CI, 0.29–0.57; **$p < 0.00001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.90$	
Huh et al. (36)	OR, 0.36; 95% CI, 0.26–0.51; **$p < 0.00001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.79$	
Kim et al. (53)	OR, 0.33; 95% CI, 0.22–0.48; **$p < 0.00001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.84$	
Liu et al. (37)	OR, 0.38; 95% CI, 0.27–0.53; **$p < 0.00001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.80$	
Marano et al. (54)	OR, 0.38; 95% CI, 0.28–0.53; **$p < 0.00001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.82$	
Oliver et al. (55)	OR, 0.37; 95% CI, 0.27–0.53; **$p < 0.00001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.77$	
Saldaña-Cortés et al. (38)	OR, 0.37; 95% CI, 0.27–0.52; **$p < 0.00001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.77$	
Sdralis et al. (56)	OR, 0.36; 95% CI, 0.26–0.50; **$p < 0.00001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.89$	
Sieda et al. (57)	OR, 0.37; 95% CI, 0.27–0.52; **$p < 0.00001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.78$	
Silecchia et al. (39)	OR, 0.38; 95% CI, 0.27–0.52; **$p < 0.00001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.78$	
Torres-Melero et al. (58)	OR, 0.37; 95% CI, 0.27–0.53; **$p < 0.00001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.80$	
Upadhyaya et al. (40)	OR, 0.39; 95% CI, 0.28–0.54; **$p < 0.00001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.90$	

↓, Significantly lower; ↑, significantly higher; I, intervention group (coated or reinforced anastomoses); C, control group.
The bold indicates significant outcomes.

Result of Synthesis

Postoperative Anastomotic Leakage Rates

Overall, 14 studies (34, 36–40, 51–58) reported postoperative AL rates occurring in 53 (4.5%) of 1,185 patients in the intervention group and 177 (9.6%) of 1,839 patients in the control group. The AL rate was significantly lower for patients with coated anastomoses using fixed-effects meta-analysis (OR, 0.37; 95% CI, 0.27–0.52; $p < 0.00001$) (**Figure 2**).

Studies were homogeneous ($I^2 = 0\%$; $p = 0.84$), and no publication bias was observed (Egger's test $p = 0.227$). Observed results remained stable throughout sensitivity analyses, excluding one study at a time (**Table 4**).

Subgroup analyses found no subgroup differences for subgroups stratified by study design (TSD: $p = 0.74$), intervention used (TSD: $p = 0.33$), age group (TSD: $p = 0.40$), anastomotic location (TSD: $p = 0.63$), indication for surgery (TSD: $p = 0.66$), and its subclassification (TSD: $p = 0.45$) (**Table 5**).

Postoperative Reoperation Rates

A total of five studies (37, 39, 51, 55, 58) examined the postoperative reoperation rates, occurring in seven (1.7%) of 405 patients in the intervention group and 39 (5.9%) of 663 patients in the control group. Rates of reoperation presented to be significantly lower for patients in the intervention group using fixed-effects meta-analysis (OR, 0.21; 95% CI, 0.10–0.47; $p = 0.0001$) (**Figure 3**).

Studies were homogeneous ($I^2 = 0\%$; $p = 0.88$), and results remained stable in sensitivity analyses. Subgroup analyses found no subgroup differences for subgroups stratified by study design (TSD: $p = 0.71$), intervention used (TSD: $p = 0.60$), anastomotic location (TSD: $p = 0.64$), and indication for surgery (TSD: $p = 0.64$) (**Table 6**).

Overall Postoperative Clavien–Dindo Major Complication Rates

Two studies (50, 52) evaluated the incidence of postoperative major complications according to the Clavien–Dindo classification of surgical complications (43). In total, 30 (10.4%) of 288 patients with external anastomotic coating and 95 (17.4%) of 545 patients in the control group developed postoperative C-DMC. The intervention group presented with significantly lower C-DMC rates using fixed-effects meta-analysis (OR, 0.54; 95% CI, 0.35–0.84; $p = 0.006$). Studies were homogeneous ($I^2 = 0\%$; $p = 0.54$) (**Figure 4**).

Length of Hospitalization

Another seven studies (34, 36, 38, 39, 52, 54, 57) monitored the length of hospitalization. The overall length of hospitalization was significantly shorter for patients in the intervention group compared to those for patients in the control group using the random-effects model meta-analysis to calculate the weighted mean difference (WMD, −1.96; 95% CI: −3.21, −0.71; $p = 0.002$). Studies showed significant substantial heterogeneity ($I^2 = 88\%$; $p < 0.00001$) but remained stable throughout sensitivity analyses. Subgroup analyses found a significant subgroup difference when the patients were stratified according to the intervention used (TSD: $p = 0.0010$), anastomotic location (TSD: $p < 0.00001$), indication for surgery (TSD: $p = 0.001$), and its subclassification (TSD: $p = 0.001$) (**Figure 5**).

TABLE 5 | Subgroup analyses of fixed-effects meta-analysis for postoperative anastomotic leakage.

Subgroup analyses		
Subgroup	**Odds ratio (OR): fixed-effects model**	**Test for subgroup difference**
Study design		$p = 0.75$
RCT	OR, 0.33; 95% CI, 0.17–0.65; **$p = 0.001$ [↓(I); ↑(C)]**	
NRS	OR, 0.27; 95% CI, 0.09–0.87; **$p = 0.03$ [↓(I); ↑(C)]**	
OS	OR, 0.40; 95% CI, 0.27–0.60; **$p < 0.00001$ [↓(I); ↑(C)]**	
Covering		$p = 0.33$
C-BLB	OR, 0.13; 95% CI, 0.02–1.12; $p = 0.06$	
FS	OR, 0.39; 95% CI, 0.28–0.54; **$p < 0.00001$ [↓(I); ↑(C)]**	
Age group		$p = 0.40$
Adult	OR, 0.39; 95% CI, 0.28–0.55; **$p < 0.00001$ [↓(I); ↑(C)]**	
Pediatric	OR, 0.24; 95% CI, 0.08–0.69; **$p = 0.008$ [↓(I); ↑(C)]**	
Anastomotic location		$p = 0.63$
Esophagus	OR, 0.28; 95% CI, 0.15–0.55; **$p = 0.0002$ [↓(I); ↑(C)]**	
Esophagojejunal or gastrojejunal	OR, 0.28; 95% CI, 0.12–0.67; **$p = 0.004$ [↓(I); ↑(C)]**	
Gastrojejunal (bariatric surgery)	OR, 0.19; 95% CI, 0.02–1.58; $p = 0.12$	
Colorectal	OR, 0.47; 95% CI, 0.31–0.71; **$p = 0.0004$ [↓(I); ↑(C)]**	
Miscellaneous	OR, 0.38; 95% CI, 0.28–0.51; $p = 0.06$	
Indication for surgery		$p = 0.66$
Malignant tumor	OR, 0.40; 95% CI, 0.28–0.58; **$p < 0.00001$ [↓(I); ↑(C)]**	
Obesity (bariatric surgery)	OR, 0.19; 95% CI, 0.02–1.58; $p = 0.12$	
Miscellaneous	OR, 0.31; 95% CI, 0.15–0.63; **$p = 0.001$ [↓(I); ↑(C)]**	
Indication for surgery (subclassified)		$p = 0.45$
Upper GIT malignancy	OR, 0.26; 95% CI, 0.12–0.56; **$p = 0.0005$ [↓(I); ↑(C)]**	
Lower GIT malignancy	OR, 0.47; 95% CI, 0.31–0.71; **$p = 0.0004$ [↓(I); ↑(C)]**	
Obesity (bariatric surgery)	OR, 0.19; 95% CI, 0.02–1.58; $p = 0.12$	
Miscellaneous	OR, 0.31; 95% CI, 0.15–0.63; **$p = 0.001$ [↓(I); ↑(C)]**	

↓, Significantly lower; ↑, significantly higher; I, intervention group (coated or reinforced anastomoses); C, control group; RCT, randomized controlled trial; NRS, nonrandomized study; OS, observational study; C-BLB, collagen-based laminar biomaterial; FS, fibrin sealant; GIT, gastrointestinal tract.
The bold indicates significant outcomes.

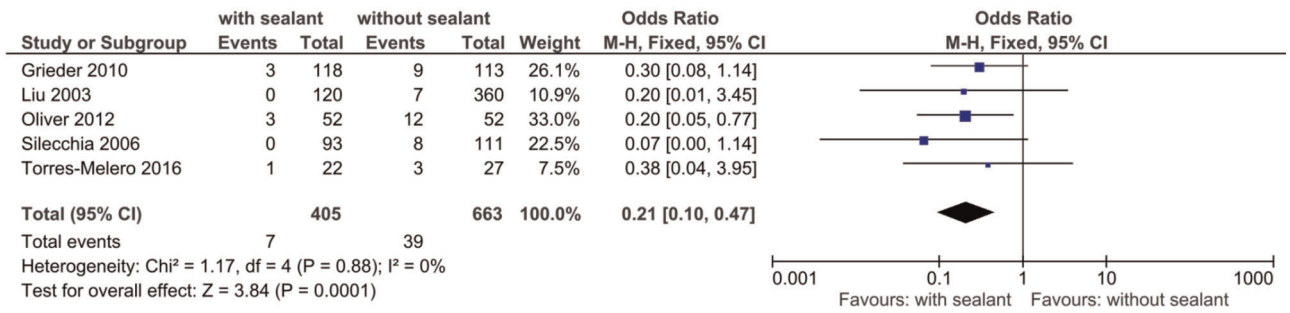

FIGURE 3 | Fixed-effects meta-analysis for the postoperative reoperation rate in the intervention (coated or reinforced anastomoses) and control group. The forest plot of all studies is included.

Patients in the intervention group presented with a significantly shorter time of hospitalization compared to the control group if undergoing intestinal surgical procedures for malignant gastrointestinal tumors (WMD, −3.06; 95% CI: −4.93, −1.19; $p = 0.001$), especially if they were located in the upper GIT (WMD, −4.94; 95% CI: −7.98, −1.90; $p = 0.001$) and were operated with the creation of an esophagojejunal or gastrojejunal anastomosis (WMD, −2.28; 95% CI: −6.35, −4.31; $p < 0.00001$) (**Table 7**).

TABLE 6 | Fixed-effects meta-analysis for postoperative reoperation in the intervention and control group.

Postoperative reoperation	Odds ratio (OR): fixed-effects model	Heterogeneity
Overall	OR, 0.21; 95% CI, 0.10–0.47; **$p = 0.0001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.88$
Sensitivity analyses		
Excluded study	**OR: fixed-effects model**	**Heterogeneity**
Grieder et al. (51)	OR, 0.18; 95% CI, 0.07–0.48; **$p = 0.0007$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.82$
Liu et al. (37)	OR, 0.21; 95% CI, 0.09–0.48; **$p = 0.0002$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.76$
Oliver et al. (55)	OR, 0.21; 95% CI, 0.08–0.57; **$p = 0.002$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.76$
Silecchia et al. (39)	OR, 0.25; 95% CI, 0.11–0.58; **$p = 0.001$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.96$
Torres-Melero et al. (58)	OR, 0.20; 95% CI, 0.08–0.46; **$p = 0.0002$ [↓(I); ↑(C)]**	$I^2 = 0\%$; $p = 0.81$
Subgroup analyses		
Subgroup	**OR: fixed-effects model**	**Test for subgroup difference**
Study design		$p = 0.71$
RCT	OR, 0.15; 95% CI, 0.04–0.49; **$p = 0.002$ [↓(I); ↑(C)]**	
NRS	OR, 0.27; 95% CI, 0.04–1.65; $p = 0.16$	
OS	OR, 0.30; 95% CI, 0.08–1.14; $p = 0.08$	
Covering		$p = 0.60$
C-BLB	OR, 0.38; 95% CI, 0.04–3.95; $p = 0.42$	
FS	OR, 0.20; 95% CI, 0.08–0.46; **$p = 0.0002$ [↓(I); ↑(C)]**	
Age group (adults only)		
Anastomotic location		$p = 0.64$
Gastrojejunal (bariatric surgery)	OR, 0.11; 95% CI, 0.01–0.81; **$p = 0.03$ [↓(I); ↑(C)]**	
Colorectal	OR, 0.32; 95% CI, 0.10–1.02; **$p = 0.05$ [↓(I); ↑(C)]**	
Miscellaneous	OR, 0.20; 95% CI, 0.05–0.77; **$p = 0.02$ [↓(I); ↑(C)]**	
Indication for surgery		$p = 0.64$
Malignant tumor (lower GIT)	OR, 0.32; 95% CI, 0.10–1.02; **$p = 0.05$ [↓(I); ↑(C)]**	
Obesity (bariatric surgery)	OR, 0.11; 95% CI, 0.01–0.81; **$p = 0.03$ [↓(I); ↑(C)]**	
Miscellaneous	OR, 0.20; 95% CI, 0.05–0.77; **$p = 0.02$ [↓(I); ↑(C)]**	

↓, Significantly lower; ↑, significantly higher; I, intervention group (coated or reinforced anastomoses); C, control group; RCT, randomized controlled trial; NRS, nonrandomized study; OS, observational study; C-BLB, collagen-based laminar biomaterial; FS, fibrin sealant; GIT, gastrointestinal tract.
The bold indicates significant outcomes.

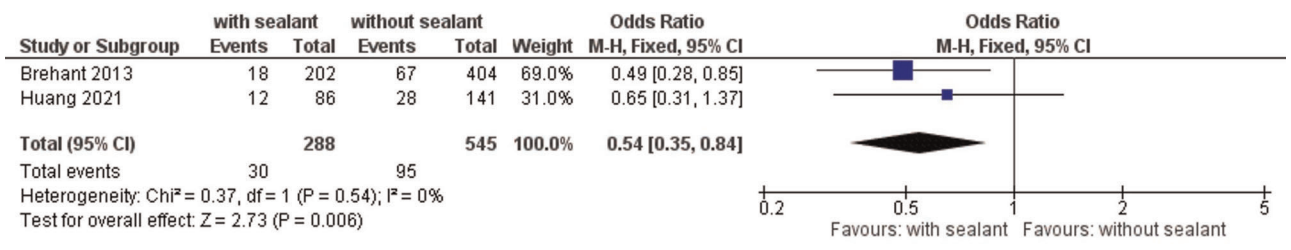

FIGURE 4 | Fixed-effects meta-analysis for the postoperative major complication rate according to the Clavien–Dindo classification of surgical complications (43) in the intervention (coated or reinforced anastomoses) and control group. The forest plot of all studies is included.

Postoperative Mortality Rate

In total, four studies recorded postoperative mortality rates (38, 40, 52, 55), occurring in six (3.4%) of 174 patients with fibrin sealant-coated anastomoses and 13 (5.5%) of 240 patients in the control group. No significant differences were found between the studied groups using fixed-effects meta-analysis (OR, 0.52; 95% CI, 0.20–1.39; $p = 0.19$) (**Figure 6**).

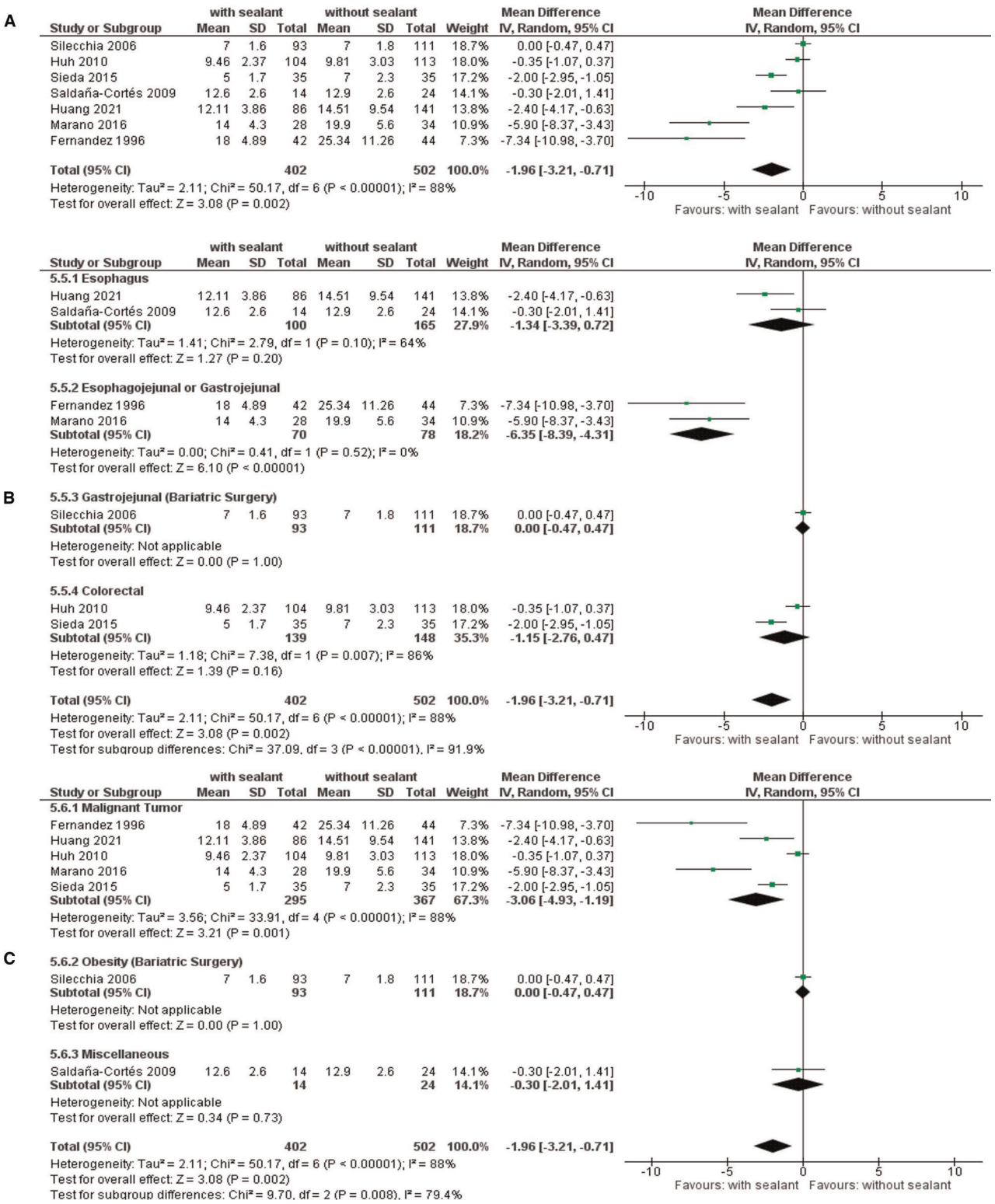

FIGURE 5 | Random-effects meta-analysis for the length of hospitalization in the intervention (coated or reinforced anastomoses) and control group. (**A**) Forest plot of all studies included. (**B**) Forest plot of subgroup analysis stratified by location of anastomoses. (**C**) Forest plot of subgroup analysis stratified by indication of surgery.

TABLE 7 | Random-effects meta-analysis for the length of hospitalization in the intervention and control group.

Length of hospitalization	Weighted mean difference (WMD): random-effects model	Heterogeneity
Overall	WMD, −1.96; 95% CI: −3.21, −0.71; **$p = 0.002$ [↓(I); ↑(C)]**	$I^2 = 88\%$; **$p < 0.00001$**
Sensitivity analyses		
Excluded study	**WMD: random-effects model**	**Heterogeneity**
Fernandez et al. (34)	WMD, −1.48; 95% CI: −2.62, −0.33; **$p = 0.01$ [↓(I); ↑(C)]**	$I^2 = 86\%$; **$p < 0.00001$**
Huang et al. (52)	WMD, −1.90; 95% CI: −3.24, −0.55; **$p = 0.006$ [↓(I); ↑(C)]**	$I^2 = 89\%$; **$p < 0.00001$**
Huh et al. (36)	WMD, −2.50; 95% CI: −4.21, −0.79; **$p = 0.004$ [↓(I); ↑(C)]**	$I^2 = 90\%$; **$p < 0.00001$**
Marano et al. (54)	WMD, −1.36; 95% CI: −2.46, −0.25; **$p = 0.02$ [↓(I); ↑(C)]**	$I^2 = 84\%$; **$p < 0.00001$**
Saldaña-Cortés et al. (38)	WMD, −2.28; 95% CI: −3.68, −0.87; **$p = 0.001$ [↓(I); ↑(C)]**	$I^2 = 90\%$; **$p < 0.00001$**
Sieda et al. (57)	WMD, −1.99; 95% CI: −3.41, −0.57; **$p = 0.006$ [↓(I); ↑(C)]**	$I^2 = 88\%$; **$p < 0.00001$**
Silecchia et al. (39)	WMD, −2.53; 95% CI: −4.12, −0.94; **$p = 0.002$ [↓(I); ↑(C)]**	$I^2 = 86\%$; **$p < 0.00001$**
Subgroup analyses		
Subgroup	**WMD: random-effects model**	**Test for subgroup difference**
Study design		$p = 0.22$
RCT	WMD, −3.44; 95% CI: −10.62, 3.74; $p = 0.35$	
NRS	WMD, −0.30; 95% CI: −2.01, 1.41; $p = 0.73$	
OS	WMD, −2.36; 95% CI: −4.10, −0.61; **$p = 0.008$ [↓(I); ↑(C)]**	
Covering		**$p = 0.0010$**
C-BLB	WMD, −5.90; 95% CI: −8.37, −3.43; **$p < 0.00001$ [↓(I); ↑(C)]**	
FS	WMD, −1.36; 95% CI: −2.46, −0.25; **$p = 0.02$ [↓(I); ↑(C)]**	
Age group		$p = 0.08$
Adult	WMD, −2.28; 95% CI: −3.68, −0.87; **$p = 0.001$ [↓(I); ↑(C)]**	
Pediatric	WMD, −0.30; 95% CI: −2.01, 1.41; $p = 0.73$	
Anastomotic location		**$p < 0.00001$**
Esophagus	WMD, −1.34; 95% CI: −3.39, 0.72; $p = 0.2$	
Esophagojejunal or gastrojejunal	WMD, −2.28; 95% CI: −6.35, −4.31; **$p < 0.00001$ [↓(I); ↑(C)]**	
Gastrojejunal (bariatric surgery)	WMD, 0.0; 95% CI: −0.47, 0.47; $p = 1.0$	
Colorectal	WMD, −1.15; 95% CI: −2.76, 0.47; $p = 0.16$	
Indication for surgery		**$p = 0.008$**
Malignant tumor	WMD, −3.06; 95% CI: −4.93, −1.19; **$p = 0.001$ [↓(I); ↑(C)]**	
Obesity (bariatric surgery)	WMD, 0.0; 95% CI: −0.47, 0.47; $p = 1.0$	
Miscellaneous	WMD, −0.30; 95% CI: −2.01, 1.41; $p = 0.73$	
Indication for surgery (subclassified)		**$p = 0.010$**
Upper GIT malignancy	WMD, −4.94; 95% CI: −7.98, −1.90; **$p = 0.001$ [↓(I); ↑(C)]**	
Lower GIT malignancy	WMD, −1.15; 95% CI: −2.76, 0.47; $p = 0.16$	
Obesity (bariatric surgery)	WMD, 0.0; 95% CI: −0.47, 0.47; $p = 1.0$	
Miscellaneous	WMD, −0.30; 95% CI: −2.01, 1.41; $p = 0.73$	

↓, Significantly lower; ↑, significantly higher; I, intervention group (coated or reinforced anastomoses); C, control group; RCT, randomized controlled trial; NRS, nonrandomized study; OS, observational study; C-BLB, collagen-based laminar biomaterial; FS, fibrin sealant; GIT, gastrointestinal tract.
The bold indicates significant outcomes.

Studies were homogeneous ($I^2 = 0\%$; $p = 0.69$) and remained stable in sensitivity analyses. Subgroup analyses found no significant subgroup difference for subgroups stratified by study design (TSD: $p = 0.66$), age group (TSD: $p = 0.78$), anastomotic location (TSD: $p = 0.59$), and indication for surgery (TSD: $p = 0.74$) (**Table 8**).

DISCUSSION

This systematic review and meta-analysis gives an overview of the efficacy of externally covering anastomoses with collagen-based laminar biomaterials or fibrin sealants in reducing postoperative rates of AL and its accompanying sequelae for

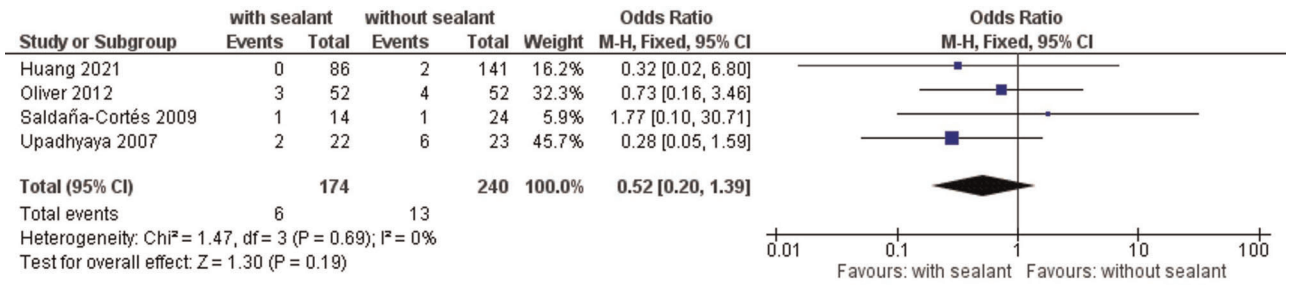

FIGURE 6 | Fixed-effects meta-analysis for the postoperative mortality rate in the intervention (coated or reinforced anastomoses) and control group. The forest plot of all studies is included.

TABLE 8 | Fixed-effects meta-analysis for postoperative mortality in the intervention and control goup.

Mortality	**Odds ratio (OR): fixed-effects model**	**Heterogeneity**
Overall	OR, 0.52; 95% CI, 0.20–1.39; $p = 0.19$	$I^2 = 0\%$; $p = 0.69$
Sensitivity analyses		
Excluded study	**OR: fixed-effects model**	**Heterogeneity**
Huang et al. (52)	OR, 0.56; 95% CI, 0.20–1.59; $p = 0.28$	$I^2 = 0\%$; $p = 0.51$
Oliver et al. (55)	OR, 0.42; 95% CI, 0.12–1.52; $p = 0.19$	$I^2 = 0\%$; $p = 0.55$
Saldaña-Cortés et al. (38)	OR, 0.44; 95% CI, 0.15–1.28; $p = 0.13$	$I^2 = 0\%$; $p = 0.70$
Upadhyaya et al. (40)	OR, 0.72; 95% CI, 0.22–2.42; $p = 0.60$	$I^2 = 0\%$; $p = 0.72$
Subgroup analyses		
Subgroup	**OR: Fixed-effects model**	**Test for subgroup difference**
Study design		$p = 0.66$
RCT	OR, 0.47; 95% CI, 0.15–1.46; $p = 0.19$	
NRS	OR, 1.77; 95% CI, 0.10–30.71; $p = 0.70$	
OS	OR, 0.32; 95% CI, 0.02–6.80; $p = 0.47$	
Covering (FS only)		
Age group		$p = 0.78$
Adult	OR, 0.60; 95% CI, 0.15–2.31; $p = 0.46$	
Pediatric	OR, 0.45; 95% CI, 0.11–1.87; $p = 0.27$	
Anastomotic Location		$p = 0.59$
Esophagus	OR, 0.42; 95% CI, 0.12–1.52; $p = 0.19$	
Miscellaneous	OR, 0.73; 95% CI, 0.16–3.46; $p = 0.70$	
Indication for Surgery		$p = 0.74$
Malignant Tumor (upper GIT)	OR, 0.32; 95% CI, 0.02–6.8; $p = 0.47$	
Miscellaneous	OR, 0.56; 95% CI, 0.20–1.59; $p = 0.28$	

RCT, randomized controlled trial; NRS, nonrandomized study; OS, observational study; FS, fibrin sealant; GIT, gastrointestinal tract.

patients undergoing surgery with the formation of an intestinal anastomosis.

The meta-analyses found significant differences for postoperative AL (**Figure 2**), reoperation rates (**Figure 3**), C-DMC (43) (**Figure 4**), and length of hospitalization (**Figure 5**). However, no significant differences between the studied groups were found in the postoperative mortality rate, even after conducting sensitivity and subgroup analyses (**Figure 6** and **Table 8**).

A significant decrease in AL (**Figure 2**; **Tables 4** and **5**) and reoperation rate (**Figure 3**; **Table 6**) was found for patients with intestinal anastomoses covered either by collagen-based laminar biomaterials or by fibrin sealants. Sensitivity analyses confirmed

the stability of these results. Subgroup analyses did not find any difference between the collagen-based laminar biomaterials and fibrin sealants in regard to their protective action. Furthermore, the outcomes remained significant regardless of the study design, age group studied, location of anastomoses, or indication of surgery. Postoperative major complications, according to the Clavien–Dindo classification for surgical complications (43), were shown to be significantly lower in the intervention group than those in the control group. Since only two studies (50, 52) reported complications categorized by this classification, no sensitivity or subgroup analysis could be conducted (**Figure 4**).

The length of hospitalization appeared to be significantly shorter for patients in the intervention group (**Figure 5**). These results remained stable throughout sensitivity analyses, and subgroup analyses did not find differences between subgroups stratified by study design, intervention used, or age group. However, a significant subgroup difference was observed for subgroups stratified by the location of anastomoses and the indication for surgery. In comparison to the control group, patients in the intervention group presented with a significantly shorter time of hospitalization if undergoing intestinal surgery with esophagojejunal or gastrojejunal anastomoses or if the indication for surgery was a malignant tumor, especially the case with upper gastrointestinal malignancies (**Table 7**).

No difference between the intervention and control group could be found in regard to postoperative mortality rates, even after performing sensitivity and subgroup analyses (**Figure 6**; **Table 8**). This outcome should be interpreted with caution, as not all studies reporting AL also reported postoperative mortality rates. To evaluate the effect of coating intestinal anastomoses with collagen-based laminar biomaterials or fibrin sealants on postoperative mortality rates, future studies should allow a longer follow-up for their patients to ensure postoperative mortality is not missed.

On the downside of the ambiguous outcomes presented in different experimental animal studies (22–31, 33, 59, 60), fibrin sealants have been utilized already in human trials, showing positive effects. Sealing postoperatively occurring anastomotic leaks of the upper and lower GIT with fibrin sealants endoscopically has been conducted with successful therapeutic outcomes (61–63). Endoscopic applications have shown to reduce exudation from the leakage site, systemic inflammatory response, and clinical symptoms of treated patients (61) and seem to serve as an efficient and safe option to manage postoperative ALs (62).

Furthermore, a recently published systematic review reported mainly positive effects on AL prevention and treatment upon covering esophageal anastomoses with collagen-based laminar biomaterials or fibrin sealants (64). Promising effects for staple-line reinforcement with absorbable materials such as fibrin sealants were reported as well for colorectal procedures (65). In the case of bariatric surgical procedures, Chen et al. (66) conducted a meta-analysis of six randomized controlled trials examining the effect of staple-line and anastomotic reinforcement with fibrin sealants on postoperative complications in morbidly obese patients undergoing laparoscopic sleeve gastrectomy or Roux-en-Y-gastric bypass. The authors demonstrated no significant difference between the studied groups' postoperative AL rates. These results coincide with our findings after conducting a subgroup analysis stratified by indication for surgery. Still, precautions should be taken to compare the results of our subgroup analysis with those of the previously conducted meta-analysis (66), as our study excluded any surgical procedure without the formation of an intestinal anastomosis.

Interestingly, Panda et al. conducted a cost analysis, evaluating the differences in economic burden in regard to resource expenses provided by the healthcare system upon covering colorectal anastomoses with fibrin sealants. The authors concluded that the application of fibrin sealants was not only associated with decreased AL rates but also contributed to cost savings of roughly 22% (using a potential model). These cost savings originate mainly from the reduction in the length of hospitalization due to postoperative reoperations, radiological interventions, and/or transfusions (67). These findings correlate with the observed outcomes of our investigation.

This study showed that coating intestinal anastomoses with collagen-based laminar biomaterials or fibrin sealants resulted in significantly reduced postoperative AL, reoperation, C-DMC rates, and shorter length of hospitalization; nevertheless, there is still room for improvement. A large proportion of postoperative anastomotic leaks is associated with anastomotic infections (68). In a recent study, Anderson et al. (68) investigated cultures of 19 patients with AL and found 74% of these patients' leaks to be colonized with collagenase-producing microorganisms. Furthermore, the authors found the presence of *Enterococcus faecalis* to be significantly associated with the development of AL (68). In the physiology of anastomotic wound healing, the risk of wound failure corresponds to the activity of collagenases (69). As collagen deposition plays a crucial role in adequate anastomotic healing (70), an infection of the anastomosis leads to collagenase enzyme activities exceeding the physiological levels needed for proper wound healing, contributing to anastomotic failure (69, 71). Furthermore, such infections could potentially compromise the functionality of anastomotic coatings with collagen-based laminar biomaterials due to the destructive effect of these microorganisms' collagenases on the biomaterial's basic framework. To assure the complete functionality of these adhesive biomaterials and adequate anastomotic healing, infections should be prevented. If sealants would contain both the healing supporting collagen fibrils and antimicrobial substances, effectively protecting the anastomoses and the adhesives from collagenase-producing microorganisms, theoretically, a much higher effect for further reducing postoperative anastomotic complications could be expected.

The results of our analysis have limitations that need to be addressed. The included studies presented with variable study designs and years of publication (1996–2021) and were of moderate quality in most cases. We decided to include studies older than 15 years (34, 37, 39, 40) in our analysis as their interventions are comparable to interventions of studies conducted in the following years and the adhesive biomaterials used correspond to those used in more recent studies. Different types and materials of sealants were compared among patients with different characteristics, such as different age groups and surgical indications, which could

have introduced potential biases to our analysis. We addressed this limitation by performing thorough subgroup analyses stratified by these potential confounding factors and investigating the stability of our results by conducting sensitivity analyses, regardless of the observed heterogeneity. Additional sources of potential bias were the possible lack of adequate blinding since none of the five RCTs (34, 39, 40, 55, 56) and three NRSs (37, 38, 58) commented on the outcome assessor's awareness of intervention, and the potential influence the manufacturer of the adhesive biomaterials used might have had by funding the study. We carefully examined the funding situations with regard to each included study and have come to the conclusion that the manufacturer—to our knowledge—did not present a funding role in any of the included studies nor was an author mentioned to be a representative for the manufacturer. Furthermore, our analysis did not evaluate the effect of coating other types of anastomoses commonly performed in abdominal surgery, such as pancreaticointestinal or biliodigestive anastomoses. Since these types of anastomoses present distinct differences in surgical techniques and specific risks for AL and its associated morbidities, we excluded all types of anastomoses other than intestinal anastomoses of the upper and lower GIT. The risk of biasing the results of our study's observed outcomes would have been potentiated by including these types of anastomoses in our study. Therefore, we did not evaluate these kinds of effects in the present analysis but would recommend analyzing the effects of coating other types of anastomoses commonly performed in abdominal surgery on postoperative complications separately in a further systematic review and meta-analysis in the future.

However, the strength of this study is its uniqueness since this is the first systematic review with a meta-analysis investigating the efficacy of coating intestinal anastomoses with the most commonly utilized absorbable adhesives (20, 21) in reducing postoperative AL rates and its accompanying sequelae.

The outcomes of this systematic review and meta-analysis present some clinical implications and justify the need for future research to consolidate our findings. Furthermore, larger RCTs examining the effects of the studied adhesives in the context of different surgical indications and patient groups need to be conducted. One could ask why coating of intestinal anastomoses with collagen-based laminar biomaterials and/or fibrin sealants has yet not been established in everyday clinical practice. Possible reasons could be the difficult and user-unfriendly application form resulting in additional time expenditure or the low adhesive strength of these biomaterials on intestinal surfaces. Since these adhesive biomaterials have shown significant efficacy in reducing postoperative morbidity after intestinal surgery, future research and innovative developments should address these unfavorable factors.

In conclusion, current evidence suggests that covering intestinal anastomoses with either collagen-based laminar biomaterials or fibrin sealants significantly reduces postoperative rates of AL, reoperation, and C-DMC. Furthermore, with these adhesives, a significant reduction in the length of hospitalization can be observed, especially for patients undergoing surgery for an upper gastrointestinal malignancy. Still, the risk of anastomotic and potential adhesive failure associated with anastomotic infection should be addressed, by investigating the efficacy of antimicrobial collagen-based sealants, for protecting intestinal anastomoses from the deleterious effect of collagenase-producing microorganisms. To consolidate our findings, there is a need for further large RCTs examining the effects of coating intestinal anastomoses with the studied adhesives on postoperative leakage. Aside from that, the effect of coating other types of anastomoses commonly performed in abdominal surgery on postoperative complications should be investigated in future studies. Finally, a simple and user-friendly application form of a somewhat stronger adhesive collagen-based laminar biomaterial and/or fibrin sealant should be developed to establish the possibility of routine use in surgical practice.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material** further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

KC, FS, SR, and P-AN contributed to the conception and design of the study. KC and FS were involved in data collection and quantitative and qualitative analyses. SR and P-AN assessed the accuracy of the data. KC organized the database. KC performed the statistical analysis. KC created figures and tables. KC drafted the manuscript. FS, SR, P-AN, AO, RB, and HF revised the manuscript for important intellectual contents. All authors contributed to manuscript revision, read, and approved the submitted version. P-AN and RB were responsible for funding.

FUNDING

This study was supported by the Bavarian Research Foundation (Grant No. AZ-1508-21).

ACKNOWLEDGMENTS

The authors acknowledge Bernhard Haller, Research Associate at the Institute for Epidemiology and Medical Statistics of the Technical University of Munich, Munich, Bavaria, Germany, for providing statistical consulting.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fsurg.2022.882173/full#supplementary-material.

Supplementary Table 1 | Search strategy. Final database search (January 17, 2022).

Supplementary Table 2 | Risk of bias assessment for included studies (abstracts excluded).

REFERENCES

1. Schmidt HM, Gisbertz SS, Moons J, Rouvelas I, Kauppi J, Brown A, et al. Defining benchmarks for transthoracic esophagectomy: a multicenter analysis of total minimally invasive esophagectomy in low risk patients. *Ann Surg*. (2017) 266(5):814–21. doi: 10.1097/sla.0000000000002445
2. Struecker B, Andreou A, Chopra S, Heilmann AC, Spenke J, Denecke C, et al. Evaluation of anastomotic leak after esophagectomy for esophageal cancer: typical time point of occurrence, mode of diagnosis, value of routine radiocontrast agent studies and therapeutic options. *Dig Surg*. (2018) 35 (5):419–26. doi: 10.1159/000480357
3. van Workum F, van der Maas J, van den Wildenberg FJ, Polat F, Kouwenhoven EA, van Det MJ, et al. Improved functional results after minimally invasive esophagectomy: intrathoracic versus cervical anastomosis. *Ann Thorac Surg*. (2017) 103(1):267–73. doi: 10.1016/j.athoracsur.2016.07.010
4. Doeksen A, Tanis PJ, Vrouenraets BC, Gooszen JA, van Lanschot JJ, van Tets WF. Outcome of rectal cancer surgery after the introduction of preoperative radiotherapy in a low-volume hospital. *J Gastrointest Cancer*. (2007) 38(2–4):63–70. doi: 10.1007/s12029-008-9018-y
5. Lindner K, Fritz M, Haane C, Senninger N, Palmes D, Hummel R. Postoperative complications do not affect long-term outcome in esophageal cancer patients. *World J Surg*. (2014) 38(10):2652–61. doi: 10.1007/s00268-014-2590-3
6. Seesing MFJ, Gisbertz SS, Goense L, van Hillegersberg R, Kroon HM, Lagarde SM, et al. A propensity score matched analysis of open versus minimally invasive transthoracic esophagectomy in the Netherlands. *Ann Surg*. (2017) 266(5):839–46. doi: 10.1097/sla.0000000000002393
7. Hagens ERC, Reijntjes MA, Anderegg MCJ, Eshuis WJ, van Berge Henegouwen MI, Gisbertz SS. Risk factors and consequences of anastomotic leakage after esophagectomy for cancer. *Ann Thorac Surg*. (2021) 112(1):255–63. doi: 10.1016/j.athoracsur.2020.08.022
8. Kang CY, Halabi WJ, Chaudhry OO, Nguyen V, Pigazzi A, Carmichael JC, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. *JAMA Surg*. (2013) 148(1):65–71. doi: 10.1001/2013.jamasurg.2
9. Akasu T, Takawa M, Yamamoto S, Yamaguchi T, Fujita S, Moriya Y. Risk factors for anastomotic leakage following intersphincteric resection for very low rectal adenocarcinoma. *J Gastrointest Surg*. (2010) 14(1):104–11. doi: 10.1007/s11605-009-1067-4
10. Watanabe M, Miyata H, Gotoh M, Baba H, Kimura W, Tomita N, et al. Total gastrectomy risk model: data from 20,011 Japanese patients in a nationwide internet-based database. *Ann Surg*. (2014) 260(6):1034–9. doi: 10.1097/sla.0000000000000781
11. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. *Ann Surg*. (2011) 253(5):890–9. doi: 10.1097/SLA.0b013e3182128929
12. Krarup PM, Nordholm-Carstensen A, Jorgensen LN, Harling H. Anastomotic leak increases distant recurrence and long-term mortality after curative resection for colonic cancer: a nationwide cohort study. *Ann Surg*. (2014) 259(5):930–8. doi: 10.1097/SLA.0b013e3182a6f2fc
13. Hammond J, Lim S, Wan Y, Gao X, Patkar A. The burden of gastrointestinal anastomotic leaks: an evaluation of clinical and economic outcomes. *J Gastrointest Surg*. (2014) 18(6):1176–85. doi: 10.1007/s11605-014-2506-4
14. Aleksandrov VB, Kapuller LL, Poliakova AM, Baranchikov VI, Slavin Iu M. The reaction of intestinal wall tissue to several types of cyacrin glue and its combined use with mechanical tantalum suture in anterior resection of the rectum (experimental study). *Eksp Khir Anesteziol*. (1971) 16(2):46–50.
15. Vishnevskiĭ AA Jr. An instrument for intestinal anastomosis with the use of glue. *Eksp Khir Anesteziol*. (1966) 11(5):21–2.
16. Rusca JA, Bornside GH, Cohn I Jr. Everting versus inverting gastrointestinal anastomoses: bacterial leakage and anastomotic disruption. *Ann Surg*. (1969) 169(5):727–35. doi: 10.1097/00000658-196905000-00010
17. Anders A, Bodemann T, Baer U, Bauknecht KJ, Lawerenz JU. Are fibrin adhesive and collagen fleece additional protective measures for colon anastomoses? *Langenbecks Arch Chir*. (1981) 1981(Suppl.):175–80. doi: 10.1007/978-3-642-68016-8_35
18. Scheele J, Herzog J, Muehe E. Fibrin glue protection of digestive anastomoses. *Zentralbl Chir*. (1978) 103(20):1325–36.
19. Spotnitz WD. Fibrin sealant: the only approved hemostat, sealant, and adhesive – a laboratory and clinical perspective. *ISRN Surg*. (2014) 2014:203943. doi: 10.1155/2014/203943
20. Takeda Pharma a/S. Tisseel [Fibrin Sealant] [Package Insert]. U.S. Food and Drug Administration. Revised 2013 Available from: https://www.fda.gov/media/71674/download (Accessed January 26, 2022).
21. Takeda Pharma a/S. Tachosil® Fibrin Sealant Patch) [Package Insert]. U.S. Food and Drug Administration. Revised July 2015. Available from: https://www.fda.gov/media/78698/download (Accessed January 26, 2022).
22. Chmelnik M, Lasch L, Weih S, Wink E, Romero P, Holland-Cunz S. Anastomotic sealing with a fibrin-coated collagen patch in small-diameter bowel. *Langenbecks Arch Surg*. (2011) 396(5):685–91. doi: 10.1007/s00423-011-0750-6
23. Garcia-Perez R, Munitiz V, Martinez-Caceres CM, Ruiz de Angulo D, Ortiz A, Martinez de Haro LF, et al. Histopathological and immunohistochemical analysis of the use of collagen dressing as a reinforcement of esophagic anastomosis in a rat experimental model. *Cir Esp*. (2017) 95(10):588–93. doi: 10.1016/j.ciresp.2017.08.008
24. Holmer C, Praechter C, Mecklenburg L, Heimesaat M, Rieger H, Pohlen U. Anastomotic stability and wound healing of colorectal anastomoses sealed and sutured with a collagen fleece in a rat peritonitis model. *Asian J Surg*. (2014) 37(1):35–45. doi: 10.1016/j.asjsur.2013.07.008
25. Nordentoft T, Rømer J, Sørensen M. Sealing of gastrointestinal anastomoses with a fibrin glue-coated collagen patch: a safety study. *J Invest Surg*. (2007) 20(6):363–9. doi: 10.1080/08941930701772173
26. Pantelis D, Beissel A, Kahl P, Wehner S, Vilz TO, Kalff JC. The effect of sealing with a fixed combination of collagen matrix-bound coagulation factors on the healing of colonic anastomoses in experimental high-risk mice models. *Langenbecks Arch Surg*. (2010) 395(8):1039–48. doi: 10.1007/s00423-010-0703-5
27. Pommergaard HC, Achiam MP, Burcharth J, Rosenberg J. Decreased leakage rate of colonic anastomoses by tachosil coating: an experimental study. *Int Surg*. (2014) 99(4):359–63. doi: 10.9738/intsurg-d-13-00093.1
28. Sabino FD, Campos CFF, Caetano CER, Trotte MNS, Oliveira AV, Marques RG. Effects of tachosil and 5-fluorouracil on colonic anastomotic healing. *J Surg Res*. (2014) 192(2):375–82. doi: 10.1016/j.jss.2014.05.067
29. Schreinemacher MH, Bloemen JG, van der Heijden SJ, Gijbels MJ, Dejong CH, Bouvy ND. Collagen fleeces do not improve colonic anastomotic strength but increase bowel obstructions in an experimental rat model. *Int J Colorectal Dis*. (2011) 26(6):729–35. doi: 10.1007/s00384-011-1158-z
30. Stumpf M, Junge K, Rosch R, Krones C, Klinge U, Schumpelick V. Suture-free small bowel anastomoses using collagen fleece covered with fibrin glue in pigs. *J Invest Surg*. (2009) 22(2):138–47. doi: 10.1080/08941930802713001
31. Suárez-Grau JM, Bernardos García C, Cepeda Franco C, Mendez García C, García Ruiz S, Docobo Durantez F, et al. Fibrinogen–thrombin collagen patch reinforcement of high-risk colonic anastomoses in rats. *World J Gastrointest Surg*. (2016) 8(9):627–33. doi: 10.4240/wjgs.v8.i9.627
32. Vaneerdeweg W, Hendriks JM, Lauwers PR, Ieven M, Eyskens EJ. Effect of gentamicin-containing sponges on the healing of colonic anastomoses in a rat model of peritonitis. *Eur J Surg*. (2000) 166(12):959–62. doi: 10.1080/110241500447137
33. Verhage RJ, Ruiz A, Verheem A, Goldschmeding R, Borel Rinkes IH, van Hillegersberg R. Fibrin-thrombin coated sealant increases strength of esophagogastric anastomoses in a rat model. *J Surg Res*. (2012) 176(2): e57–63. doi: 10.1016/j.jss.2011.12.028
34. Fernandez Fernandez L, Tejero E, Tieso A. Randomized trial of fibrin glue to seal mechanical oesophagojejunal anastomosis. *Br J Surg*. (1996) 83(1):40–1. doi: 10.1002/bjs.1800830111
35. Grieder F, Gelpke H, Cadosch D, Decurtins M. Fibrin glue reduces the rate of anastomotic leakage in colorectal surgery. *Br J Surg*. (2010) 97:4.
36. Huh JW, Kim HR, Kim YJ. Anastomotic leakage after laparoscopic resection of rectal cancer: the impact of fibrin glue. *Am J Surg*. (2010) 199(4):435–41. doi: 10.1016/j.amjsurg.2009.01.018
37. Liu CD, Glantz GJ, Livingston EH. Fibrin glue as a sealant for high-risk anastomosis in surgery for morbid obesity. *Obes Surg*. (2003) 13(1):45–8. doi: 10.1381/096089203321136575
38. Saldaña-Cortés JA, Larios-Arceo F, Prieto-Díaz-Chávez E, De Buen EP, González-Mercado S, Alvarez-Villaseñor AS, et al. Role of fibrin glue in the prevention of cervical leakage and strictures after esophageal reconstruction

of caustic injury. *World J Surg*. (2009) 33(5):986–93. doi: 10.1007/s00268-009-9949-x
39. Silecchia G, Boru CE, Mouiel J, Rossi M, Anselmino M, Tacchino RM, et al. Clinical evaluation of fibrin glue in the prevention of anastomotic leak and internal hernia after laparoscopic gastric bypass: preliminary results of a prospective, randomized multicenter trial. *Obes Surg*. (2006) 16(2):125–31. doi: 10.1381/096089206775565249
40. Upadhyaya VD, Gopal SC, Gangopadhyaya AN, Gupta DK, Sharma S, Upadyaya A, et al. Role of fibrin glue as a sealant to esophageal anastomosis in cases of congenital esophageal atresia with tracheoesophageal fistula. *World J Surg*. (2007) 31(12):2412–5. doi: 10.1007/s00268-007-9244-7
41. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. *Handbook for Systematic Reviews of Interventions. Version 6.2* (updated February 2021) (2021). Available from: www.training.cochrane.org/handbook [Accessed January 26, 2022].
42. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. (2021) 88, 372: 105906. doi: 10.1016/j.ijsu.2021.105906
43. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. (2004) 240(2):205–13. doi: 10.1097/01.sla.0000133083.54934.ae
44. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. (2019) 366:l4898, doi: 10.1136/bmj.l4898
45. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. (2016) 355:i4919. doi: 10.1136/bmj.i4919
46. Wells G. A., Shea B., O'Connell D., Peterson J., Welch V., Losos M., et al. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses* (2007). Available from: www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed January 26, 2022].
47. McGrath S, Zhao X, Steele R, Thombs BD, Benedetti A. Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. *Stat Methods Med Res*. (2020) 9:1–8. doi: 10.1177/0962280219889080
48. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. (2002) 21(11):1539–58. doi: 10.1002/sim.1186
49. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. (1997) 315(7109):629–34. doi: 10.1136/bmj.315.7109.629
50. Brehant O, Sabbagh C, Lehert P, Dhahri A, Rebibo L, Regimbeau JM. The gentamicin–collagen sponge for surgical site infection prophylaxis in colorectal surgery: a prospective case-matched study of 606 cases. *Int J Colorectal Dis*. (2013) 28(1):119–25. doi: 10.1007/s00384-012-1557-9
51. Grieder F, Gelpke H, Cadosch D, Decurtins M, editors. Fibrin glue reduces the rate of anastomotic leakage in colorectal surgery. *Br J Surg*. 2010.
52. Huang Y, Hu Y, Lin Y, Fu J, Wu J, Fang C, et al. Evaluation of fibrin sealant in prevention of cervical anastomotic leakage after McKeown esophagectomy: a single-center, retrospective study. *Ann Surg Oncol*. (2021) 28(11):6390–7. doi: 10.1245/s10434-021-09877-0
53. Kim HJ, Huh JW, Kim HR, Kim YJ. Oncologic impact of anastomotic leakage in rectal cancer surgery according to the use of fibrin glue: case-control study using propensity score matching method. *Am J Surg*. (2014) 207(6):840–6. doi: 10.1016/j.amjsurg.2013.07.047
54. Marano L, Di Martino N. Efficacy of human fibrinogen–thrombin patch (tachosil) clinical application in upper gastrointestinal cancer surgery. *J Invest Surg*. (2016) 29(6):352–8. doi: 10.1080/08941939.2016.1181229
55. Oliver JL, Medina IA, Garcia-Almenta EM, Gil JM, Sanchez MS, Diaz MDP, et al. Use of fibrin based biological adhesives in the prevention of anastomotic leaks in the high risk digestive tract: preliminary results of the multicentre, prospective, randomised, controlled, and simple blind phase IV clinical trial: Protissucol001. *Cir Esp*. (2012) 90(10):647–55. doi: 10.1016/j.ciresp.2012.05.007
56. Sdralis E, Tzaferai A, Davakis S, Syllaios A, Kordzadeh A, Lorenzi B, et al. Reinforcement of intrathoracic oesophago-gastric anastomosis with fibrin sealant (Tisseel®) in oesophagectomy for cancer: a prospective comparative study. *Am J Surg*. (2020) 219(1):123–8. doi: 10.1016/j.amjsurg.2019.06.013
57. Sieda B, Gharib O. Comparative study of single-layer anastomosis in high-risk colonic anastomosis versus single layer reinforced using fibrin glue. *Egypt J Surg*. (2015) 34:215. doi: 10.4103/1110-1121.167380
58. Torres-Melero J, Motos-Micó JJ, Lorenzo-Liñán M, Morales-González Á, Rosado-Cobián R. Use of absorbable fibrin sealant patch to strengthen the gastrointestinal anastomosis performed on patients with peritoneal carcinomatosis treated with intention to cure by debulking surgery and intraoperative hyperthermic intraperitoneal chemotherapy. *Cir Cir*. (2016) 84(2):102–8. doi: 10.1016/j.circir.2015.09.005
59. Pommergaard HC, Achiam MP, Rosenberg J. External coating of colonic anastomoses: a systematic review. *Int J Colorectal Dis*. (2012) 27 (10):1247–58. doi: 10.1007/s00384-012-1547-y
60. Nordentoft T, Pommergaard HC, Rosenberg J, Achiam MP. Fibrin glue does not improve healing of gastrointestinal anastomoses: a systematic review. *Eur Surg Res*. (2015) 54(1–2):1–13. doi: 10.1159/000366418
61. Chen X, Yuan X, Chen Z, Zhu L. Endoscopic injection of human fibrin sealant in treatment of intrathoracic anastomotic leakage after esophageal cancer surgery. *J Cardiothorac Surg*. (2020) 15(1):96. doi: 10.1186/s13019-020-01127-w
62. Del Rio P, Dell'Abate P, Soliani P, Ziegler S, Arcuri M, Sianesi M. Endoscopic treatment of esophageal and colo-rectal fistulas with fibrin glue. *Acta Biomed*. (2005) 76(2):95–8.
63. Lippert E, Klebl FH, Schweller F, Ott C, Gelbmann CM, Schölmerich J, et al. Fibrin glue in the endoscopic treatment of fistulae and anastomotic leakages of the gastrointestinal tract. *Int J Colorectal Dis*. (2011) 26(3):303–11. doi: 10.1007/s00384-010-1104-5
64. Plat VD, Bootsma BT, van der Wielen N, Straatman J, Schoonmade LJ, van der Peet DL, et al. The role of tissue adhesives in esophageal surgery: a systematic review of literature. *Int J Surg*. (2017) 40:163–8. doi: 10.1016/j.ijsu.2017.02.093
65. Cheragwandi A, Nieuwenhuis DH, Gagner M, Consten EC. An update of available innovative staple line reinforcement materials in colorectal surgery. *Surg Technol Int*. (2008) 17:131–7.
66. Chen Y-S, Loh E-W, Shen S-C, Su Y-H, Tam K-W. Efficacy of fibrin sealant in reducing complication risk after bariatric surgery: a systematic review and meta-analysis. *Obes Surg*. (2021) 31(3):1158–67. doi: 10.1007/s11695-020-05098-8
67. Panda S, Connolly MP, Ramirez MG, de Heredia JB. Costs analysis of fibrin sealant for prevention of anastomotic leakage in lower colorectal surgery. *Risk Manage Healthc Policy*. (2020) 13:5–11. doi: 10.2147/RMHP.S221008
68. Anderson DI, Keskey R, Ackerman MT, Zaborina O, Hyman N, Alverdy JC, et al. *Enterococcus faecalis* is associated with anastomotic leak in patients undergoing colorectal surgery. *Surg Infect (Larchmt)*. (2021) 22 (10):1047–51. doi: 10.1089/sur.2021.147
69. Thompson SK, Chang EY, Jobe BA. Clinical review: healing in gastrointestinal anastomoses, Part I. *Microsurgery*. (2006) 26(3):131–6. doi: 10.1002/micr.20197
70. Neumann PA, Twardy V, Becker F, Geyer C, Schwegmann K, Mohr A, et al. Assessment of MMP-2/-9 expression by fluorescence endoscopy for evaluation of anastomotic healing in a murine model of anastomotic leakage. *PLoS One*. (2018) 13(3):e0194249. doi: 10.1371/journal.pone.0194249
71. Thornton FJ, Barbul A. Healing in the gastrointestinal tract. *Surg Clin North Am*. (1997) 77(3):549–73. doi: 10.1016/s0039-6109(05)70568-5

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Surgery

ORIGINAL RESEARCH
published: 09 May 2022
doi: 10.3389/fsurg.2022.885244

Endoscopic Management of Large Leakages After Upper Gastrointestinal Surgery

*Stanislaus Reimer[1], Johan F. Lock[2], Sven Flemming[2], Alexander Weich[1], Anna Widder[2], Lars Plaßmeier[2], Anna Döring[2], Ilona Hering[2], Mohammed K. Hankir[2], Alexander Meining[1], Christoph-Thomas Germer[2], Kaja Groneberg[1] and Florian Seyfried[2]**

[1]Department of Gastroenterology, University Hospital of Würzburg, Würzburg, Germany, [2]Department of General, Visceral, Transplant, Vascular and Pediatric Surgery, University Hospital of Würzburg, Würzburg, Germany

Background: Endoscopic vacuum therapy (EVT) is an evidence-based option to treat anastomotic leakages of the upper gastrointestinal (GI) tract, but the technical challenges and clinical outcomes of patients with large defects remain poorly described.
Methods: All patients with leakages of the upper GI tract that were treated with endoscopic negative pressure therapy at our institution from 2012–2021 were analyzed. Patients with large defects (>30 mm) as an indicator of complex treatment were compared to patients with smaller defects (control group).
Results: Ninety-two patients with postoperative anastomotic or staplerline leakages were identified, of whom 20 (21.7%) had large defects. Compared to the control group, these patients required prolonged therapy (42 vs. 14 days, $p < 0.001$) and hospital stay (63 vs. 26 days, $p < 0.001$) and developed significantly more septic complications (40 vs. 17.6%, $p = 0.027$.) which often necessitated additional endoscopic and/or surgical/interventional treatments (45 vs. 17.4%, $p = 0.007$.) Nevertheless, a resolution of leakages was achieved in 80% of patients with large defects, which was similar compared to the control group ($p = 0.42$). Multiple leakages, especially on the opposite side, along with other local unfavorable conditions, such as foreign material mass, limited access to the defect or extensive necrosis occurred significantly more often in cases with large defects ($p < 0.001$).
Conclusions: Overall, our study confirms that EVT for leakages even from large defects of the upper GI tract is feasible in most cases but comes with significant technical challenges.

Keywords: anastomotic leakage, endoluminal, vacuum-assisted closure, negative pressure, endoscopic

OPEN ACCESS

Edited by:
Giuseppe Di Buono, University of Palermo, Italy

Reviewed by:
Giacomo Lo Secco, University of Turin, Italy
Alexander Reinisch, Wetzlar Clinic, University of Giessen, Germany

***Correspondence:**
Florian Seyfried
Seyfried_F@ukw.de

Speciality section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *27 February 2022*
Accepted: *14 April 2022*
Published: *09 May 2022*

Citation:
Reimer S, Lock JF, Flemming S, Weich A, Widder A, Plaßmeier L, Döring A, Hering I, Hankir MK, Meining A, Germer C-T, Groneberg K and Seyfried F (2022) Endoscopic Management of Large Leakages After Upper Gastrointestinal Surgery. Front. Surg. 9:885244. doi: 10.3389/fsurg.2022.885244

INTRODUCTION

There is a growing body of evidence showing the remarkable efficacy of endoscopic vacuum therapy (1) to prevent (2–5) or treat (6, 7) anastomotic leakages of the upper GI tract. Overall, EVT has success rates of up to 90% in large meta-analyses (1) and prevents the need for difficult salvage operations that often necessitate demanding secondary reconstructions of the

alimentary tract. Thus, EVT has evolved from an experimental procedure to an evidence-based option of choice to treat anastomotic leakages of the upper GI tract in the majority of cases (1). However, the successful application of EVT may come with a significant learning curve (Reimer et al.) associated with various technical challenges and limitations (8), especially in difficult cases. In the present study, we systematically analyzed our prospectively collected database containing detailed information on patients undergoing EVT treatment focusing on patients with large defects (>30 mm) which we considered as a marker for case severity. We then summarize in detail how we overcame the technical challenges we encountered during EVT treatment.

MATERIALS AND METHODS

All consecutive patients with leakages of the upper GI tract that were treated with endoscopic negative pressure therapy at our visceral medical center at the University Hospital Wuerzburg, Germany from 2012–2021 were included in this study. Approval was obtained from the local ethics review board (Ethics committee, Würzburg University).

Study Design and Ethics

For the analysis, all patients with anastomotic or stapler line leakages were included. Patients with large defects (>30 mm) as an indicator of complex treatment were compared to patients with smaller defects (control group). The technical challenges and the evolution of solution being employed were identified, categorized and described in detail.

Endoscopic Vacuum Therapy

This technique requires a flexible endoscope to place an open-pored polyurethane sponge into the cavity behind the leak (intracavitary) or within the intestinal lumen (intraluminal) (9). The sponge was connected by a nasogastric tube to a negative pressure system. An intracavitary sponge was usually adopted for accessible extraluminal cavities; an intraluminal sponge was generally preferred for defects with diffuse local inflammation or shallow cavities. The sponge was changed regularly every 3–4 days (10). Endoscopic vacuum therapy was terminated when stable granulation tissue was present with no signs of necrosis or leakage.

The vast majority of reported EVT applications at our center was carried out with modified commercially available open-pore polyurethane foam drains that are approved as medical devices for treatment of the esophagus and rectum (EndoSPONGE® and EsoSPONGE®, both B. Braun Melsungen AG, Melsungen, Germany). The modification included removal of the sponge from the original draining tube at the proximal end. The sponge was then carefully cleaned and attached to a 14F gastric tube with 10 perforations on both sides over a length of 6 cm (Vygon, Ecouen, France) with several stitches. A 16F tube was used to drain particularly viscous mucus and a 12F probe was used for angled approaches, smaller cavities, less compliant patients and duodenal lesions. The tip of the tube was snipped off after the sponge was attached to the probe and about 5–7 mm was pulled back into the sponge so that the sponge tip was soft. For localized tissue defects, care was taken to ensure that the suction effect was focused on the defect so that it closed and did not spread to surrounding tissue for avoidance of stricture formation. In our experience, the number and arrangement of the holes on the gastric tube should be limited and restricted to the area carrying the sponge. Therefore, the tube was shortened and additional holes were created on the probe using pliers when necessary (Knipex-Werk C. Gustav Putsch KG, Wuppertal Germany). EndoSPONGE® was used mainly during the first period. In total, <5% of treatments required a sponge longer than 5 cm (V.A.C. Granufoam Dresssing, 3 M, San Antonio, USA or Invia Foam Dressing, Medela, Baar, Switzerland were used).

Foreign body forceps (Rat Tooth Forceps, Endo-Flex GmbH, Voerde, Germany) were applied for endoscopic sponge placement. Standard biopsy forceps and foreign body forceps (Radial Jaw 4, standard capacity, Radial Jaw 4, Jumbo, Boston Scientific, Marlborough, USA and Rat Tooth Forceps, Endo-Flex GmbH, Voerde, Germany) were used for necrosectomy and cleaning the defect margins. In addition, an over-the-scope grasper (OTSG, Xcavator, Ovesco AG, Germany) was occasionally used if extended necrosectomy was necessary. A biliary cytology brush (Cytomax II double lumen, cytology brush, Cook medical, Bloomington, USA) was used to refresh the fistula opening and canal if necessary.

TABLE 1 | Patient and leakage characteristics.

Characteristic	Patients, No. (%)		
	Large defects (*n* = 20)	Control (*n* = 72)	*p* value
Sex ratio, No. (M:F)	13:7	59:33	.94
Age, mean (SD), y	60.7 (8.8)	58.8 (14.1)	.57
BMI, mean (SD), kg/m^2	27.8 (5.5)	28.3 (9.5)	.80
Charlson comorbidity index, mean (SD)	3.8 (2.3)	4.2 (2.5)	.52
ASA classification ≥III	14 (70.0)	62 (67.4)	.82
Neoadjuvant therapy	7 (35.0)	44 (47.8)	.19
Oncological surgery	9 (56.3)	49 (63.6)	.58
UGI surgery	7 (43.8)	28 (36.4)	
Type of leakage			
Esophago-gastrostomy	8 (40.0)	33 (35.9)	.34
Esophago-jejunostomy	2 (10.0)	28 (30.4)	
Gastro-jejunostomy	5 (25.0)	17 (18.5)	
Other	5 (25.0)	14 (15.2)	
Interval from surgery to diagnosis of leakage, mean (95%CI), d	8.8 (4–22)	11.5 (2–31)	.27
Initial leakage diameter, mean (95%CI), mm	24.5 (17.7–31.2)	7.4 (6.2–8.6)	<.001

Values are n (%) unless otherwise indicated.
UGI, upper gastrointestinal tract; SD, standard deviation; 95%CI, 95% confidence interval.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics 26 (International Business Machines Corporation, Armonk, NY). Descriptive data are reported as means with standard deviations, unless otherwise stated. Comparisons between the analyzed cohorts were performed using chi-square, Fisher's exact, Mann–Whitney *U*-tests or one-way analysis of variance, in accordance with data scale and distribution. The time-intervals were compared by Kaplan-Meier analysis with log rank test. The level of statistical significance was 0.05 (two-sided).

RESULTS

Out of 170 patients with EVT for leakages of the upper GI tract including several entities, 92 patients with a postoperative anastomotic or staplerline leakage were identified. Of those, 20 patients (anastomotic leak $n = 16$ and staplerline leak $n = 4$) with large defects (>30 mm) were detected and compared to patients with smaller defects ($n = 72$). Baseline characteristics are summarized in **Table 1**.

Baseline characteristics including age, gender, comorbidities, entity and side of the leakage did not differ between both groups. Patients with a large defect size of the leakage (with an estimated size of over 30 mm or half of the anastomotic circumference, respectively) had prolonged treatment duration (**Figure 1**). Treatment outcomes are summarized in **Table 2**. Patients with larger defect sizes required prolonged therapy and, consequently, experienced extended hospital stay. Compared to the control group, they developed significantly more septic complications and more often required additional endoscopic and/or surgical/interventional treatments. Nevertheless, leakages resolved in 80% of patients with large defects compared to 90% of patients in the control group, which was not significantly different.

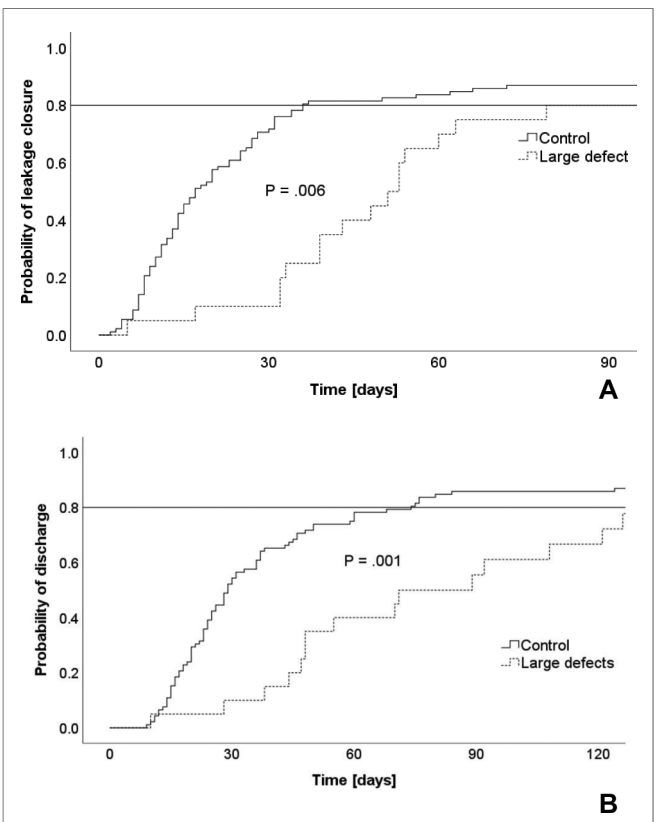

FIGURE 1 | Impact of large defects on recovery. (**A**) Duration of leakage therapy. (**B**) Length-of-hospitalization.

Challenging Endoscopic Situations and Proposed Solutions

Table 3 summarizes the main technical challenges associated with EVT and the proposed solutions. Multiple leakages, especially on

TABLE 2 | Endoscopic leakage therapy and outcome.

Characteristic	Patients, No. (%)		
	Large defects ($n = 20$)	Control ($n = 72$)	*p* value
Duration of leakage therapy, median (quartiles), d	42 (32–54)	14 (8–25)	<.001
Sponge changes, median (quartiles)	12 (10–16)	4 (2–6)	<.001
Challenging endoscopic situations			
Leakage with >1 defect	10 (50)	5 (5.4)	<.001
Foreign material within leakage	10 (50)	2 (2.2)	<.001
Limited endoscopic access to leakage	10 (50)	3 (3.3)	<.001
Extensive necrosis	12 (60)	6 (6.5)	<.001
Additional Procedures during EVT			
Any reoperation	10 (50)	24 (26.1)	.035
Percutaneous abscess drainage	8 (40)	15 (16.3)	.017
Complications during EVT			
Recurrent sepsis	8 (40)	16 (17.6)	.027
Stenosis/ stricture	4 (20)	12 (13)	.48
Efficacy of EVT			
Improvement of leakage	18 (90)	82 (89.1)	.91
Resolution of leakage	16 (80)	80 (87.0)	.42
Resolution without additional procedures during or after EVT	9 (45)	63 (68.5)	.047
Failure-to-cure[a]	3 (15)	10 (10.9)	.61
Additional Procedures after EVT	9 (45)	16 (17.4)	.007
Endoscopic clip	4 (20)	12 (13.0)	.42
SEMS	5 (25)	4 (4.4)	.002
In-hospital mortality	2 (10)	6 (6.5)	.58
Length-of-stay, median (quartiles), d	63 (45–104)	26 (18–45)	<.001
Oral nutrition on discharge	14 (70)	70 (76.1)	.57

Values are n (%) unless otherwise indicated.
EVT, endoscopic vacuum therapy; 95%CI, 95% confidence interval; SEMS, self-expanding metal stent.
[a]*Conversion to surgical therapy due to deteriorating leakage during EVT or death.*

TABLE 3 | Challenging endoscopic situations and proposed solutions.

Technical challenges	Problem	Proposed solution
Leaks with more than one (deep) defect	Intraluminal EVT may be ineffective to sufficiently drain deep defects	Intracavital sponge placement by applying two or more sponge systems
Foreign material mass	Foreign material may preclude sufficient suction and/or collapse of the defect	Extracting foreign material whenever possible
Limited access to the leak/defect (small caliber, tissue bridges, deep cannels)	Inefficient suction/drainage of the defect	Optimizing access to the defect (e.g., by tissue dissection, pneumatic dilatation (11), creation of alterative routes (e.g., stoma formation, (12))
Extensive necrosis at leak/defect site	EVT induced tissue granulation needs vital tissue	Early and extensive necrosectomy

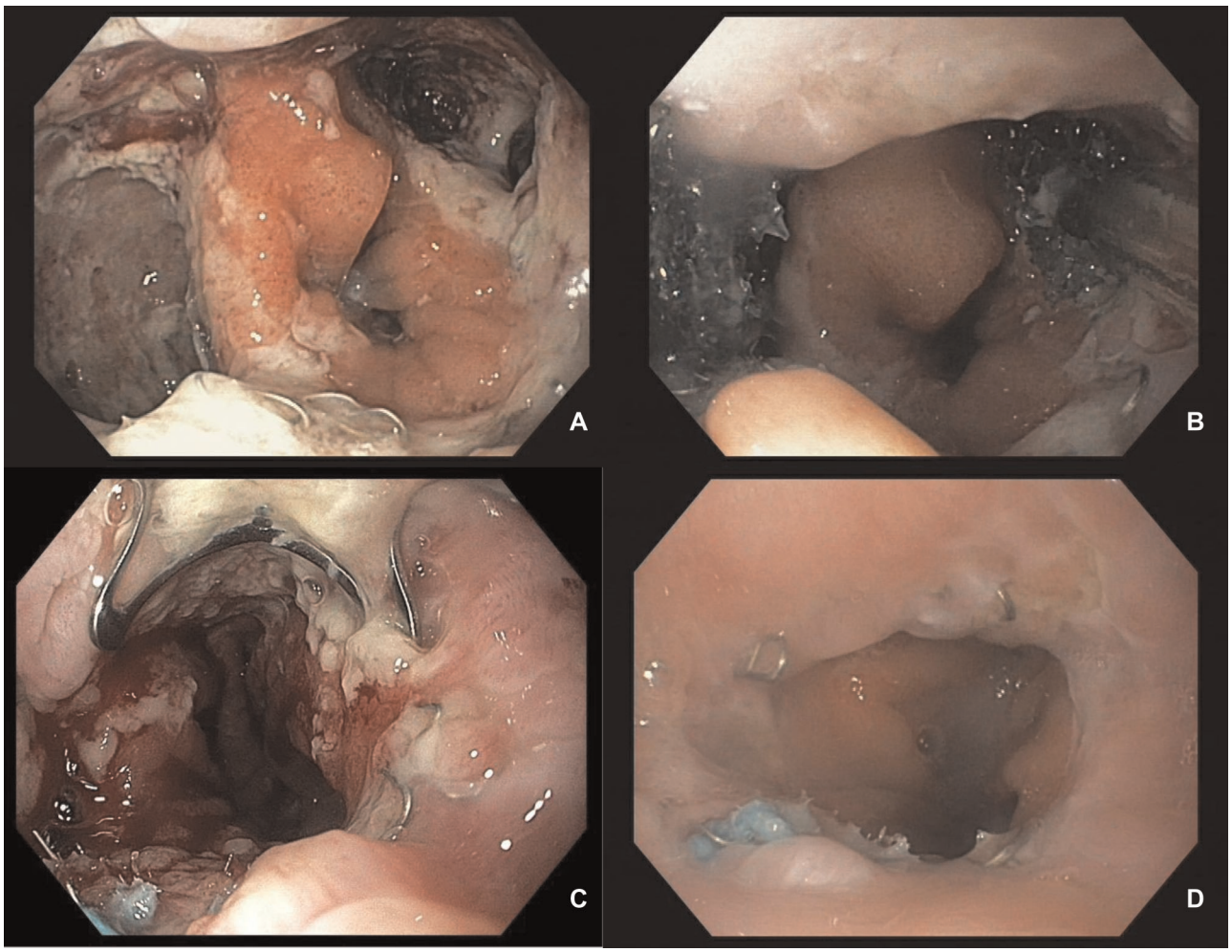

FIGURE 2 | (**A–D**) Usage of two independent sponge systems in a case with two large defects of the oseophagojejunostomy (Merendino Procedure) and results. Initial endoscopy showed an evident anastomotic leakage between 02:00 and 05:00 and between 08:00 and 11:00. After extensive necrosectomy on both leakages (**A**), two separate sponge systems were inserted into both insufficiency cavities (**B**). In order to accelerate further healing and to minimize the risk of fistula formation, the healed leakage cavities were gathered using mini OTSC, 8 mm (**C**) and an intraluminal sponge was inserted. Re-endoscopy of the anastomotic region after 14 days (**D**). OTSC is completely grown into the wall. Anastomosis is largely free of irritation.

the opposite side, along with other local unfavorable conditions, such as foreign material mass, limited access to the defect or extensive necrosis was found significantly more often in cases with large defects (85% vs. 14.1%, $p < 0.001$, **Table 2**).

Within this group the majority of patients even showed multiple endoscopic difficulties (75% vs. 3.3%, $p < 0.001$). We found an association of the number of challenging endoscopic situations and the median duration of EVT (none: 12 days,

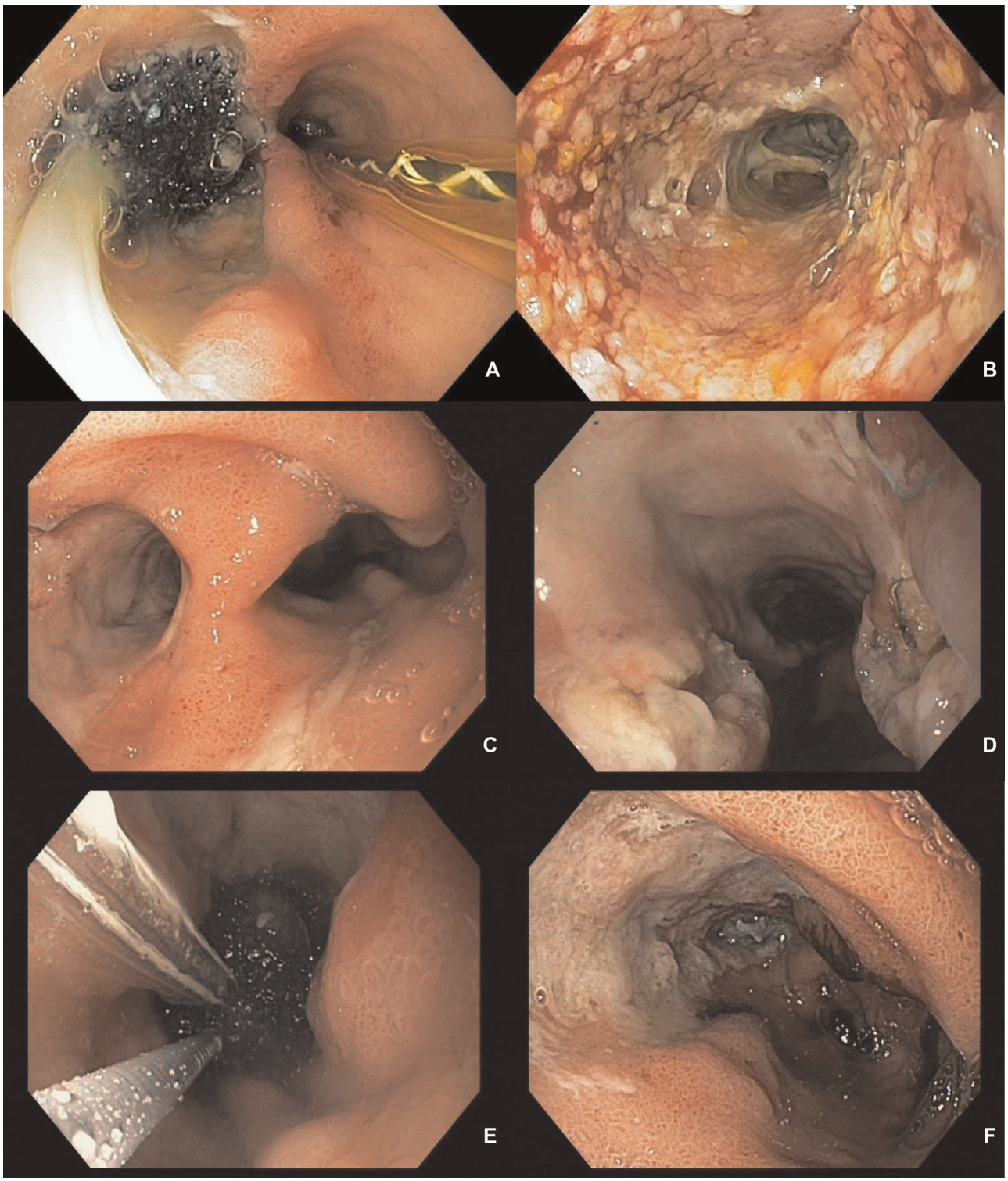

FIGURE 3 | (**A–F**) Creation of an optimal access route to the leakage defect in a patient after sleeve gastrectomy. Endoscopic pictures of a female patient with a chronic large defect of the proximal stapler line after sleeve gastrectomy transferred to our institution for complication management. Initial endoscopy found a 40 × 15 mm long EVT sponge in an approx. 12 cm long and 15mm wide paragastral defect. A gastric tube was placed intraluminary of the sleeve stomach (**A**). In the area of the defect ground, no suction marks but necrosis and fibrin deposits were detected (**B**). Necrosis and fibrin were removed using forceps and a brush. In a further step, in order to enable wide endoscopic access to the defect ground the canal was opened towards the gastric tube using a clutch cutter (Fjuifilm). (**C,D**) After further EVT (**E**), a gastric tube with a continuous lumen of approx. 4 cm is found. The approximately 12 cm long former defect canal is completely epithelialized in the proximal half and almost completely epithelialized in the distal area (**F**).

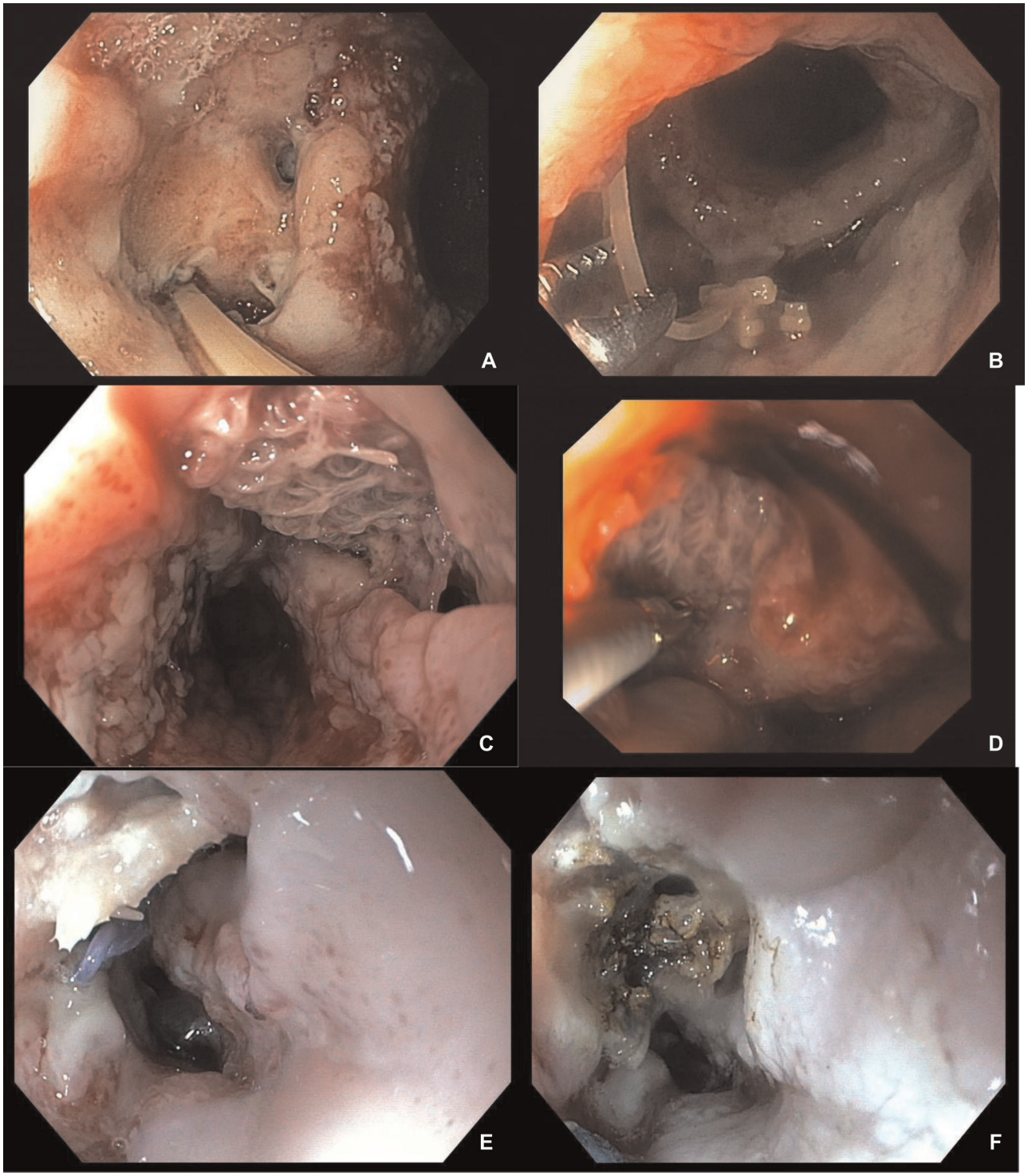

FIGURE 4 | (**A–F**) exemplary presentation of foreign material at the anastomotic leak site. Leak of the oesophagogastrostomy after minimally invasive Ivor Lewis surgery. Detectable vessel clip on the azygos vein (**A**). Removal of vessel clips using forceps (**B**). Leakage of the esophagus after revisional hiatal surgery with mesh augmented hiatoplasty (**C**, **E**). Partial repositioning (**D**) and status after thermal destruction of the intraluminal mesh portion by argon plasma coagulation (**F**).

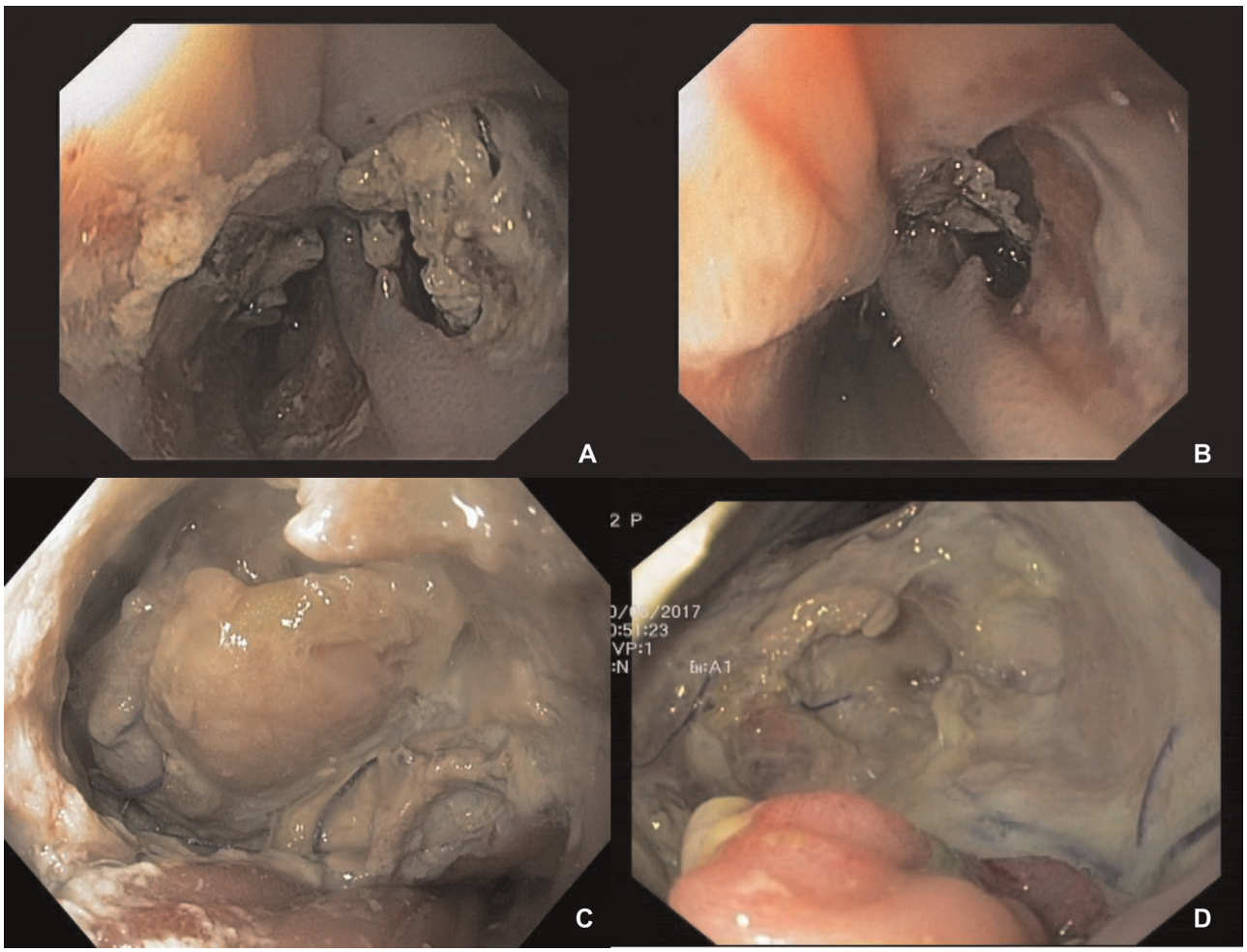

FIGURE 5 | (**A–D**) Endoluminal view of an esophageal defect with tissue necrosis. Initial necrosis (**A**, **C**) and condition after necrosectomy (**B**, **D**). It can be seen after necrosectomy that the transmural portion of necrosis is smaller than initially assumed.

1 difficulty: 27 days, >2 difficulties: 42 days, $p < 0.001$).For these problems, several solutions were identified and successfully applied in our patients. **Figures 2–5** demonstrate the endoscopic management of these challenging endoscopic situations.

DISCUSSION

Surgical options available for the management of complex leakages of the upper GI tract are limited and usually contain a high risk of morbidity and mortality (10). Our results confirm previous findings on the effectiveness of EVT for treating anastomotic and suture-line leakages of the upper GI tract (1).

In this study, we focused on the technical challenges and clinical outcomes of patients with large defects. We found that endoscopic management of large leakages after upper GI surgery is feasible but contains technical challenges which need to be mastered to achieve good results.

Interestingly, baseline patient characteristics of the group with larger defects were not different to the control group with smaller leakages. While consistent risk factors for the development of an anastomotic or stapler line have been reported (13), our data does not provide further insights on which patients may develop larger defects leading to a more challenging course. Larger defects may have occurred due to insufficient perfusion of the anastomotic region, even though mucosal signs of ischemia during endoscopic treatment were not detected. Combined hyperspectral imaging (HIS) or florescence Imaging (FI) with indocyanine green (ICG) were not routinely performed but could provide further insights in the future.

It could also be possible that a delayed start or initially insufficient treatment of the leakage may have contributed to a larger defect size (14) as some of the patients treated at our tertiary hospital underwent surgery elsewhere and were transferred for leakage management during the later course.

We previously showed that experience with EVT in conjunction with adjustments in institutional factors, patient management and technical details positively impact on its overall efficacy (Reimer et al). Given the remarkable success

rates of EVT, it seems reasonable to implement this promising technique for more complex cases.

The successful treatment of large defects contains some technical challenges which frequently occur during treatment. Of note, it is not unusual that the initial defect size increases during early treatment.

If a leakage with more than one deep defect with spatial distance to each other occurs, we recommend the usage of more than one sponge system so that an intracavital placement is possible to sufficiently drain all defects. Foreign material may preclude sufficient suction and the collapse of the defect and should therefore be removed. Extensive necrosis at the anastomotic leakage site should also be removed as early as possible since EVT induced tissue granulation needs healthy tissue (15). If access to endoscopic treatment is limited, several options can be considered including tissue dissection, dilatation or creation of alternative routes (11, 12). When these principles are applied, there are only very few conditions where an EVT does not provide good outcomes.

Whenever a difficult leakage is treated by EVT, it is extremely important to evaluate carefully and constantly both, the local leak situation but, more importantly, the patient's systemic condition. An interdisciplinary board of experienced gastroenterologists and visceral surgeons should consider alternative endoscopic or surgical treatment options whenever necessary (8, 16).

Our results show that patients with larger defect sizes needed prolonged therapy. Compared to the control group, they developed significantly more septic complications and required more often additional endoscopic and/or surgical/interventional treatment. However, also in this cohort a resolution of the leakage was achieved in 80%, with an improvement in 90% of patients, respectively. Thus, neither the success nor the mortality rates were different compared to the control group.

This is to our knowledge is the first study comparing patients with large defects to patients with small anastomotic leakages. A limitation may be the small number of patients with large leakages. Nevertheless, this is one of the largest prospectively collected databases focusing on EVT treatment for more than 10 years. Due to the small number, we may have missed the opportunity to detect some other potential differences with the control group because of statistical power. Additionally, it is difficult to systematically categorize all of the technical challenges which may occur during EVT treatment either alone or even in combination.

In summary, our study confirms that EVT for leakages even with large defects in the upper GI tract is successful in the vast majority of cases but contains some technical challenges which need to be addressed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkomission Universität Würzburg. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

S.R., F.S. and J.F.L. conceived and designed the experiment; S.R., S.F., A.W., A.W., L.P., A.D., I.H. and K.G. acquired the data; S.R., F.S. and J.F.L. analyzed and interpreted the data; software, layout, and visualization were performed by J.F.L., S.R. and A.W.; S.R., F.S. and J.F.L. drafted the work (writing—original draft preparation); A.M., C-T.G. and M.K.H. revised it critically for important intellectual content (review and editing). All authors contributed to the article and approved the submitted version.

REFERENCES

1. Jung DH, Yun HR, Lee SJ, Kim NW, Huh CW. Endoscopic vacuum therapy in patients with transmural defects of the upper gastrointestinal tract: a systematic review with meta-analysis. *J Clin Med*. (2021) 10(11):2346. doi: 10.3390/jcm10112346
2. Loske G, Muller J, Schulze W, Riefel B, Muller CT. Pre-emptive active drainage of reflux (PARD) in Ivor-Lewis oesophagectomy with negative pressure and simultaneous enteral nutrition using a double-lumen open-pore film drain (dOFD). *Surg Endosc*. (2022) 36(3):2208–16. doi: 10.1007/s00464-021-08933-w
3. Muller PC, Morell B, Vetter D, Raptis DA, Kapp JR, Gubler C, et al. Preemptive endoluminal vacuum therapy to reduce morbidity after minimally invasive ivor lewis esophagectomy: including a novel grading system for postoperative endoscopic assessment of GI-Anastomoses. *Ann Surg*. (2021) 274(5):751–7. doi: 10.1097/SLA.0000000000005125
4. Gubler C, Vetter D, Schmidt HM, Muller PC, Morell B, Raptis D, et al. Preemptive endoluminal vacuum therapy to reduce anastomotic leakage after esophagectomy: a game-changing approach? *Dis Esophagus*. (2019) 32(7):32. doi: 10.1093/dote/doy126
5. Neumann PA, Mennigen R, Palmes D, Senninger N, Vowinkel T, Laukoetter MG. Pre-emptive endoscopic vacuum therapy for treatment of anastomotic ischemia after esophageal resections. *Endoscopy*. (2017) 49(5):498–503. doi: 10.1055/s-0042-123188
6. Schorsch T, Muller C, Loske G. Endoscopic vacuum therapy of anastomotic leakage and iatrogenic perforation in the esophagus. *Surg Endosc*. (2013) 27 (6):2040–5. doi: 10.1007/s00464-012-2707-4
7. Laukoetter MG, Mennigen R, Neumann PA, Dhayat S, Horst G, Palmes D, et al. Successful closure of defects in the upper gastrointestinal tract by endoscopic vacuum therapy (EVT): a prospective cohort study. *Surg Endosc*. (2017) 31(6):2687–96. doi: 10.1007/s00464-016-5265-3
8. de Moura DTH, de Moura B, Manfredi MA, Hathorn KE, Bazarbashi AN, Ribeiro IB, et al. Role of endoscopic vacuum therapy in the management of gastrointestinal transmural defects. *World J Gastrointest Endosc*. (2019) 11(5):329–44. doi: 10.4253/wjge.v11.i5.329
9. Newton NJ, Sharrock A, Rickard R, Mughal M. Systematic review of the use of endo-luminal topical negative pressure in oesophageal leaks and perforations. *Dis Esophagus*. (2017) 30(3):1–5. doi: 10.1111/dote.12531
10. Schniewind B, Schafmayer C, Voehrs G, Egberts J, von Schoenfels W, Rose T, et al. Endoscopic endoluminal vacuum therapy is superior to other regimens

in managing anastomotic leakage after esophagectomy: a comparative retrospective study. *Surg Endosc*. (2013) 27(10):3883–90. doi: 10.1007/s00464-013-2998-0
11. Lock JF, Reimer S, Pietryga S, Jakubietz R, Flemming S, Meining A, et al. Managing esophagocutaneous fistula after secondary gastric pull-up: A case report. *World J Gastroenterol*. (2021) 27(16):1841–6. doi: 10.3748/wjg.v27.i16.1841
12. Kelm M, Seyfried F, Reimer S, Krajinovic K, Miras AD, Jurowich C, et al. Proximal jejunal stoma as ultima ratio in case of traumatic distal duodenal perforation facilitating successful EndoVAC((R)) treatment: A case report. *Int J Surg Case Rep*. (2017) 41:401–3. doi: 10.1016/j.ijscr.2017.11.022
13. Noble F, Curtis N, Harris S, Kelly JJ, Bailey IS, Byrne JP, et al. Risk assessment using a novel score to predict anastomotic leak and major complications after oesophageal resection. *J Gastrointest Surg*. (2012) 16(6):1083–95. doi: 10.1007/s11605-012-1867-9
14. Akesson O, Heyman I, Johansson J, Rissler P, Falkenback D. Early endoscopic assessment after esophagectomy can predict anastomotic complications: a novel scoring system. *Surg Endosc*. (2022) 36(3):1903–9. doi: 10.1007/s00464-021-08472-4
15. Morykwas MJ, Simpson J, Punger K, Argenta A, Kremers L, Argenta J. Vacuum-assisted closure: state of basic research and physiologic foundation. *Plast Reconstr Surg*. (2006) 117(7 Suppl):121S–6S. doi: 10.1097/01.prs.0000225450.12593.12
16. Kuehn F, Schiffmann L, Janisch F, Schwandner F, Alsfasser G, Gock M, et al. Surgical endoscopic vacuum therapy for defects of the upper gastrointestinal tract. *J Gastrointest Surg*. (2016) 20(2):237–43. doi: 10.1007/s11605-015-3044-4

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Surgery

ORIGINAL RESEARCH
published: 16 May 2022
doi: 10.3389/fsurg.2022.874223

Antibiotic Bowel Decontamination in Gastrointestinal Surgery—A Single-Center 20 Years' Experience

*Josefine Schardey[1,2], Thomas von Ahnen[2,3], Emily Schardey[2], Alina Kappenberger[1], Petra Zimmermann[1], Florian Kühn[1], Joachim Andrassy[1], Jens Werner[1], Helmut Arbogast[1‡] and Ulrich Wirth[1,2†‡]**

[1]Department of General, Visceral and Transplant Surgery, Ludwig-Maximilians-University Munich, Munich, Germany, [2]Institute for Surgical Research Oberbayern, Hausham, Germany, [3]Department for General, Visceral, Endocrine and Vascular Surgery, Krankenhaus Agatharied GmbH, Hausham, Germany

OPEN ACCESS

Edited by:
Sven Flemming
University Hospital of Wuerzburg, Germany

Reviewed by:
John Chris Alverdy,
University of Chicago, United States
Matthias Kelm,
University Hospital Würzburg, Germany

***Correspondence**:
Ulrich Wirth
Ulrich.Wirth@med.uni-muenchen.de

†ORCID:
Ulrich Wirth
orcid.org/0000-0003-2366-8524

‡These authors have contributed equally to this work and share senior authorship

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: 11 February 2022
Accepted: 25 April 2022
Published: 16 May 2022

Citation:
Schardey J, von Ahnen T, Schardey E, Kappenberger A, Zimmermann P, Kühn F, Andrassy J, Werner J, Arbogast H and Wirth U (2022) Antibiotic Bowel Decontamination in Gastrointestinal Surgery—A Single-Center 20 Years' Experience. Front. Surg. 9:874223. doi: 10.3389/fsurg.2022.874223

Objective: Anastomotic leakage, surgical site infections, and other infectious complications are still common complications in gastrointestinal surgery. The concept of perioperative antibiotic bowel decontamination demonstrates beneficial effects in single randomized controlled trials (RCTs), but data from routine clinical use are still sparse. Our aim was to analyze the data from the routine clinical use of perioperative antibiotic bowel decontamination in gastrointestinal surgery.

Methods: Based on 20 years' experience, we performed a retrospective analysis of all cases in oncologic gastrointestinal surgery with the use of antibiotic bowel decontamination in gastric, sigmoid, and rectal cancer. Clinical data and perioperative outcomes were analyzed, especially regarding anastomotic leakage, surgical site infections, and other infectious complications.

Results: A total of $n = 477$ cases of gastrointestinal surgery in gastric cancer ($n = 80$), sigmoid cancer ($n = 168$), and rectal cancer ($n = 229$) using a perioperative regimen of antibiotic bowel decontamination could be included in this analysis. Overall, anastomotic leakage occurred in 4.4% (2.5% gastric cancer, 3.0% sigmoid cancer, 6.1% rectal cancer) and surgical site infections in 9.6% (6.3% gastric cancer, 9.5% sigmoid cancer, 10.9% rectal cancer). The incidence of all infectious complications was 13.6% (12.5% gastric cancer, 11.3% sigmoid cancer, 15.7% rectal cancer). Mortality was low, with an overall rate of 1.1% (1.3% gastric cancer, 1.8% sigmoid cancer, 0.4% rectal cancer). Antibiotic decontamination was completed in 98.5%. No adverse effects of antibiotic bowel decontamination could be observed.

Conclusion: Overall, in this large cohort, we can report low rates of surgery-related serious morbidity and mortality when perioperative antibiotic bowel decontamination is performed. The rates are lower than other clinical reports. In our clinical experience, the use of perioperative antibiotic bowel decontamination appears to improve patient safety and surgical outcomes during gastrointestinal oncologic procedures in a routine clinical setting.

Keywords: antibiotic bowel decontamination, gastrointestinal surgery, anastomotic leakage, SDD, colorectal cancer, gastric cancer

INTRODUCTION

Digestive tract surgery is associated with high rates of surgical site infections (SSIs) as well as other infectious complications (1–5) and major elevation of treatment costs (6). The rate is the highest in colorectal cancer surgery, where infectious complications affect up to 26% of patients (7–9). The most severe complication of digestive tract surgery however is anastomotic leakage (AL), with an incidence in colorectal resections ranging from 5% to 15% and an associated mortality rate of 6%–30% (10–13). The leakage rate of esophagojejunal anastomosis following total gastrectomy is reported to be between 4% and 15% in recent literature (14–16), and the mortality in case of AL reaches up to 60% (17). AL of upper and lower gastrointestinal tract surgery not only causes morbidity and postoperative mortality but also impairs long-term cancer survival (2, 18–21).

While the role of bacteria in the development of SSI is unquestioned, their role in the pathogenesis of AL is not well accepted (10, 22–24). Today however there is experimental and clinical evidence, indicating that microbiota is directly involved in the pathogenesis of intestinal AL (10, 23, 25, 26). In 1994, Schardey demonstrated that deliberate postoperative contamination of esophagointestinal anastomoses with virulent *Pseudomonas aeruginosa* in rats resulted in AL rates of 95% (24). A topical application of nonresorbable antibiotics administered perioperatively until the 10th postoperative day reduced bacterial counts by 95%, and no AL occurred (24). He modified the selective decontamination of the digestive tract regimen (SDD), originally reported by Stoutenbeek et al. for the prevention of pneumonia in ventilated patients, adding vancomycin for double antibiotic coverage of relevant germs (27).

In a clinical multicenter randomized controlled trial (RCT), for the first time, Schardey demonstrated a significant reduction of AL in patients using the modified SDD regimen in patients with total gastrectomy for topical decontamination in gastric cancer surgery (28). It is also noteworthy that the number of postoperative pneumonia decreased significantly, and treatment costs were reduced by about 20% (28, 29). In a further clinical RCT, this modified SDD regimen was used in patients undergoing (low) anterior resection for rectal cancer (30). There was a significant reduction of AL in treatment compared to the control group, with a cost reduction in the treatment group of up to 37% (30).

Nevertheless, the use of bowel decontamination in gastrointestinal surgery is not widespread in Europe or United States (31–33), despite reliable data are available from prospective studies, meta-analyses, and large clinical registry cohorts (34, 35). Currently, several randomized trials have recently been published on the role of perioperative antibiotic bowel decontamination in colorectal surgery to prevent SSI, AL, and other infectious complications (9, 36, 37). However, only sparse data from the routine clinical use of decontamination in gastrointestinal surgery are available at present. Furthermore, there are other concepts in which antibiotic bowel decontamination is performed only preoperatively with or without combination with mechanical bowel preparation (38).

Based on the work by Schardey et al., there is 20 years' experience in the routine use of antibiotic decontamination in nearly all patients undergoing gastric or colorectal surgery with primary anastomosis (28, 30, 39, 40). Especially patients with intestinal anastomoses to the esophagus, rectum, and anus have a higher risk for AL compared to other localizations in the gastrointestinal tract (10, 13, 28). The aim of this work is to analyze the routine clinical use of decontamination in surgery for gastric and colorectal cancer (CRC) concerning AL, SSI, and possible side effects over the available 20 years' period in a single center.

MATERIALS AND METHODS

Study Design

We designed a single-center retrospective cohort study including patients who received the preoperative and postoperative (modified) SDD regimen in upper and lower GI cancer surgery between 1999 and 2020 (on treatment) in an academic teaching hospital. The study was approved by the local review board (19-621 and 22-0013).

All elective procedures of gastric cancer surgery and of lower GI surgery for sigmoid and rectal cancer were analyzed. The hospital's electronic database was used to identify all patients undergoing gastrectomy for gastric cancer as well as a sigmoid or rectal resection for CRC with primary anastomosis. In colorectal cancer surgery, cases without primary anastomosis (*Hartmann* procedure) or abdomino-perineal rectal amputations were excluded from the analysis. Overall, $n = 477$ cases met the selection criteria and received perioperative antibiotic bowel decontamination (SDD), with $n = 80$ cases of gastric, $n = 168$ cases of sigmoid, and $n = 229$ cases of rectal cancer.

Antibiotic Decontamination (SDD) Regimen

An SDD regimen consisting of polymyxin B (100 mg), gentamicin (80 mg), and amphotericin B (500 mg) in sigmoid resections and a modified SDD regimen with additional use of vancomycin (125 mg) in gastric and rectal cancer surgery (PTVA) were used as previously described (28, 30). Patients without any perioperative SDD treatment were excluded from analysis (on treatment). The medication was administered four times daily. Amphotericin B was administered 30 min after the antibiotics. SDD application was usually started in the evening before surgery and continued every 6 h until the 7th postoperative day. For patients undergoing gastrectomy, the antimicrobial agents were dissolved in distilled water and administered as a solution per os (28). Patients with surgery for sigmoid or rectal cancer took these antibiotics as capsules per os (40). If a diverting stoma was created, an unblocked Foley catheter was placed transanally after the creation of the anastomosis, and antibiotics were then applied topically *via* the catheter dissolved in distilled water (30). The compliance of application as well as the completeness of decontamination regimen was controlled by evaluation of all patient files. All patients undergoing rectal cancer surgery received additional mechanical bowel preparation; the patient with sigmoid cancer

had mild laxative therapy only. Gastric cancer patients received no additional bowel preparation.

Rectal cancer surgery was performed according to current technical standards, especially the total mesorectal excision (TME) technique was used for all low anterior rectal resections. Circular double-row staplers (Ethicon Circular Stapler, Ethicon Endo-Surgery, Johnson and Johnson, USA) were used for anastomoses in different sizes in gastric, sigmoid, and rectal cancer surgery. Intraoperative routine leak testing with a methylene blue solution was performed in every case. The extent of resection in gastric cancer patients depended on preoperative pathhistologic report and localization of the tumor according to medical evidence and national guidelines (41, 42). In all cases, a D2 lymphadenectomy was performed (43).

Outcome Measures

Perioperative data (extent and type of surgery: subtotal/total/transhiatal extended gastrectomy, sigmoid resection, (low) anterior rectal resection [(L)AR] and multivisceral resection, use of minimally invasive surgery (MIC), TNM stage and UICC classification, all perioperative 30 day complications like infectious complications (AL, SSIs, urinary tract or pulmonary infections), and general complications (myocardial infarction, stroke, mortality)) were documented as well as other demographic data. The Charlson comorbidity index was calculated for all patients (44). Perioperative complications were classified according to the Clavien–Dindo classification (45), and additionally, the Clavien–Dindo comprehensive complication index (CCI) was calculated (46). Laboratory values such as white blood cell count and C-reactive protein (CRP) were assessed perioperatively. Potential adverse events associated with the SDD/PTVA regimen were also examined. Multivisceral resection was defined as additional resection of the small bowel, liver, or urogenital tract.

As previously described (39), AL was defined and classified according to the recommendation of the International Study Group for Rectal Cancer (47). AL was usually diagnosed by endoscopy, CT scan, or relaparotomy. Due to the retrospective design, only cases with clinically apparent AL could be included.

The primary endpoint is the rate of AL. Secondary endpoints are rates of surgical site infections (SSIs), infectious complications, overall morbidity and mortality, and adverse events related to the SDD/PTVA regimen.

Statistical Analysis

For statistical analysis, SPSS 28 (IBM) and Graph Pad Prism V7 (V7 (GraphPad Software, Inc.)) were used. We performed a descriptive evaluation of perioperative outcome since no comparison of groups was possible as all patients received SDD treatment. Comparative analysis of patients with or without above-mentioned complications was carried out. A correlation of the Charlson comorbidity index and other risk factors with perioperative outcome was performed and an ROC analysis of laboratory parameters with regard to infectious complications. Patient characteristics and perioperative data were summarized using descriptive statistics and calculation of mean values. For comparison between different groups, we used the Mann–Whitney *U*-test (MW) for non-normally distributed values and Student's *t*-test for normally distributed values. The normal distribution of mean differences was tested with the Kolmogorov–Smirnov test. Fisher's exact and χ^2 tests were used to compare data between subgroups involving nominal or categorical data. p values <0.05 were considered statistically significant.

RESULTS

Patient Characteristics

In total, 477 surgical procedures with primary anastomosis and perioperative SDD treatment were included. Patients' characteristics are summarized in **Table 1**.

Most of the patients underwent surgery for CRC (sigmoid cancer $n = 168$, rectal cancer $n = 229$), and most often LAR (39.1%; $n = 187$), sigmoid resection (32.8%; $n = 156$) and AR (11.3%; $n = 54$) were performed. In patients with gastric cancer ($n = 80$), total gastrectomy (55%; $n = 44$) and partial gastrectomy (45%; $n = 36$) were performed. In surgery for gastric cancer, all procedures were carried out using the conventional open technique, whereas in 44% ($n = 74$) of patients undergoing surgery for sigmoid cancer and in 18.3% ($n = 42$) of patients with rectal cancer, the procedures were performed using the minimal invasive surgical technique (MIC). Multivisceral resection was necessary in approximately 15%–20% of procedures independent of underlaying disease (**Table 1**).

CRC

Patients with CRC had a mean age of 67.9 ± 11.2 years and 67.8 ± 10.7 years for sigmoid and rectal cancer, respectively. The mean Charlson comorbidity index for patients with sigmoid cancer was 6.0 ± 2.4 and that for rectal cancer was 5.8 ± 2.4. Patients with sigmoid cancer were mostly classified as UICC III-IV with 51.8% of cases ($n = 87$) and 47.0% of cases UICC I-II ($n = 79$). In rectal cancer patients, 53.9% were classified as UICC (y0)I-II ($n = 130$) and 41.1% were classified as UICC III-IV ($n = 99$) (**Table 1**). Decontamination was completed in $n = 165$ (98.2%) cases in sigmoid and $n = 227$ (99.1%) cases in rectal cancer patients.

Gastric Cancer

For gastric cancer, patients were slightly older, with a mean age of 71.6 ± 10.4 years. The mean Charlson comorbidity index for patients with gastric cancer was 6.2 ± 2.3. The majority of patients with gastric cancer were classified UIC I-II in 67.5% ($n = 54$) and UICC III-IV in 32.5% ($n = 26$) (**Table 1**). The decontamination regimen was complete in $n = 78$ (97.5%) of gastric cancer patients and not completed in $n = 2$ cases (2.5%).

Perioperative Outcome

Outcome parameters are summarized in **Table 2** (separated for diagnosis) and **Table 3** (separated for surgical procedures). The CCI was the highest with a mean of 17.06 ± 17.65 for gastric cancer, with 23.75% major morbidity Clavien–Dindo IIIa–V ($n = 19$). In 35% ($n = 28$), no complications were reported, and

TABLE 1 | Demographic and descriptive information about the patients' cohort.

		Gastric cancer *N* (%)	Sigmoid cancer *N* (%)	Rectal cancer *N* (%)
N		80	168	229
Sex, female/male		43/37	91/77	92/137
Age (mean ± SD)		71.6 ± 10.4	67.9 ± 11.2	67.8 ± 18.8
MIC		0	74 (44.0)	42 (18.3)
UICC	0	1 (1.3)	2 (1.2)	13 (5.7)
	I(a)	26 (32.5)	40 (23.8)	60 (26.2)
	Ib	11 (13.8)		
	IIa	12 (15.0)	38 (22.6)	55 (24.0)
	IIb	4 (5.0)	1 (0.6)	2 (0.9)
	IIIa	3 (3.8)	6 (3.6)	10 (4.4)
	IIIb	7 (8.8)	30 (17.9)	32 (14.0)
	IIIc	3 (3.8)	17 (10.1)	18 (7.9)
	IV	13 (16.3)	34 (20.2)	39 (17)
Mean Charlson comorbidity index (mean ± SD)		6.2 ± 2.3	6.0 ± 2.4	5.8 ± 2.4
Decontamination completed		78 (97.5%)	165 (98.2%)	227 (99,1%)
Multivisceral resection		17 (21.3%)	33 (19.6%)	34 (14.8%)

TABLE 2 | Outcome parameters for different diagnoses.

Dindo–Clavien classification	Gastric cancer *n* (%)	Sigmoid cancer *n* (%)	Rectal cancer *n* (%)	*p*-value χ^2
No complication	28 (35.0)	122 (72.6)	103 (45.0)	$p < 0.001$*
I	12 (15.0)	19 (11.3)	49 (21.4)	
II	21 (26.3)	7 (4.2)	32 (14.0)	
IIIa	7 (8.8)	2 (1.2)	7 (3.1)	
IIIb	8 (10.0)	14 (8.3)	27 (11.8)	
IVa	3 (3.8)	0	8 (3.5)	
IVb	0	1 (0.6)	2 (0.9)	
V/mortality	1 (1.3)	3 (1.8)	1 (0.4)	
Comprehensive complication index	17.06 ± 17.65	7.50 ± 17.42	14.06 ± 18.41	$p < 0.001$*
Stroke	0	1 (0.6)	1 (0.4)	$p = 0.793$
Myocardial infarction	1 (1.3)	2 (1.2)	1 (0.4)	$p = 0.729$
Infectious complication	10 (12.5)	19 (11.3)	36 (15.7)	$p = 0.426$
Anastomotic leakage	2 (2.5)	5 (3.0)	14 (6.1)	$p = 0.312$
Pneumonia	2 (2.5)	3 (1.8)	3 (1.3)	$p = 0.768$
SSI	5 (6.3)	16 (9.5)	25 (10.9)	$p = 0.635$
Type 1	4 (5.0)	11 (6.5)	13 (5.7)	
Type 2	0	4 (2.4)	8 (3.5)	
Type 3	1 (1.3%)	1 (0.6)	4 (1.7)	
Urinary tract infection	1 (1.3)	1 (0.6)	1 (0.4)	$p = 0.729$
In-hospital stay	27.6 ± 21.2	13.3 ± 10.4	17.6 ± 12.0	$p < 0.001$*

**Statistically significant (p-value < 0.05).*

in 41.3% ($n = 33$), only minor complications (Clavien–Dindo I–II) occurred.

For sigmoid cancer in 72.6% ($n = 122$), no complications occurred, whereas in 15.5% ($n = 26$), minor complications (Clavien–Dindo I–II) were reported. In 11.9% of cases ($n = 20$), major complications occurred (Clavien–Dindo IIIa–V). The mean CCI was 7.50 ± 17.42.

In rectal cancer, in 45.0% of cases ($n = 103$), no complication and in 35.4% minor complications ($n = 81$) were documented. In 19.7% ($n = 45$), major morbidity (Clavien–Dindo IIIa–V) occurred. The mean CCI was 14.06 ± 18.41. The distribution of complications according to the Clavien–Dindo classification was different between gastric, sigmoid, and rectal cancer (χ^2: $p < 0.001$) as well as between different surgical procedures (χ^2: $p < 0.001$).

TABLE 3 | Outcome parameters for the type of surgery.

Disease	Colorectal cancer (CRC)			Gastric cancer		*p* value χ^2
Type of surgery	Low anterior rectal resection (%)	Anterior rectal resection (%)	Sigmoid resection (%)	Total gastrectomy (%)	Partial gastrectomy (%)	
n	187	54	156	44	36	
Completeness of decontamination	185 (98.8)	54 (100)	153 (98.1)	43 (97.7)	35 (97.2)	$p < 0.001$*
Infectious complications	32 (17.1)	5 (9.3)	18 (11.5)	5 (11.4)	5 (13.9)	$p = 0.466$
AL	14 (7.5)	0	5 (3.2)	2 (4.5)	0	$p = 0.131$
SSI	22 (11.8)	4 (7.4%)	15 (9.6)	2 (4.5)	2 (5.6)	$p = 0.384$
I	11 (5.9)	2 (3.7)	11 (7.1)	2 (4.5)	2 (5.6)	
II	8 (4.3)	0	4 (2.6)	0	0	
III	3 (1.6)	2 (3.7)	0	0	1 (2.8%)	
Mortality	1 (0.5)	0	3 (1.9)	1 (2.3)	0	$p = 0.522$

**Statistically significant (p-value < 0.05).*

CCI was different between different diagnoses (KW: $p < 0.001$) and between the surgical procedures (KW: $p < 0.001$). Both stroke and myocardial infarction occurred only in three cases of CRC patients and in one patient suffering from gastric cancer.

Anastomotic Leakage

AL occurred in a total of $n = 21$ cases and was most frequent in rectal cancer surgery ($n = 14$; 6.1%). Regarding the procedure, AL occurred only in LAR ($n = 14$) and not in AR ($n = 0$) procedures. Another $n = 5$ cases occurred in sigmoid resections (3.0%) and $n = 2$ in surgery for gastric cancer (2.5%) (**Table 2**).

In patients with gastric carcinoma, there was one AL classified as grade B and C. In patients with sigmoid carcinoma, all cases of AL required surgical therapy (grade C). In patients with rectal cancer, AL was classified as grade A ($n = 2$; 1.9%), grade B ($n = 4$; 1.7%), and grade C ($n = 8$; 3.5%), requiring surgical treatment. The mean time (range) to the diagnosis of AL was 17 days (13–20) in gastric cancer, 7.6 days (5–10) in sigmoid cancer, and 8.6 days (1–15) in patients with rectal cancer surgery.

There was no significant difference in rates of AL between groups regarding the type of surgical procedure (LAR, AR, sigmoid resection, total gastrectomy, subtotal gastrectomy; χ^2: $p = 0.064$). Also, multivisceral resection was not associated with increased rates of AL (Fisher: $p = 0.252$). There was no difference in rates of AL in open vs. MIC surgery (Fisher: $p = 0.404$), and rates of AL were not higher if conversion to open surgery was necessary (Fisher: $p = 0.835$). AL significantly prolonged the in-hospital stay (MW: $p < 0.001$).

Patients with AL had a significantly higher Charlson comorbidity index (MW: $p = 0.048$) across all diagnoses. Age did not significantly differ between patients with and without AL (MW: $p = 0.258$).

Infectious Complications

Overall, none of the diagnoses (rectal, sigmoid, or gastric carcinoma) showed an increased rate of infectious complications in general compared to the others (χ^2: $p = 0.426$). However, there was a nonsignificant trend toward fewer infectious complications with minimally invasive surgery (χ^2: $p = 0.071$). In the case of conversion to open surgery, infectious complications did not occur more frequently (Fisher: $p = 0.425$).

Patients with infectious complications showed a significantly higher Charlson comorbidity index than patients without infectious complications (MW: $p = 0.010$). These patients were significantly older than patients without infectious complications (MW: $p = 0.049$). As expected, hospital stay was significantly prolonged in patients with infectious complications (MW: $p < 0.001$).

Surgical Site Infection

SSIs occurred in 6.3% of cases in gastrectomies. SSI grade I–III was reported in 9.5% of cases for sigmoid cancer surgery ($n = 16$) and in 10.9% of cases ($n = 25$) for rectal cancer surgery (**Table 2**).

SSIs were distributed equally between groups of gastric, sigmoid, and rectal cancer surgery (χ^2: $p = 0.635$). Even for the different types of surgical procedures, the rates of SSI were not different (χ^2: $p = 0.384$). The in-hospital stay of patients suffering from SSI was significantly longer (30.5 ± 15.3 days vs. 16.1 ± 13.4 days; MW: $p < 0.001$). The Charlson comorbidity index was significantly higher in patients with SSI (6.7 ± 2.8 vs. 5.8 ± 2.3; MW: $p = 0.042$).

There was no significant difference in rates of SSI for the use of minimally invasive surgery (χ^2: $p = 0.187$), conversion to open surgery (χ^2: $p = 0.478$), or multi-visceral resection (χ^2: $p = 0.234$). There was no difference in the distribution of SSI in different UICC stages (χ^2: $p = 0.335$). Completed decontamination had no significant impact on the rate of SSI (χ^2: $p = 0.767$).

Mortality

In gastric cancer cohort, there was a mortality rate of 1.3% ($n = 1$), 1.8% ($n = 3$) in sigmoid cancer and 0.4% ($n = 1$) rectal cancer surgery. Overall, the distribution of mortality was equal between

gastric, sigmoid, and rectal cancer (χ^2: $p = 0.419$). Patients who eventually died had a significantly higher age (79.6 ± 8.7 vs. 68.34 ± 10.8 years; MW: $p = 0.028$) and Charlson comorbidity index (9.2 ± 1.3 vs. 5.87 ± 2.4; MW: $p = 0.003$) than patients without in-hospital mortality. Patients who died had a significantly longer in-hospital stay than those who survived (24.2 ± 4.0 vs. 17.7 ± 14.4 days; MW: $p = 0.022$). Mortality rates were not different between MIC and open surgery (Fisher: $p = 0.647$) or if conversion to open surgery was necessary (Fisher: $p = 0.959$). In cases of multivisceral resections, mortality was not increased (Fisher: $p = 0.214$). The distribution of mortality was not different for UICC stages (χ^2: $p = 0.836$). Complete decontamination did not have a significant impact on mortality rates (χ^2: $p = 0.926$).

In the gastric cancer cohort, there was one patient who died due to AL-related septic complications. In patients with sigmoid cancer, one patient with AL and wound healing disorder developed a status epilepticus and died from septic complications and another patient died due to septic complications following grade II SSI with progressive multiorgan failure and pneumonia after aspiration, respectively. One patient developed a rapid cancer progression and associated pulmonary complications and died from respiratory insufficiency. In rectal cancer surgery, only one patient died from AL-related septic complications. This patient refused the necessary surgical therapy for AL.

Analysis for Risk Factors in Univariate Analysis

In univariate analysis, the Charlson comorbidity index and multivisceral resection had a significant impact on the incidence of infectious complications, SSI, and AL. Additionally, the UICC stage had a significant impact on infectious complications in general only. However, diagnosis, use of MIC surgery, and completeness of decontamination had no effect on the occurrence of infectious complications, SSI, and AL. The univariate analysis revealed no significant risk factors for mortality (**Table 4**).

TABLE 4 | Univariate analysis for infectious complications, anastomotic leakage, SSI, and mortality (p values < 0.05 are marked with an *).

		Df	Mean of squares	F	Sig.
Infectious complications ($R^2 = 0.044$; $p < 0.001$*)	Charlson comorbidity index	1	1.431	12.592	$p < 0.001$*
	UICC stage	1	0.689	6.060	$p = 0.014$*
	Multivisceral resection	1	0.567	4.988	$p = 0.026$*
	Completeness of decontamination	1	0.061	0.539	$p = 0.463$
	Diagnosis	1	0.249	2.193	$p = 0.139$
	MIC	1	0.293	2.575	$p = 0.109$
Anastomotic leakage ($R^2 = 0.246$; $p = 0.001$*)	Charlson comorbidity index	1	4.708	146.133	$p < 0.001$*
	UICC stage	1	0.025	0.765	$p = 0.382$
	Multivisceral resection	1	0.167	5.186	$p = 0.023$*
	Completeness of decontamination	1	0.058	1.806	$p = 0.180$
	Diagnosis	1	0.062	1.933	$p = 0.165$
	MIC	1	0.109	3.392	$p = 0.066$
Surgical site infections ($R^2 = 0.044$; $p = 0.025$*)	Charlson comorbidity index	1	0.968	3.918	$p = 0.048$*
	UICC stage	1	0.917	3.711	$p = 0.055$
	Multivisceral resection	1	1.198	4.851	$p = 0.028$*
	Completeness of decontamination	1	0.038	0.153	$p = 0.696$
	Diagnosis	1	0.785	3.176	$p = 0.075$
	MIC	1	0.438	1.772	$p = 0.184$
Mortality ($R^2 = 0.023$; $p = 0.091$)	Charlson comorbidity index	1	0.059	5.746	$p = 0.017$*
	UICC stage	1	0.003	0.306	$p = 0.580$
	Multivisceral resection	1	0.004	0.360	$p = 0.549$
	Completeness of decontamination	1	<0.001	0.017	$p = 0.896$
	Diagnosis	1	0.006	0.556	$p = 0.456$
	MIC	1	<0.001	0.007	$p = 0.933$

Statistically significant (p-value < 0.05).

Diagnosis of Infectious Complications and Anastomotic Leakage Based on CRP Values

Whereas the white blood cell count was not significantly different between patients with and without infectious complications or AL, the course of CRP values differed significantly (**Figures 1A,B**). ROC analysis showed that CRP values on days 4 and 5 discriminate not as good for diagnosis of infectious complications (AUC 0.739 and 0.737; **Figure 2A**) as for diagnosis of AL (AUC 0.826 and 0.830; **Figure 2B**) on days 4 and 5, respectively.

Adverse Events Related to the SDD Regimen

Overall, in $n = 2$ patients with gastric cancer and $n = 3$ patients with sigmoid cancer, the SDD regimen was not completed due to nausea and possible intolerance, whereas in rectal cancer surgery in $n = 2$ cases, the catheter at the anastomotic site was dislocated or removed accidentally so that the SDD regimen could not be continued. Other side effects such as allergic reactions or intolerance did not occur.

Only in rectal cancer surgery there was one patient with clostridium difficile-associated diarrhea.

DISCUSSION

The routine clinical use of antibiotic decontamination in 477 patients with gastric, sigmoid, and rectal cancer surgery seems to be not only feasible but also successful with regard to the overall low rates of SSI, AL, and mortality. Certainly, the rates for AL and SSIs were higher in colorectal compared to gastric cancer surgery.

Although this is a retrospective study lacking a control group, the complication rates compare well with results achieved in double-blind RCTs for gastric (28) and rectal cancer surgery

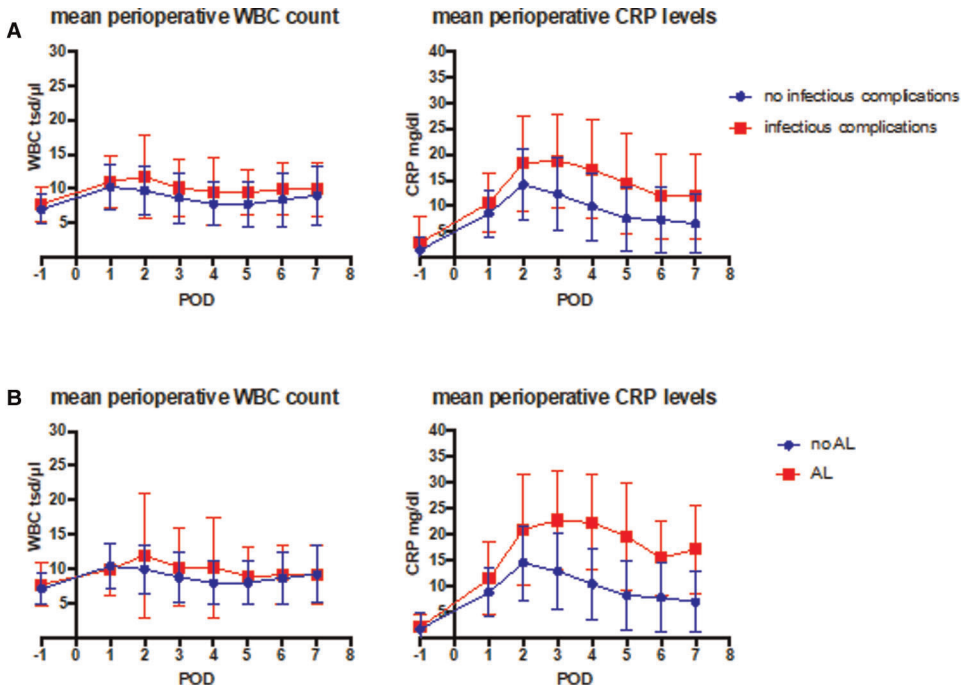

FIGURE 1 | Laboratory values such as white blood cell count (WBC) and C-reactive protein (CRP) were assessed perioperatively from the day before surgery until the 7th postoperative day. (**A**) Comparison of the course of parameters between patients with (red) and without (blue) infectious complications. (**B**) Comparison of the course of the parameters between patients with (red) and without (blue) AL.

with the use of this SDD/PTVA regimen (30). Mortality rates were low and major complications were more frequent in gastric and rectal compared to sigmoid cancer patients. Patients with SSI, AL, and infectious complications in general and mortality had a significantly higher Charlson comorbidity index compared to patients without infectious complications. Hospital stay was significantly prolonged in these patients. Nearly all patients completed the perioperative antibiotic decontamination regimen, and no adverse events could be detected.

Data on Gastric Cancer Surgery

In a recent review, AL of esophagointestinal anastomosis was reported with an incidence between 2.1% and 14.6% and associated mortality of up to 50% (48). Yoo et al. reported AL in 6.7% following curative resection of gastric cancer. Poor performance status and tumor localization were risk factors for leakage in the latter study (17). In our data, the Charlson comorbidity index was higher for patients with gastric cancer compared to CRC patients. Nonetheless, rates for infectious complications in our gastric cancer patients were low by any standard. In our patients, leaks occurred late in the postoperative course, which may be an effect of decontamination. In our experience, late leaks are less dangerous compared to leaks in the early postoperative course. Overall, only scarce data are available about the use of perioperative antibiotic decontamination in gastric cancer surgery. Scheufele et al. recently conducted a systematic review and meta-analysis of the current evidence for the role of SDD in RCTs of upper gastrointestinal tract surgery reporting a significant reduction in AL and postoperative pneumonia after total gastrectomy and esophagectomy using SDD regimens. These data support the routine use of the SDD regimen in gastrointestinal surgery (16).

Data on Colorectal Cancer Surgery

The complication rates for sigmoid and rectal cancer surgery were much higher than our previously reported data on surgery for diverticulitis using the same SDD regimen (40). For rectal cancer surgery, reliable data about outcome measures without the use of antibiotic bowel decontamination are available from a large German cohort with rates for AL of 11.9% and overall in-hospital mortality of 2.1% (13).

Roos et al., based on their data of a systematic review, stated that a combination of perioperative SDD and perioperative intravenous antibiotic prophylaxis in elective gastrointestinal surgery reduces the rate of postoperative infections, including AL, compared with the use of intravenous antibiotics alone (5). These results have been confirmed by Abis et al., who analyzed the use of SDD in esophageal, gastric, and colorectal surgeries (49).

Results from recently published RCTs and meta-analyses report contrary outcomes of combined bowel preparation. The SELECT trial using a perioperative SDD regimen demonstrated a significant reduction of SSI but not AL (9). The MOBILE trial adding neomycin and metronidazole to mechanical bowel preparation preoperatively only failed to show a relevant difference in SSI or AL between the treatment

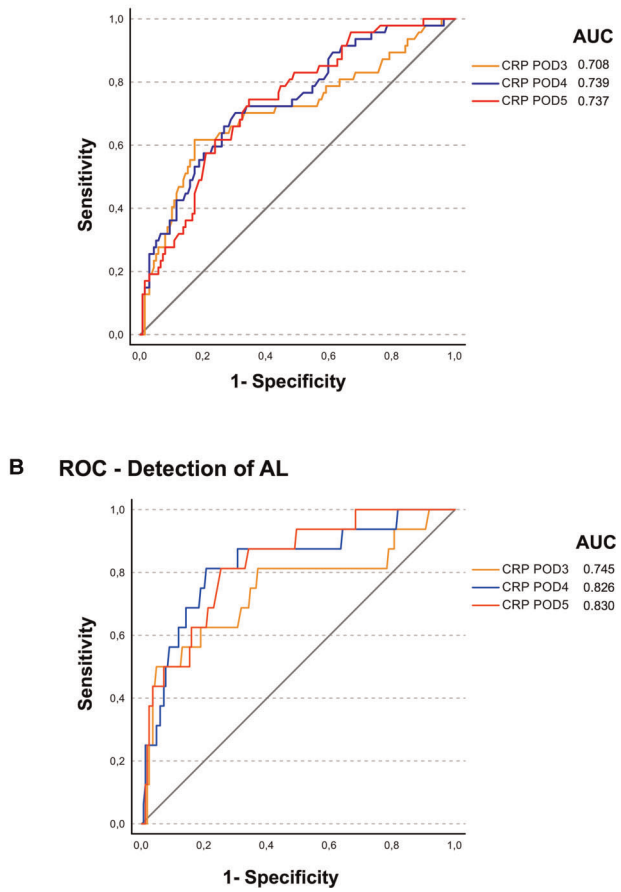

FIGURE 2 | ROC analysis was perfomed for the postoperative CRP levels from postoperative days (POD) 3, 4, and 5 for (**A**) diagnosis of infectious complications and (**B**) diagnosis of AL with the area under curve (AUC) given in the figures.

and control groups (36). However, both trials included only a limited number of left-sided colonic and rectal resections. A meta-analysis recently published by Rollins et al. demonstrated a reduction in SSIs and AL mostly based on the included registry data. The meta-analysis of the RCTs alone did not show a relevant reduction of AL (38).

The available data lack consistency as different types of antibiotic regimens and durations of application are used as well as different types of surgical procedures are included (4, 9, 30, 36, 38, 49). Compared to the available RCTs and other data on the use of a perioperative SDD regimen in combination with mechanical bowel preparation, our analysis shows similar results regarding rates of infectious complication, SSI, and AL, despite the fact that most of these studies excluded UICC stage IV patients, whereas about 18% of UICC stage IV cases are included in our analysis (4, 5, 9, 30, 49). In summary, the relevant data on the use of the perioperative SDD regimen in colorectal surgery support the strategy of topical antibiotics in a reasoned combination (4, 9, 30, 39, 40).

Effect of SDD on Multidrug Resistant Germs and Possible Side Effects

We are aware that there are increasing numbers of vancomycin-resistant Enterococci species (50), but published data on routine use of topical antibiotics like SDD in intensive care units show even a decrease in colonization of Enterococci species (51). Furthermore, there are reliable data on oral vancomycin, as it is widely used in Clostridioides difficile infections. Few antibiotic resistances to vancomycin occurred over time, with a treatment duration of 10 days or even longer (52–54). However, recent experimental data demonstrated a significant role of Enterococci species in the pathogenesis of AL (25, 55). Schardey et al. modified the SDD regimen for antibiotic decontamination by adding vancomycin to the usual SDD regimen. This modified SDD regimen seems to be much more efficacious as it covers a much larger spectrum of potentially pathogenic germs, most of them even twice, including Enterococci species, while these are not sufficiently covered by a conventional SDD regimen (24, 28, 30). On the other hand, the widespread use of antibiotics is a major concern regarding the development of antimicrobial resistance. Presently, the beneficial effect of topical antibiotics in the prevention of AL, in our opinion, outweighs the possible adverse side effects. In over 20 years of the use of these modified SDD regimens in gastrectomy and colorectal surgery, no adverse events regarding multidrug-resistant germs or other relevant side effects have been observed (30, 39, 40).

Risk Factors for Anastomotic Leakage and Other Infectious Complications

In our data, we could detect some risk factors in univariate analysis like the Charlson comorbidity index and multivisceral resections for AL, SSI, and infectious complications in general. Other data already demonstrated male sex, obesity, neoadjuvant (radio)chemotherapy, an impaired preoperative physical and nutritional state or ASA ≥ 3 patients, smoking, UICC stage, and operative factors like level of anastomosis, surgeon volume, and not creating a diverting stoma in low anterior rectal resections as risk factors for AL (12, 13, 56). In our data, due to a limited number of events, no reliable analysis of risk factors for anastomotic leakage and other infectious complications despite the results of the univariate analysis has been possible.

Furthermore, our analysis shows that CRP levels on postoperative days 4 and 5, to some extent, seem to be predictive for AL and less for infectious complications in general in ROC analysis (**Figures 1**, **2**). One can only speculate that due to less nonspecific infectious complications, CRP course on postoperative day 4/5 seems to be a more sensitive marker for the occurrence of AL. In a meta-analysis, Paradis et al. also investigated the diagnostic characteristics of CRP levels between postoperative days 3–5 (8). Overall, elevated CRP levels do not prove AL, but especially further increasing CRP levels are reliable markers for potential alterations of routine postoperative course and may result in further diagnostics (8).

Limitations

Due to the retrospective character, this study has several limitations. All patients were operated on over a period of 20 years in the same academic teaching hospital, which nonetheless is a low-volume community hospital, not expected to reach excellence. Also, due to technical improvements over time, more and more minimal invasive and robotic procedures have been performed (9, 57, 58) and neoadjuvant treatment concepts have been introduced into clinical practice (59–61). Over this time period, there have been major improvements in the perioperative management using "enhanced recovery after surgery" concepts (62, 63). Thus, we can only report on the surgical outcomes. In contrast to these expectations, the complication rates especially regarding SSI, AL, and mortality in this retrospective analysis of routine use of antibiotic decontamination in gastrointestinal surgery compare very well with the results of cancer surgery in currently published studies, reviews, and meta-analyses (4, 5, 9, 28, 30, 49).

Furthermore, one must assume that minor complications (Dindo–Clavien grade I–II) may be rather underrepresented. However, major complications with the need for interventional or surgical reintervention (Clavien–Dindo IIIa–V) are very well documented. Our data are heterogeneous as we report all cases using a perioperative antibiotic decontamination regimen representing high-risk anastomosis in gastric, sigmoid, and rectal cancer surgery. Our data lack a control group because in our center nearly all patients are on treatment using the SDD or modified SDD regimen. However, otherwise, a lot of outcome data and some comparable outcome data using similar SDD regimens are available in the literature for comparison (4, 5, 9, 13, 16, 17, 48, 49).

CONCLUSION

The concept of perioperative antibiotic bowel decontamination in gastrointestinal surgery based on the use of a (modified) SDD regimen may be able to improve patient safety and surgical outcome in gastrointestinal oncologic surgery in a routine clinical setting. Based on new experimental data, agents other than antibiotics, such as polyphosphates or protease inhibitors, may be an alternative in the future but have not yet been introduced into clinical practice (64, 65).

CONTRIBUTIONS TO THE FIELD STATEMENT

Antibiotic bowel decontamination and SDD are still not widely used concepts in gastrointestinal surgery, despite the existing evidence not only from registry data but also from the different available RCTs. The impact of bacterial factors on surgical site infections and especially anastomotic leakage is proven, but rates of surgical site infections and anastomotic leakage remain stable over the past years.

In our center, we have 20 years' experience in the use of antibiotic bowel decontamination. Overall, in the here-presented large cohort, we have low rates for surgery-related major morbidity and mortality. Compared to available international data, we have low rates of AL and surgery-related mortality. No relevant side effects of SDD regimens occurred.

Therefore, the use of the SDD regimen seems to improve patient safety and surgical outcome in gastrointestinal oncologic surgery in a routine clinical setting, but further evidence from RCTs is still necessary.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission Medizinische Fakultät LMU München. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JS: conceptualization, methodology, data extraction and analysis, and writing the original draft. TA: methodology, data extraction and curation, and critical revision. ES: data extraction and curation and critical revision. AK: methodology, data extraction and curation, and critical revision. PZ: methodology, data curation, and critical revision. FK: methodology, project administration, and critical revision. JA: methodology, data curation, and critical revision. JW: conceptualization, methodology, supervision, and critical revision. HA: conceptualization, methodology, project administration, and critical revision. UW: conceptualization, methodology, data extraction and analysis, writing original draft, and project administration. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Vazquez-Aragon P. Nosocomial infection and related risk factors in a general surgery service: a prospective study. *J Infect*. (2003) 46:17–22. doi: 10.1053/jinf.2002.1073
2. Li J, Zhang Y, Hu D-M, Gong T-P, Xu R, Gao J. Impact of postoperative complications on long-term outcomes of patients following surgery for gastric cancer: A systematic review and meta-analysis of 64 follow-up studies. *Asian J Surg*. (2020) 43:719–29. doi: 10.1016/j.asjsur.2019.10.007
3. Papenfuss WA, Kukar M, Oxenberg J, Attwood K, Nurkin S, Malhotra U, et al. Morbidity and mortality associated with gastrectomy for gastric cancer. *Ann Surg Oncol*. (2014) 21:3008–14. doi: 10.1245/s10434-014-3664-z
4. Roos D, Dijksman LM, Oudemans-van Straaten HM, de Wit LT, Gouma DJ, Gerhards MF. Randomized clinical trial of perioperative selective

decontamination of the digestive tract versus placebo in elective gastrointestinal surgery. *Br J Surg*. (2011) 98:1365–72. doi: 10.1002/bjs.7631
5. Roos D, Dijksman LM, Tijssen JG, Gouma DJ, Gerhards MF, Oudemans-van Straaten HM. Systematic review of perioperative selective decontamination of the digestive tract in elective gastrointestinal surgery: perioperative selective decontamination of the digestive tract. *Br J Surg*. (2013) 100:1579–88. doi: 10.1002/bjs.9254
6. Hammond J, Lim S, Wan Y, Gao X, Patkar A. The burden of gastrointestinal anastomotic leaks: an evaluation of clinical and economic outcomes. *J Gastrointest Surg*. (2014) 18:1176–85. doi: 10.1007/s11605-014-2506-4
7. Ghuman A, Kasteel N, Brown CJ, Karimuddin AA, Raval MJ, Wexner SD, et al. Surgical site infection in elective colonic and rectal resections: effect of oral antibiotics and mechanical bowel preparation compared with mechanical bowel preparation only. *Colorectal Dis*. (2020) 22:1686–93. doi: 10.1111/codi.15153
8. Paradis T, Zorigtbaatar A, Trepanier M, Fiore JF, Fried GM, Feldman LS, et al. Meta-analysis of the diagnostic accuracy of C-reactive protein for infectious complications in laparoscopic versus open colorectal surgery. *J Gastrointest Surg*. (2020) 24:1392–401. doi: 10.1007/s11605-020-04599-2
9. Abis GSA, Stockmann HBAC, Bonjer HJ, van Veenendaal N, van Doorn-Schepens MLM, Budding AE, et al. Randomized clinical trial of selective decontamination of the digestive tract in elective colorectal cancer surgery (SELECT trial): selective decontamination of the digestive tract in colorectal cancer surgery. *Br J Surg*. (2019) 106:355–63. doi: 10.1002/bjs.11117
10. Shogan BD, Carlisle EM, Alverdy JC, Umanskiy K. Do we really know why colorectal anastomoses leak? *J Gastrointest Surg*. (2013) 17:1698–707. doi: 10.1007/s11605-013-2227-0
11. Paun BC, Cassie S, MacLean AR, Dixon E, Buie WD. Postoperative complications following surgery for rectal cancer. *Ann Surg*. (2010) 251:807–18. doi: 10.1097/SLA.0b013e3181dae4ed
12. Matthiessen P, Hallböök O, Rutegard J, Simert G, Sjödahl R. Defunctioning ctoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. *Ann Surg*. (2007) 246:207–14. doi: 10.1097/SLA.0b013e3180603024
13. Jannasch O, Klinge T, Otto R, Chiapponi C, Udelnow A, Lippert H, et al. Risk factors, short and long term outcome of anastomotic leaks in rectal cancer. *Oncotarget*. (2015) 6:36884–93. doi: 10.18632/oncotarget.5170
14. Haga Y, Wada Y, Takeuchi H, Ikejiri K, Ikenaga M. Prediction of anastomotic leak and its prognosis in digestive surgery. *World J Surg*. (2011) 35:716–22. doi: 10.1007/s00268-010-0922-5
15. Inokuchi M. Systematic review of anastomotic complications of esophagojejunostomy after laparoscopic total gastrectomy. *WJG*. (2015) 21:9656. doi: 10.3748/wjg.v21.i32.9656
16. Scheufele F, Schirren R, Friess H, Reim D. Selective decontamination of the digestive tract in upper gastrointestinal surgery: systematic review with meta-analysis of randomized clinical trials. *BJS Open*. (2020) 4:bjs5.50332. doi: 10.1002/bjs5.50332
17. Yoo HM, Lee HH, Shim JH, Jeon HM, Park CH, Song KY. Negative impact of leakage on survival of patients undergoing curative resection for advanced gastric cancer: leakage and survival after gastrectomy. *J Surg Oncol*. (2011) 104:734–40. doi: 10.1002/jso.22045
18. Andreou A, Biebl M, Dadras M, Struecker B, Sauer IM, Thuss-Patience PC, et al. Anastomotic leak predicts diminished long-term survival after resection for gastric and esophageal cancer. *Surgery*. (2016) 160:191–203. doi: 10.1016/j.surg.2016.02.020
19. Boccola MA, Buettner PG, Rozen WM, Siu SK, Stevenson ARL, Stitz R, et al. Risk factors and outcomes for anastomotic leakage in colorectal surgery: a single-institution analysis of 1576 patients. *World J Surg*. (2011) 35:186–95. doi: 10.1007/s00268-010-0831-7
20. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. *Ann Surg*. (2011) 253:890–9. doi: 10.1097/SLA.0b013e3182128929
21. Lu ZR, Rajendran N, Lynch AC, Heriot AG, Warrier SK. Anastomotic leaks after restorative resections for rectal cancer compromise cancer outcomes and survival. *Dis Colon Rectum*. (2016) 59:236–44. doi: 10.1097/DCR.0000000000000554
22. Scheufele F, Aichinger L, Jäger C, Demir IE, Schorn S, Sargut M, et al. Effect of preoperative biliary drainage on bacterial flora in bile of patients with periampullary cancer: influence of preoperative biliary drainage on the biliary microbiome. *Br J Surg*. (2017) 104:e182–8. doi: 10.1002/bjs.10450
23. Alverdy JC, Hyoju SK, Weigerinck M, Gilbert JA. The gut microbiome and the mechanism of surgical infection: the gut microbiome and the mechanism of surgical infection. *Br J Surg*. (2017) 104:e14–e23. doi: 10.1002/bjs.10405
24. Schardey HM, Kamps T, Rau HG, Gatermann S, Baretton G, Schildberg FW. Bacteria: a major pathogenic factor for anastomotic insufficiency. *Antimicrob Agents Chemother*. (1994) 38:2564–7. doi: 10.1128/AAC.38.11.2564
25. Shogan BD, Belogortseva N, Luong PM, Zaborin A, Lax S, Bethel C, et al. Collagen degradation and MMP9 activation by *Enterococcus faecalis* contribute to intestinal anastomotic leak. *Sci Transl Med*. (2015) 7:286ra68. doi: 10.1126/scitranslmed.3010658
26. Olivas AD, Shogan BD, Valuckaite V, Zaborin A, Belogortseva N, Musch M, et al. Intestinal tissues induce an SNP mutation in *Pseudomonas aeruginosa* that enhances its virulence: possible role in anastomotic leak. *PLoS ONE*. (2012) 7:e44326. doi: 10.1371/journal.pone.0044326
27. Stoutenbeek CP, van Saene HKF, Miranda DR, Zandstra DF. The effect of selective decontamination of the digestive tract on colonisat ion and infection rate in multiple trauma patients. *Intensive Care Med*. (1984) 10:185–92. doi: 10.1007/BF00259435
28. Schardey HM, Joosten U, Finke U, Staubach KH, Schauer R, Heiss A, et al. The prevention of anastomotic leakage after total gastrectomy with local decontamination: a prospective, randomized, double-blind, placebo-controlled multicenter trial. *Ann Surg*. (1997) 225:172–80. doi: 10.1097/00000658-199702000-00005
29. Schardey HM, Joosten U, Finke U, Schauer R, Staubach KH, Exner H, et al. Cost reduction by decontamination to prevent anastomotic leakage following total gastrectomy. *Chirurg*. (1997) 68:416–24. doi: 10.1007/s001040050207
30. Schardey HM, Wirth U, Strauss T, Kasparek MS, Schneider D, Jauch KW. Prevention of anastomotic leak in rectal cancer surgery with local antibiotic decontamination: a prospective, randomized, double-blind, placebo-controlled single center trial. *Int J Colorect Dis*. (2020) 35:847–57. doi: 10.1007/s00384-020-03544-8
31. Devane LA, Proud D, O'Connell PR, Panis Y. A European survey of bowel preparation in colorectal surgery. *Colorectal Dis*. (2017) 19:O402–6. doi: 10.1111/codi.13905
32. McChesney SL, Zelhart MD, Green RL, Nichols RL. Current U.S. preoperative bowel preparation trends: a 2018 survey of the American Society of Colon and Rectal Surgeons Members. *Surg Infect*. (2020) 21:1–8. doi: 10.1089/sur.2019.125
33. Buia A, Post S, Buhr HJ, Hanisch E. Darmvorbereitung bei elektiven kolorektalen Resektionen in Deutschland 2017: Ergebnisse einer Umfrage unter den Mitgliedern der DGAV. *Chirurg*. (2019) 90:564–9. doi: 10.1007/s00104-018-0773-4
34. Cannon JA, Altom LK, Deierhoi RJ, Morris M, Richman JS, Vick CC, et al. Preoperative oral antibiotics reduce surgical site infection following elective colorectal resections. *Dis Colon Rectum*. (2012) 55:1160–6. doi: 10.1097/DCR.0b013e3182684fac
35. Scarborough JE, Mantyh CR, Sun Z, Migaly J. Combined mechanical and oral antibiotic bowel preparation reduces incisional surgical site infection and anastomotic leak rates after elective colorectal resection: an analysis of colectomy-targeted ACS NSQIP. *Ann Surg*. (2015) 262:331–7. doi: 10.1097/SLA.0000000000001041
36. Koskenvuo L, Lehtonen T, Koskensalo S, Rasilainen S, Klintrup K, Ehrlich A, et al. Mechanical and oral antibiotic bowel preparation versus no bowel preparation for elective colectomy (MOBILE): a multicentre, randomised, parallel, single-blinded trial. *Lancet*. (2019) 394:840–8. doi: 10.1016/S0140-6736(19)31269-3
37. Bretagnol F, Panis Y, Rullier E, Rouanet P, Berdah S, Dousset B, et al. Rectal cancer surgery with or without bowel preparation: the French GRECCAR III multicenter single-blinded randomized trial. *Ann Surg*. (2010) 252:863–8. doi: 10.1097/SLA.0b013e3181fd8ea9
38. Rollins KE, Javanmard-Emamghissi H, Acheson AG, Lobo DN. The role of oral antibiotic preparation in elective colorectal surgery: a meta-analysis. *Ann Surg*. (2019) 270:43–58. doi: 10.1097/SLA.0000000000003145
39. Wirth U, Rogers S, Haubensak K, Schopf S, von Ahnen T, Schardey HM. Local antibiotic decontamination to prevent anastomotic leakage short-

term outcome in rectal cancer surgery. *Int J Colorect Dis*. (2018) 33:53–60. doi: 10.1007/s00384-017-2933-2
40. Wirth U, Schardey J, von Ahnen T, Zimmermann P, Kühn F, Werner J, et al. Oral antibiotic bowel decontamination in open and laparoscopic sigmoid resections for diverticular disease. *Int J Colorectal Dis*. (2021) 36:1667–76. doi: 10.1007/s00384-021-03890-1
41. Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari L. Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. *Ann Surg*. (1999) 230:170. doi: 10.1097/00000658-199908000-00006
42. Moehler M, Al-Batran S-E, Andus T, Anthuber M, Arends J, Arnold D, et al. S3-Leitlinie "Magenkarzinom". *Z Gastroenterol*. (2011) 49:461–531. doi: 10.1055/s-0031-1273201
43. Ravichandran D, Carty N, Lamah M, Johnson C. Extended lymph node dissection (D2 resection) should now be performed routinely in the curative surgical treatment of gastric carcinoma. *Ann R Coll Surg Eng*. (1995) 77:431–6. PMID: 8540662; PMCID: PMC2502460
44. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol*. (1994) 47:1245–51. doi: 10.1016/0895-4356(94)90129-5
45. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. (2004) 240:205–13. doi: 10.1097/01.sla.0000133083.54934.ae
46. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien P-A. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Ann Surg*. (2013) 258:1–7. doi: 10.1097/SLA.0b013e318296c732
47. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the international study group of rectal cancer. *Surgery*. (2010) 147:339–51. doi: 10.1016/j.surg.2009.10.012
48. Makuuchi R, Irino T, Tanizawa Y, Bando E, Kawamura T, Terashima M. Esophagojejunal anastomotic leakage following gastrectomy for gastric cancer. *Surg Today*. (2019) 49:187–96. doi: 10.1007/s00595-018-1726-8
49. Abis GSA, Stockmann HBAC, van Egmond M, Bonjer HJ, Vandenbroucke-Grauls CMJE, Oosterling SJ. Selective decontamination of the digestive tract in gastrointestinal surgery: useful in infection prevention? a systematic review. *J Gastrointest Surg*. (2013) 17:2172–8. doi: 10.1007/s11605-013-2379-y
50. Markwart R, Willrich N, Haller S, Noll I, Koppe U, Werner G, et al. The rise in vancomycin-resistant *Enterococcus faecium* in Germany: data from the German Antimicrobial Resistance Surveillance (ARS). *Antimicrob Resist Infect Control*. (2019) 8:147 (eCollection). doi: 10.1186/s13756-019-0594-3
51. van der Bij AK, Frentz D, Bonten MJM. Gram-positive cocci in Dutch ICUs with and without selective decontamination of the oropharyngeal and digestive tract: a retrospective database analysis. *J Antimicrob Chemother*. (2016) 71:816–20. doi: 10.1093/jac/dkv396
52. Gonzales M, Pepin J, Frost EH, Carrier JC, Sirard S, Fortier LC, et al. Faecal pharmacokinetics of orally administered vancomycin in patients with suspected *Clostridium difficile* infection. *BMC Infect Dis*. (2010) 10:363. doi: 10.1186/1471-2334-10-363
53. van Prehn J, Reigadas E, Vogelzang EH, Bouza E, Hristea A, Guery B, et al. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for *Clostridioides difficile* infection in adults. *Clin Microbiol Infect*. (2021) 27(Suppl 2):S1–S21. doi: 10.1016/j.cmi.2021.09.038
54. Eubank TA, Gonzales-Luna AJ, Hurdle JG, Garey KW. Genetic mechanisms of vancomycin resistance in *Clostridioides difficile*: a systematic review. *Antibiot (Basel)*. (2022) 11(258):258. doi: 10.3390/antibiotics11020258
55. Jacobson RA, Wienholts K, Williamson AJ, Gaines S, Hyoju S, van Goor H, et al. Enterococcus faecalis exploits the human fibrinolytic system to drive excess collagenolysis: implications in gut healing and identification of druggable targets. *Am J Physiol Gastrointest Liver Physiol*. (2020) 318:G1–G9. doi: 10.1152/ajpgi.00236.2019
56. Sciuto A, Merola G, Palma GDD, Sodo M, Pirozzi F, Bracale UM, et al. Predictive factors for anastomotic leakage after laparoscopic colorectal surgery. *WJG*. (2018) 24:2247–60. doi: 10.3748/wjg.v24.i21.2247
57. Andolfi C, Umanskiy K. Appraisal and current considerations of robotics in colon and rectal surgery. *J Laparoendosc Adv Surg Tech*. (2019) 29:152–8. doi: 10.1089/lap.2018.0571
58. Blackmore AE. Evolution of laparoscopy in colorectal surgery: an evidence-based review. *WJG*. (2014) 20:4926. doi: 10.3748/wjg.v20.i17.4926
59. Tokunaga M, Sato Y, Nakagawa M, Aburatani T, Matsuyama T, Nakajima Y, et al. Perioperative chemotherapy for locally advanced gastric cancer in Japan: current and future perspectives. *Surg Today*. (2020) 50:30–7. doi: 10.1007/s00595-019-01896-5
60. Petrelli F, Trevisan F, Cabiddu M, Sgroi G, Bruschieri L, Rausa E, et al. Total neoadjuvant therapy in rectal cancer: a systematic review and meta-analysis of treatment outcomes. *Ann Surg*. (2020) 271:440–8. doi: 10.1097/SLA.0000000000003471
61. Lagarde SM, Navidi M, Gisbertz SS, van Laarhoven HWM, Sumpter K, Meijer SL, et al. Prognostic impact of extracapsular lymph node involvement after neoadjuvant therapy and oesophagectomy. *Br J Surg*. (2016) 103:1658–64. doi: 10.1002/bjs.10226
62. Cavallaro P, Bordeianou L. Implementation of an ERAS pathway in colorectal surgery. *Clin Colon Rectal Surg*. (2019) 32:102–8. doi: 10.1055/s-0038-1676474
63. Wind J, Polle SW, Fung Kon Jin PHP, Dejong CHC, von Meyenfeldt MF, Ubbink DT, et al. Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg*. (2006) 93:800–9. doi: 10.1002/bjs.5384
64. Jacobson RA, Williamson AJ, Wienholts K, Gaines S, Hyoju S, van Goor H, et al. Prevention of anastomotic leak via local application of tranexamic acid to target bacterial-mediated plasminogen activation: a practical solution to a complex problem. *Ann Surg*. (2019) 274:e1038–e1046. doi: 10.1097/SLA.0000000000003733
65. Hyoju SK, Klabbers RE, Aaron M, Krezalek MA, Zaborin A, Wiegerinck M, et al. Oral polyphosphate suppresses bacterial collagenase production and prevents anastomotic leak due to *Serratia marcescens* and *Pseudomonas aeruginosa*. *Ann Surg*. (2018) 267:1112–8. doi: 10.1097/SLA.0000000000002167

Conflict of Interest: The author TvA is employed by Krankenhaus Agatharied GmbH, Hausham, Germany. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Surgery

REVIEW
published: 07 June 2022
doi: 10.3389/fsurg.2022.904810

Intestinal Anastomotic Healing: What do We Know About Processes Behind Anastomotic Complications

J. Rosendorf[1,2], M. Klicova[3], I. Herrmann[4], A. Anthis[4], L. Cervenkova[2], R. Palek[1,2], V. Treska[2] and V. Liska[1,2]*

[1]Department of Surgery, University Hospital in Pilsen, Pilsen, Czech Republic, [2]Laboratory of Cancer Treatment and Tissue Regeneration, Biomedical Center, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic, [3]Department of Nonwovens and Nanofibrous Materials, Faculty of Textile Engineering, Technical University of Liberec, Liberec, Czech Republic, [4]Department of Mechanical and Process Engineering, Nanoparticle Systems Engineering Laboratory, ETH Zurich, Switzerland

Colorectal surgery has developed rapidly in the recent decades. Nevertheless, colorectal anastomotic leakage continues to appear postoperatively in unpleasant rates and leads to life-threatening conditions. The development of valid complication-preventing methods is inefficient in many aspects as we are still lacking knowledge about the basics of the process of anastomotic wound healing in the gastrointestinal tract. Without the proper understanding of the crucial mechanisms, research for prevention of anastomotic leakage is predestined to be unsuccessful. This review article discusses known pathophysiological mechanisms together with the most lately found processes to be further studied. The aim of the article is to facilitate the orientation in the topic, support the better understanding of known mechanisms and suggest promising possibilities and directions for further research.

Keywords: colorectal anastomosis, anastomotic healing, intestinal healing, anastomotic leakage, wound healing

OPEN ACCESS

Edited by:
Hans Martin Schardey, Agatharied Hospital GmbH, Germany

Reviewed by:
Narimantas Samalavicius, Vilnius University, Lithuania
Cihangir Akyol, Ankara University, Turkey

****Correspondence:***
Jachym Rosendorf
jachymrosendorf@gmail.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *25 March 2022*
Accepted: *11 May 2022*
Published: *07 June 2022*

Citation:
Rosendorf J., Klicova M., Herrmann I., Anthis A., Cervenkova L., Palek R., Treska V. and Liska V. (2022) Intestinal Anastomotic Healing: What do We Know About Processes Behind Anastomotic Complications. Front. Surg. 9:904810. doi: 10.3389/fsurg.2022.904810

INTRODUCTION

Colorectal surgery has developed rapidly in the recent decades. Many new techniques have been introduced lately and the perioperative care keeps changing quite agilely (1–3). Milestones have been taken towards better oncological outcomes, minimally invasive procedures, and improved postoperative quality of life (QoL). Individualized care and the role of the patient's opinion on their treatment based on their good information and insight into the topic come to the fore. However, this article will discuss the unresolved issues in colorectal surgery, which raise questions not only in this specialization, but across gastrointestinal surgery in its full spectrum.

An essential part of gastrointestinal surgery is a construction of an anastomosis. The concept of resection and reconnection of the hollow parts of the tract is one of the cornerstones of visceral surgery and as such is not expected to be overcome or replaced by other treatment modalities in the foreseeable future.

Just as any other surgical procedure, this one has its specific complications as well. The dreaded anastomotic leak (AL), or dehiscence of the anastomosis, comes to mind first. It is a severe complication that requires a tailored approach depending on its severity. It poses a threat to the

patient's life in the early postoperative period, in many cases requires reoperation, and it is the cause of both longer hospitalizations and reduced postoperative QoL, altogether higher medical care expenses, and according to some studies even worse oncological results (4).

Anastomotic strictures or fistulae are other complications that can occur quite often (5). Strictures, in contrast to leaks, develop over a period of months, so patients are at risk of developing them after they have been placed in home care. In many cases, such stricture may be endoscopically affected, however, a large proportion of patients undergo eventually an additional surgery with resection of the stenotic section of the intestine and are thus again exposed to the risks of major surgical procedure (and risk of stoma for acute procedures) (5, 6). A relatively large number of experimental studies have been performed to find the optimal means to prevent these complications (7, 8). However, few will receive the transfer to clinical medicine.

This article aims to analyze current views on gastrointestinal anastomosis healing and its disorders, to develop the boundaries of these different approaches, the current state of knowledge and to outline areas for further research. The secondary intent of this work is also to draw attention to the fact that, however appealing it may appear to be, hopes for clinical success of current leak prevention research are modest.

LIMITATIONS OF CLINICAL PERSPECTIVE

The essence of the development of the complications mentioned above are disorders of the healing process. Because the healing process is very complex, the specific cause of the pathology can be located on a wide range of levels (9, 10).

Our current view on the prevention or eventual elimination of these complications relies on the identification of risk factors identified by the correlation of known information about patients with their postoperative course. Based on these data, patients are stratified according to the risk of these complications and appropriate precautions are performed on patients assessed as being at risk (11).

The problem is that we are only able to distinguish AL risk markers for standardly evaluated data. Very broad units such as the presence of immunosuppression, diabetes, old age or male sex thus become markers of high AL risk (**Table 1**) (11). Such large units in the planning of treatment modalities (Hartman's resection, protective ileostomies, etc.) are difficult to grasp. Stratification is inaccurate and only some patients benefit from it. We assume AL occurs from a combination of healing abnormalities based on several factors that negatively affect the whole healing process.

TABLE 1 | Modifiable and non-modifiable risk factors examples from clinical studies (11–13).

Modifiable	Non-modifiable
Smoking	Male gender
Obesity	Elderly patient
Malnutrition	Emergency procedure
Immunosuppressant treatment	Low anastomosis
Neoadjuvant radiotherapy	Locally advanced tumor
	Diabetes

At present, the process of skin wound healing, including some pathological conditions, is relatively well described (14). However, a similar depth of knowledge is on the digestive tract our utopia. The process is not well documented even in its physiological nature, and certainly the basis of individual pathophysiological deviations is well not researched either (10). Several important points emerge from this statement:

1. Although we know some, we do not know all the risk factors
2. The stratification of patients according to risk is therefore far from being perfect
3. We do not have the opportunity to effectively intervene in the healing process based on its knowledge
4. Applied research in the field of means to prevent anastomotic leakage is in many cases untargeted and ineffective

The degree of unexploredness of such a basic process is an unusual vacuum in scientific knowledge, and the knowledge of the human body.

LEAK MECHANISMS CURRENTLY IN FOCUS

Before we make the leap into the unexplored, we will introduce the following text with a short discussion about some known pathophysiological mechanisms:

Anastomotic Leakage and Blood Supply

Blood supply is a key basis not only for the healing process but also for maintaining the vitality of any tissue. Depending on the subtlety of the surgical technique and the condition of the patient's vascular anatomy and disease, the blood supply to the tissues may be compromised in the terrain of surgery. However, the presence of a sufficient blood supply is a generally valid condition not only to enable any healing process, but also to maintain tissue vitality in any other location. Lacking new information, the frequent research goal is to develop means both for perioperative evaluation of the quality of blood circulation and means to improve the regional blood supply to the anastomosed intestinal tissues. In the first of these, great progress has been made with the introduction of protocols involving the intravenous administration of indocyanine green (ICG) (15). Depending on the quality and speed of ICG distribution to the tissues of the anastomotic intestine, it is then possible to decide on a modification of the resection line. According to published works, individual protocols have the potential to reduce the incidence of anastomotic leakage by tens of percent (16). However, even such a refined technique has not contributed fully to elimination of this complication.

Anastomotic Leakage and Microbial Infection

Another specific aspect comes to light especially in colorectal surgery. The results of both experimental and some clinical works show the association of the anastomotic leak with infection or colonization of the patient by typical bacterial strains (17). The anastomotic leak caused by the dehiscence of the intestinal anastomosis is certainly an infectious complication, however, the medical society has generally not accepted (at least until recently) the thought that the anastomotic leak is a complication caused by the infection. According to published works, this infection is either a direct cause of leakage development or at least a significant contributor if it develops over an existing healing disorder (17). Pseudomonas Aeruginosa or Streptococcus Faecalis belong among those risk associated pathogens (18, 19). The mechanism of the anastomotic dehiscence lays in the bacterial ability of production of special enzymes consuming newly formed connective tissue of the forming scar – bacterial collagenases (17). These were however identified also in other bacterial strains. If we keep in mind that the basis of collagenase production are bacterial plasmids, which bacteria can share across strains, it may be practically impossible to identify all risky bacterial strains. The second way of negative bacterial influence on the connective tissues of the intestinal anastomosis is mediated by human collagenases, where the bacteria do not produce collagenase itself, but a human collagenase activator, which acts locally by breaking down collagen fibers in a similar way as bacterial collagenases. Bacterial activator of matrix metalloproteinase 9 can play such role (20). During the process of formation the collagen-rich extracellular matrix is degraded by these enzymes. This can lead to mechanical weakness of the anastomosis or even dehiscence (20).

EMERGING PATHOPHYSIOLOGICAL MECHANISMS, PROCESSES TO BE STUDIED FURTHER

As stated before, today's knowledge about intestinal anastomotic healing is limited (10). Wound healing is a process probably far more complex than we describe it by today's view. Many works rely on similarities between the cutaneous wound healing and anastomotic wound healing. This is despite the fact these are completely different organs, located in a completely different environment of the human body. These organs differ in their morphology, representation of individual cell types, blood supply, type of function, etc. While monitoring skin healing is less technically demanding both in the clinical environment as well as in the experiment, direct monitoring of intestinal anastomosis healing inside the abdomen is at least for now, practically impossible. In addition, the intestinal wall consists of several completely different layers, where we can say with certainty that the contribution of each of them to a successful healing process is different, while the essence of the proper function of one of the layers is not to adhere to anything (the mucosa). Pathology in the process of peritoneal healing can form extensive peritoneal adhesions, at the level of the muscular layer, pseudodiverticula may form, and if the process of healing of the intestinal mucosa is altered, fistulas may develop (21). On the other hand, the large intestine is able to heal despite contamination by common feculent flora, while essentially any contamination of a similar type leads to a purulent complication in the skin wound.

The small and the large intestines comprise many different cell types that are also specific for the location on the gastrointestinal tract. The current histological view recognizes in both the small and the large intestine four basic morphological layers: serosa, muscularis, submucosa and mucosa. However, these can be divided into even more units, and even these have their morphological variations depending on the level on the gastrointestinal tract. This situation is the reason why it is so complicated to describe the whole process, including its pathophysiological abnormalities, and why no one has yet been able to describe it in full scale (10).

It is practically impossible to create a comprehensive study monitoring all cell types and their metabolic changes in the healing process at once. Thus, although projects focusing on individual small aspects of the process, such as research into the effects of transient ischemia on peritoneal fibroblast metabolism, have received little attention and often little success in terms of financial support, they are the only means to push forward our current view on the issues of physiology and pathophysiology and the possibility of influencing the healing process in the digestive tract in a targeted matter.

Given the above lack of knowledge, we are not sure which cells, or which intestinal wall layers are the most important for the healing process, or if the interplay of individual layers in the whole process is essential.

The wound healing process is traditionally divided into several overlapping phases for the purpose of simplification: hemostasis, inflammation, proliferation, and remodeling phase (22) by the todays view. The initial three phases form together the acute period which is important for the possible development of anastomotic leakage. However, subtle disbalance can cause problems in the following period resulting in the healing pathologies as anastomotic strictures or fistulae formation.

We propose several issues appearing lately in the literature, that should be studied further for each intestinal layer to resolve some key questions about the healing process. These research topics are just the tip of the iceberg which is the yet to be discovered:

The Peritoneum

The peritoneum: The healing capacity of peritoneum is enormous (23). Most of the relevant known pathophysiological processes are described in studies focusing on the problematics of postoperative formation of extensive peritoneal adhesions, and not on the problematics of insufficient peritoneal healing. However, both processes start with peritoneal injury followed by inflammation.

A wide range of experimental models were created for the study of peritoneal adhesions, in which not only anti-adhesion

agents were systematically verified, but also the very nature of their formation: patient related factors, perioperative factors, influence of surgical techniques on morphology, amount and properties of adhesions (24). The role of molecular factors, cytokines, in the cellular metabolism of peritoneal cells is also being discussed relatively deeply.

Because peritoneal adhesions have been studied extensively, also the peritoneal injury process that precedes the formation of adhesions is well described. The injured surface starts producing a thin fluid which is rich in many proteins and signal molecules as well as inflammatory and other cells (25). This fluid coagulates within 3 h and thus it ensures stable contact of the two peritoneal surfaces. A process of fibrinolysis takes place at the same time and inhibits the formation of adhesion in normal peritoneal healing within the first 72 h after the injury (25). A prolonged persistence (3–5 days) of this coagulated mass is needed for fibroblasts to migrate in it and start producing the extracellular matrix and other substances. This new scaffold is afterwards occupied by mesothelial cells (26, 27). Healthy peritoneum has fibrinolytic activity (prevents obliteration of abdominal cavity in normal circumstances), which can be however decreased in different situations (hypoxia, injury, infection, etc.) leading to adhesion formation (28).

In the formation of peritoneal adhesions, a permanent transformation of peritoneal fibroblasts into so called adhesion fibroblasts was described. It is a change causing increase in proliferation and deposition of collagenous fiber rich extracellular matrix. A variety of signal molecules play their role in regulation of this process but the pathways leading to adhesions formation seem to have common triggers, which are ischemia, hypoxia, and hypercapnia etc. (26, 27, 29). The changes are described as permanent on the cellular level.

The biological role of the peritoneum appears to be relatively clear in the injury: with the highest priority, it is necessary to prevent perforation of the gastrointestinal tract into the free space of the abdominal cavity. Factors such as localized incomplete tissue hypoxia, hypercapnia, or other local markers of cell damage are thus triggers for the proliferation of peritoneum cells and the production of connective tissue to an intense extent, which seems to hastily prevent an acute threat. A long-term disadvantage of the process is that it is a probable cause of over-deposition of collagen-rich connective tissue, for example in the construction of gastrointestinal anastomosis, and thus contributes to stricture formation.

Dysregulation of these molecular factors has been described in the literature to be triggered by local ischemia: Tissue plasminogen activator (tPA), Transforming growth factor-β1 (TGF-β1), Tumor necrosis factor α (TNF-α), Interleukin 6 (IL-6), Matrix metalloproteinases (MMPs), Cyclo-oxygenases (COX) (30–38). However, the aim of this article is not to describe individual events that are relatively complex, so we recommend the cited literature for a deeper study.

The Muscular Layer

Isolated defects of muscular layer can be seen in imperfectly healed anastomoses as fistulae or can form a pseudodiverticula when the peritoneal surface maintains integrity. However, fistulas are more suspicious of being a mucosal healing imperfection. The hypertrophy of the muscular layer is not usually recognized in intestinal anastomoses but often in patients with chronic inflammatory bowel disease, where it is responsible for intestinal wall thickening and formation of strictures. A state of chronic inflammation with constant production of inflammatory signal molecules and infiltration by inflammatory cells causes a change of metabolism of smooth muscle cells (SMCs). The SMCs gain proliferative ability and start producing extracellular matrix (ECM) (39, 40). The role of ischemia on the SMCs was not described though, and the effect of inflammatory cytokines on SMCs in the process of anastomotic healing is unknown as well. This is certainly material for further basic research.

The Submucosa

The submucosa is the layer that is known to be the mechanically strongest. The fact that it contains a lot of collagen rich ECM makes most of clinicians suppose it is the most important layer for optimal anastomotic healing (41). Yet it is not known whether it really is activated in the process of anastomotic healing in sufficient amount to regain mechanical strength in time. And moreover, there is yet no proof suggesting that mechanical strength can be relied on in intestinal anastomosis and there is a probability that there is no link between anastomotic leakage risk and the mechanical strength. The metabolism of the submucosal tissue has not been studied thoroughly neither in normal circumstances nor after injury. Further basic research needs to be conducted urgently.

The Mucosa

Intestinal epithelial cells belong among the most rapidly proliferating cells in human body. In normal situation thousands of cells are scrubbed from the mucosal surface by food passage every day. Mature enterocytes however do not have any proliferative capacity and so the mucosal renewal depends on proliferation and differentiation of stem cells located in intestinal crypts. They are responsible for re-epithelization when it comes to anastomotic healing as the mature enterocytes cannot regain this ability. Epithelial mesenchymal transition is a healing associated cellular transformation responsible for de-differentiation of mature epithelial cells and for their regain of the proliferative activity. Newly formed epithelial cells keep covering denuded luminal surface, but do not adhere to epithelized surfaces (One of the basic biological assumptions is that the mucosa must not grow another mucosa surface to surface in order to avoid loss of intestinal lumina). It has been described that the process of superficial proliferation is probably responsible for fistulae formation in patients with anorectal inflammatory bowel disease (42–44), whether the process is behind fistulae formation in case of intestinal and bowel anastomosis is not confirmed, but the mechanisms could be similar. The epithelium is not considered to participate in formation of anastomotic strictures, but not enough research has been conducted to rule out even this assumption.

An interesting view that has not been sufficiently explored is also the importance of barrier function of the mucosa and its loss from intestinal injury, the process of its regeneration, the factors that affect it, and last but not least, how this loss affects the metabolism of the remaining gastrointestinal wall. The basis for the loss of this function is, among other mechanisms, a disorder of tight junctions between enterocytes. It occurs, for example, in septic conditions, where it is another probable contributor to the healing disorder (45). The barrier function suffers also during diarrheic diseases and can be altered also by aggressive laxatives that are used for mechanical bowel preoperative preparation (46).

DISCUSSION

At present, we have the advantage of the existence of advanced laboratory methods that allow us to observe both metabolic and proliferative changes of individual cells of the gastrointestinal wall, as well as their dynamics and mutual interaction. It is necessary to maximize the use of these auxiliary methods in combination with a clinically relevant experimental model of gastrointestinal healing, both in physiological conditions and to compare these processes with processes taking place in the presence of pathological changes, factors negatively affecting the healing process.

There are many unanswered questions in the process of gastrointestinal healing. Only a thorough research of partial processes, changes at the level of cellular metabolism, at the level of individual layers of the gastrointestinal tract wall, the dynamics of these processes and their interactions under both physiological and pathophysiological conditions can contribute to advances in clinical visceral surgery and other targeted prevention of anastomotic complications including leaks and stenoses. Even though new methods and techniques are emerging in colorectal surgery, the anastomotic leakage continues to haunt us. New technologies allow us to create new kinds of materials for both local or systemic treatment, but not knowing the physiological process and its pathological changes means not knowing what we treat.

AUTHOR CONTRIBUTIONS

Conceptualization: J.R., V.L., V.T.; methodology: I.H., L.C., writing original draft: J.R., M.K., formal analysis: V.L., A.A., R.P., V.T. All authors contributed to the article and approved the submitted version.

FUNDING

The research was funded by the project Czech health research council project AZV NU20J-08-00009 Prevention of intestinal anastomotic leakage and postoperative adhesions by using nanofibrous biodegradable materials, and by European Regional Development Fund-Project AMTMI No. CZ.02.1.01/0.0/0.0/17_048/0007280, grant UNCE/MED006 Center of Excellence (Charles University "Center of Clinical and Experimental Liver Surgery").

REFERENCES

1. Rentsch M, Schiergens T, Khandoga A, Werner J. Surgery for colorectal cancer - trends, developments, and future perspectives. *Visc Med*. (2016) 32(3):184–91. doi: 10.1159/000446490
2. Daher R, Chouillard E, Panis Y. New trends in colorectal surgery: single port and natural orifice techniques. *World J Gastroenterol*. (2014) 20 (48):18104–20. doi: 10.3748/wjg.v20.i48.18104.
3. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for perioperative care in elective colorectal surgery: enhanced recovery after surgery (ERAS®) society recommendations: 2018. *World J Surg*. (2019) 43(3):659–95. doi: 10.1007/s00268-018-4844-y.
4. Lee SW, Gregory D, Cool CL. Clinical and economic burden of colorectal and bariatric anastomotic leaks. *Surg Endosc*. (2019). doi: 10.1007/s00464-019-07210-1.
5. Clifford RE, Fowler H, Manu N, Vimalachandran D. Management of benign anastomotic strictures following rectal resection: a systematic review. *Colorectal Dis*. (2021) 23(12):3090–100. doi: 10.1111/codi.15865
6. Acar T, Aslan F, Acar N, Kamer E, Ünsal B, Hacıyanlı M. Role of endoscopic interventions and electroincision in benign anastomotic strictures following colorectal surgery. *Turk J Gastroenterol*. (2019) 30(8):673–9. doi: 10.5152/tjg.2019.18673
7. Rosendorf J, Klicova M, Cervenkova L, Horakova J, Klapstova A, Hosek P, et al. Reinforcement of colonic anastomosis with improved ultrafine nanofibrous patch: experiment on pig. *Biomedicines*. (2021) 9(2):102. doi: 10.3390/biomedicines9020102
8. Yauw ST, Wever KE, Hoesseini A, Ritskes-Hoitinga M, van Goor H. Systematic review of experimental studies on intestinal anastomosis. *Br J Surg*. (2015) 102(7):726–34. doi: 10.1002/bjs.9776
9. Thornton FJ, Barbul A. Healing in the gastrointestinal tract. *Surg Clin North Am*. (1997) 77(3):549–73. doi: 10.1016/s0039-6109(05)70568-5
10. Bosmans JW, Jongen AC, Bouvy ND, Derikx JP. Colorectal anastomotic healing: why the biological processes that lead to anastomotic leakage should be revealed prior to conducting intervention studies. *BMC Gastroenterol*. (2015) 15:180. doi: 10.1186/s12876-015-0410-3
11. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. *Br J Surg*. (2015) 102(5):462–79. doi: 10.1002/bjs.9697
12. Vasiliu EC, Zarnescu NO, Costea R, Neagu S. Review of risk factors for anastomotic leakage in colorectal surgery. *Chirurgia (Bucur)*. (2015) 110 (4):319–26
13. Zarnescu EC, Zarnescu NO, Costea R. Updates of risk factors for anastomotic leakage after colorectal surgery. *Diagnostics (Basel)*. (2021) 11(12):2382. doi: 10.3390/diagnostics1112238
14. Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound healing: a cellular perspective. *Physiol Rev*. (2019) 99(1):665–706. doi: 10.1152/physrev.00067.2017
15. Safiejko K, Tarkowski R, Kozlowski TP, Koselak M, Jachimiuk M, Tarasik A, et al. Safety and efficacy of indocyanine green in colorectal cancer surgery: a systematic review and meta-analysis of 11,047 patients. *Cancers (Basel)*. (2022) 14(4):1036. doi: 10.3390/cancers14041036
16. Blanco-Colino R, Espin-Basany E. Intraoperative use of ICG fluorescence imaging to reduce the risk of anastomotic leakage in colorectal surgery: a systematic review and meta-analysis. *Tech Coloproctol*. (2018) 22(1):15–23. doi: 10.1007/s10151-017-1731-8
17. Sparreboom CL, Wu ZQ, Ji JF, Lange JF. Integrated approach to colorectal anastomotic leakage: communication, infection and healing disturbances. *World J Gastroenterol*. (2016) 22(32):7226–35. doi: 10.3748/wjg.v22.i32.7226

18. Christley S, Shogan B, Levine Z, Koo H, Guyton K, Owens S, et al. Comparative genetics of Enterococcus faecalis intestinal tissue isolates before and after surgery in a rat model of colon anastomosis. *PLoS One*. (2020) 15(4):e0232165. doi: 10.1371/journal.pone.0232165
19. Shogan BD, Belogortseva N, Luong PM, Zaborin A, Lax S, Bethel C, et al. Collagen degradation and MMP9 activation by Enterococcus faecalis contribute to intestinal anastomotic leak. *Sci Transl Med*. (2015) 7 (286):286ra68. doi: 10.1126/scitranslmed.3010658
20. Edomskis P, Goudberg MR, Sparreboom CL, Menon AG, Wolthuis AM, D'Hoore A, et al. Matrix metalloproteinase-9 in relation to patients with complications after colorectal surgery: a systematic review. *Int J Colorectal Dis*. (2021) 36(1):1–10. doi: 10.1007/s00384-020-03724-6
21. Lam A, Fleischer B, Alverdy J. The biology of anastomotic healing-the unknown overwhelms the known. *J Gastrointest Surg*. (2020) 24(9):2160–6. doi: 10.1007/s11605-020-04680-w
22. Wang PH, Huang BS, Hornr HC, Yeh CC, Chen YJ. Wound healing. *J Chin Med Assoc*. (2018) 81(2):94–101. doi: 10.1016/j.jcma.2017.11.002.
23. Cheong YC, Laird SM, Li TC, Shelton JB, Ledger WL, Cooke ID. Peritoneal healing and adhesion formation/reformation. *Hum Reprod Update*. (2001) 7 (6):556–66. doi: 10.1093/humupd/7.6.556
24. Tang J, Xiang Z, Bernards MT, Chen S. Peritoneal adhesions: occurrence, prevention and experimental models. *Acta Biomater*. (2020) 116:84–104. doi: 10.1016/j.actbio.2020.08.036
25. Arung W, Meurisse M, Detry O. Pathophysiology and prevention of postoperative peritoneal adhesions. *World Journal of Gastroenterology*. (2011) 17(41):4545–53. doi: 10.3748/wjg.v17.i41.4545
26. Saed GM, Diamond MP. Molecular characterization of postoperative adhesions: the adhesion phenotype. *J Am Assoc Gynecol Laparosc*. (2004) 11(3):307–14. doi: 10.1016/S1074-3804(05)60041-2
27. Alpay Z, Saed GM, Diamond MP. Postoperative adhesions: from formation to prevention. *Semin Reprod Med*. (2008) 26(4):313–21. doi: 10.1055/s-0028-1082389
28. Braun KM, Diamond MP. The biology of adhesion formation in the peritoneal cavity. *Semin Pediatr Surg*. (2014) 23(6):336–43. doi: 10.1053/j.sempedsurg.2014.06.004
29. Fletcher NM, Jiang ZL, Diamond MP, Abu-Soud HM, Saed GM. Hypoxia-generated superoxide induces the development of the adhesion phenotype. *Free Radic Biol Med*. (2008) 45(4):530–6. doi: 10.1016/j.freeradbiomed.2008.05.002
30. Brokelman WJA, Lensvelt M, Rinkes IHMB, Klinkenbijl JHG, Reijnen MMPJ. Peritoneal changes due to laparoscopic surgery. *Surg Endosc*. (2011) 25(1):1–9. doi: 10.1007/s00464-010-1139-2
31. Saed GM, Diamond MP. Modulation of the expression of tissue plasminogen activator and its inhibitor by hypoxia in human peritoneal and adhesion fibroblasts. *Fertil Steril*. (2003) 79(1):164–8. doi: 10.1016/S0015-0282(02)04557-0
32. Ivarsson ML, Diamond MP, Falk P, Holmdahl L. Plasminogen activator/plasminogen activator inhibitor-1 and cytokine modulation by the PROACTTM System. *Fertil Steril*. (2003) 79(4):987–92. doi: 10.1016/S0015-0282(02)04851-3
33. Ambler DR, Fletcher NM, Diamond MP, Saed GM. Effects of hypoxia on the expression of inflammatory markers IL-6 and TNF-a in human normal peritoneal and adhesion fibroblasts. *Syst Biol Reprod Med*. (2012) 58 (6):324–9. doi: 10.3109/19396368.2012.713439
34. Chegini N, Zhao Y, Kotseos K, Ma C, Bennett B, Diamond MP, et al. Differential expression of matrix metalloproteinase and tissue inhibitor of MMP in serosal tissue of intraperitoneal organs and adhesions. *BJOG An Int J Obstet Gynaecol*. (2002) 109(9):1041–9. doi: 10.1111/j.1471-0528.2002.01334.x
35. Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. *Circ Res*. (2003) 92(8):827–39. doi: 10.1161/01.RES.0000070112.80711.3D
36. Rout UK, Oommen K, Diamond MP. Altered expressions of VEGF mRNA splice variants during progression of uterine-peritoneal adhesions in the rat. *Am J Reprod Immunol*. (2000) 43(5):299–304. doi: 10.1111/j.8755-8920.2000.430509.x
37. Diamond MP, El-Hammady E, Munkarah A, Bieber EJ, Saed G. Modulation of the expression of vascular endothelial growth factor in human fibroblasts. *Fertil Steril*. (2005) 83(2):405–9. doi: 10.1016/j.fertnstert.2004.06.073
38. Saed GM, Munkarah AR, Abu-Soud HM, Diamond MP. Hypoxia upregulates cyclooxygenase-2 and prostaglandin E2 levels in human peritoneal fibroblasts. *Fertil Steril*. (2005) 83(Suppl 1):1216–9. doi: 10.1016/j.fertnstert.2004.11.037
39. Stanzel RD, Lourenssen S, Nair DG, Blennerhassett MG. Mitogenic factors promoting intestinal smooth muscle cell proliferation. *Am J Physiol Cell Physiol*. (2010) 299(4):C805–17. doi: 10.1152/ajpcell.00086.2010
40. Owens MW, Grisham MB. *Inflammation*. (1993) 17:481. doi: https://doi.org/10.1007/BF00916587.
41. Yu J, Zeng Y, Zhao J, Liao D, Gregersen H. Quantitative analysis of collagen fiber angle in the submucosa of small intestine. *Comput Biol Med*. (2004) 34 (6):539–50. doi: 10.1016/j.compbiomed.2003.06.001
42. Lovisa S, Genovese G, Danese S. Role of epithelial-to-mesenchymal transition in inflammatory bowel disease. *J Crohns Colitis*. (2019) 13(5):659–68. doi: 10.1093/ecco-jcc/jjy201.
43. Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. *Nat Rev Mol Cell Biol*. (2014) 15(3):178–96. doi: 10.1038/nrm3758.
44. Jiang H, Shen J, Ran Z. Epithelial-mesenchymal transition in Crohn's disease. *Mucosal Immunol*. (2018) 11(2):294–303. doi: 10.1038/mi.2017.107
45. Obermüller B, Frisina N, Meischel M, Singer G, Stanzl-Tschegg S, Lichtenegger H, et al. Examination of intestinal ultrastructure, bowel wall apoptosis and tight junctions in the early phase of sepsis. *Sci Rep*. (2020) 10(1):11507. doi: 10.1038/s41598-020-68109-9
46. Teo I, Toms SM, Marteyn B, Barata TS, Simpson P, Johnston KA, et al. Preventing acute gut wall damage in infectious diarrhoeas with glycosylated dendrimers. *EMBO Mol Med*. (2012) 4(9):866–81. doi: 10.1002/emmm.201201290

Conflict of Interest: The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Surgery

SYSTEMATIC REVIEW
published: 08 June 2022
doi: 10.3389/fsurg.2022.919744

Surgical Site Infection Following Single-Port Appendectomy: A Systematic Review of the Literature and Meta-Analysis

Franziska Köhler[1], Lena Reese[1], Carolin Kastner[1,2], Anne Hendricks[1], Sophie Müller[1], Johan F. Lock[1], Christoph-Thomas Germer[1,3] and Armin Wiegering[1,2,3]*

[1]Department of General, Visceral, Transplantation, Vascular and Pediatric Surgery, University Hospital, University of Wuerzburg, Wuerzburg, Germany, [2]Department of Biochemistry and Molecular Biology, University of Wuerzburg, Wuerzburg, Germany, [3]Comprehensive Cancer Center Mainfranken, University of Wuerzburg Medical Centre, Wuerzburg, Germany

OPEN ACCESS

Edited by:
Mauro Podda, Azienda Ospedaliero-Universitaria Cagliari, Italy

Reviewed by:
Goran Augustin, School of Medicine, University of Zagreb, Croatia
Andrea Balla, Hospital San Paolo, Italy

***Correspondence:**
Franziska Köhler
Koehler_F2@ukw.de

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *13 April 2022*
Accepted: *29 April 2022*
Published: *08 June 2022*

Citation:
Köhler F, Reese L, Kastner C, Hendricks A, Müller S, Lock JF, Germer C-T and Wiegering A (2022) Surgical Site Infection Following Single-Port Appendectomy: A Systematic Review of the Literature and Meta-Analysis. Front. Surg. 9:919744. doi: 10.3389/fsurg.2022.919744

Introduction: Surgical site infections (SSIs) are one of the most common postoperative complications after appendectomy leading to recurrent surgery, prolonged hospital stay, and the use of antibiotics. Numerous studies and meta-analyses have been published on the effect of open versus conventional laparoscopic appendectomy (CLA) reporting faster postoperative recovery and less postoperative pain for CLA. A development from CLA has been the single-port appendectomy (SPA), associated with a better cosmesis but seemingly having a higher risk of wound infections. The aim of this systematic literature review and meta-analysis is to investigate whether reduced port or SPA alters the ratio of SSIs.

Methods: Pubmed, Embase, and Cochrane databases were screened for suitable articles. All articles published between January 1, 2002, and March 23, 2022, were included. Articles regarding children below the age of 18 were excluded as well as manuscripts that investigated solemnly open appendectomies. Articles were screened for inclusion criteria by two independent authors. Incidence of SSI was the primary outcome. Duration of operation and length of hospital stay were defined as secondary outcomes.

Results: A total of 25 studies were found through a database search describing 5484 patients. A total of 2749 patients received SPA and 2735 received CLA. There was no statistical difference in the rate of SSI ($P = 0.98$). A total of 22 studies including 4699 patients reported the duration of operation (2223 SPA and 2476 CLA). There was a significantly shorter operation time seen in CLA. The length of hospital stay was reported in 23 studies (4735 patients: 2235 SPA and 2500 CLA). A shorter hospital stay was seen in the SPA group ($P < 0.00001$). Separately performed analysis of randomized controlled trials could not confirm this effect ($P = 0.29$).

Discussion: SPA is an equally safe procedure considering SSI compared to CLA and does not lead to an increased risk of SSI. A longer operation time for SPA and a minor difference in the length of stay does lead to the use of SPA in selected patients only.

Keywords: appendicitis, appendectomy, surgical site infection, single-port appendectomy, conventional laparoscopic appendectomy, wound infection, SSI

INTRODUCTION

Acute appendicitis (AA) is one of the most common causes of acute abdominal pain and the most frequent indication of abdominal emergency surgery worldwide (1, 2). AA can be divided into uncomplicated appendicitis i.e., phlegmonous and complicated appendicitis including perforation, abscess, and peritonitis (2).

The current gold standard treatment is appendectomy, in the majority of cases performed laparoscopically. However, antibiotic therapy seems to be an alternative in uncomplicated cases (3–7). In recent years, single-port appendectomy (SPA) using only one incision in or below the umbilicus has become more and more popular (8). It is thought to provide better wound cosmesis and faster recovery compared to conventional laparoscopic appendectomy (CLA) (9, 10). SPA can be performed in different techniques, first, by using designated single ports that have been developed for single-port laparoscopy. These trocars provide three single channels through which the instruments are inserted (11). Second, three conventional trocars can be inserted in or below the umbilicus (12). With this technique, it is important to incision the fascia sparingly and insert each trocar through its own fascial incision to reduce gas efflux (13). Third, self-made single ports have been established using rings, bands, and surgical gloves (14).

Appendectomy, performed open or laparoscopically, are surgical procedures with manageable perioperative risk and low mortality (15). Bleeding, stump insufficiency, or intraabdominal abscess are rather rare complications (16). Surgical site infections (SSIs) appear in up to 9% of appendectomies and therefore present the most frequent complication after appendectomy (15, 17).

According to the Center of Disease Control (CDC), SSI can be divided into superficial incisional surgical site infection, deep incisional site infection, and organ/space surgical site infection (see **Table 1**) (18, 19).

The aim of this study was to evaluate the influence of SPA on the occurrence of superficial incisional and deep incisional surgical site infection compared to CLA.

TABLE 1 | Classification of surgical site infection according to the CDC (Center of Disease Control) (11, 12).

Surgical site infection	Criteria
Superficial incisional surgical site infection	Occurs within 30 days after surgery; involves only the skin and subcutaneous tissue of the incision
Deep incisional surgical site infection	Occurs within 30 or 90 days after surgery; involves deep soft tissues of the incision (muscle and fascial layers)
Organ/space surgical site infection	Occurs within 30 or 90 days after surgery; involves tissue deeper than fascial/muscle layers that have been opened or manipulated during the surgery

TABLE 2 | Table of primary and secondary outcomes of interest and inclusion and exclusion criteria.

Primary outcome of interest	Secondary outcome of interest
Incidence of surgical site infection (SSI)	Length of hospital stay in days Operation time in minutes
Inclusion criteria	**Exclusion criteria**
Studies published between January 1, 2002 and March 23, 2022 reporting the incidence of SSI	Studies focusing on patients below the age of 18

METHODS

Study Selection and Search Strategy

PubMed database, Embase database, and Cochrane database were searched on March 23, 2022. Search terms were *append** and *SSI* or *surgical site infection* or *local infection*. Studies with available full text in English or German language were included in the analysis. No study type was excluded. Manuscripts that focused on pediatric patients (below the age of 18) were excluded. Outcomes of interest were defined and are listed in **Table 2** with the primary outcome being the incidence of SSI.

Duplicates were removed and articles were first screened by title and abstract and second reviewed in full text for eligibility criteria by two independent reviewers (FK and LR). Disagreement on the eligibility of articles was discussed and solved by consensus.

Additionally, studies used in preexisting meta-analysis were screened and included if full-text screening did not reveal exclusion criteria.

The systematic review and meta-analysis were performed in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. The study selection process is pictured in the PRISMA flowchart (**Figure 1**) (20).

Literature organization was performed using program EndNoteX9, while charts, tables, and statistical analysis were obtained using RevMan5, Prism Graphpad, Microsoft Word, and PowerPoint. The measure of effects was assessed with the odds ratio (OR) and fixed effects model as well as the corresponding 95% confidence interval (CI 95%). Statistical significance was assessed by performing descriptive statistics. Statistical heterogeneity was assessed by calculating the χ^2 and I^2 tests.

Risk of Bias Assessment

The risk of bias was assessed using the ROBINS-I tool for uncontrolled before-after studies (21), as the minority of studies were randomized controlled trials. Evaluated risks of bias were as follows: bias due to confounding, in the selection of participants in the study, in the classification of intervention, due to deviations from intended interventions, due to missing data, in the measurement of outcome, and in the selection of the reported result as well as the overall risk of bias.

The risk of bias was divided into low, medium, and high risk of bias as well as unclear risk of bias if no information regarding the evaluated risk of bias was available in the study. Detailed risk of bias is listed in **Table A1** in the Appendix.

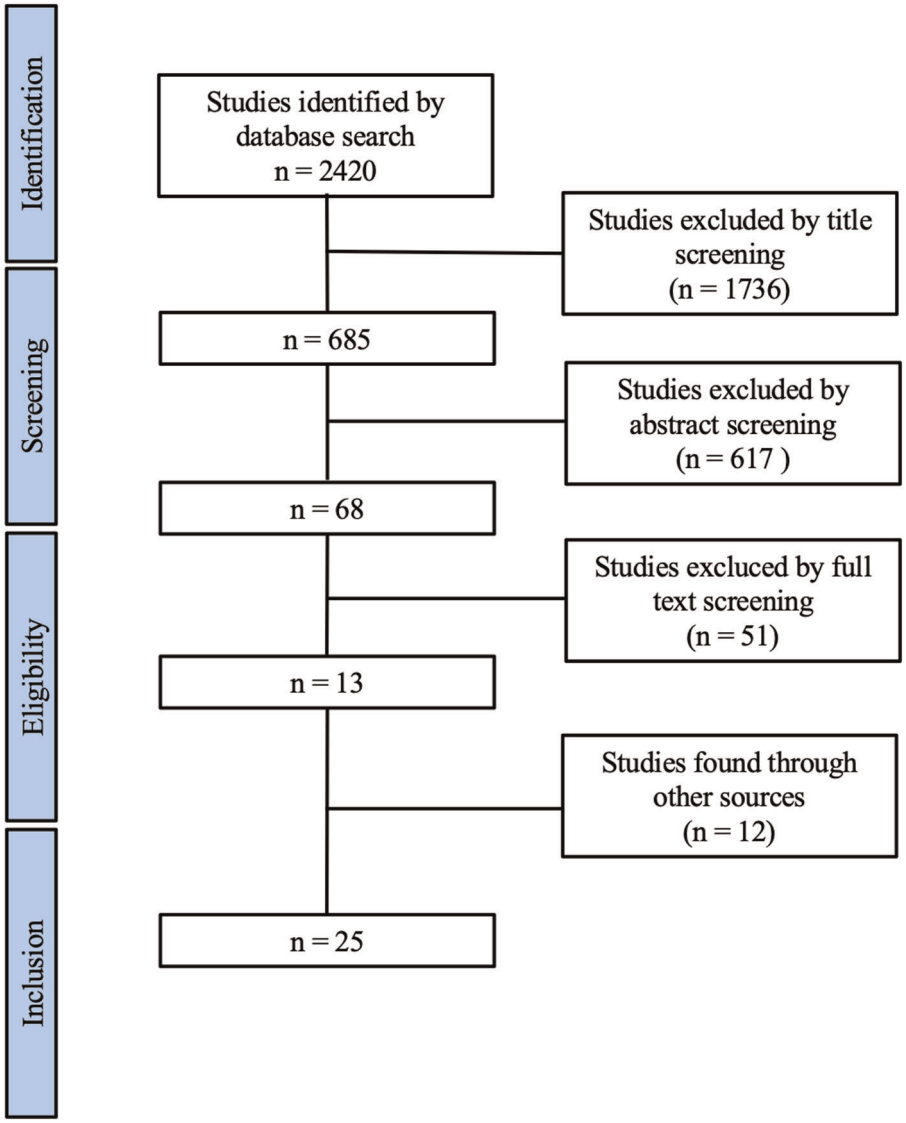

FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram of the study identification and selection process (13).

The overall risk of bias assessment revealed a low risk, even in the non-randomized controlled trials.

RESULTS

After removing duplicates, a literature search revealed 2420 studies. Through title and abstract screening, 68 manuscripts were found to be suitable for full-text screening. A total of 13 studies meet the inclusion criteria. Throughout the literature search additionally six meta-analyses were found. By screening the literature that was used to perform these meta-analyses, 12 further studies were identified that met the inclusion criteria. Overall 25 manuscripts were included in the meta-analysis (see **Figure 1**).

Primary Outcome

The primary outcome was defined as the incidence of SSI. A total of 25 studies were identified that investigated the effect of single-port or reduced-port appendectomy on the incidence of SSI (11–13, 22–44). In two studies (35, 37) both groups did not report any SSIs, therefore OR was not estimable. Overall 5484 patients were included in the analysis. A total of 2749 patients received SPA and 2735 patients CLA. Of the patients treated with SPA 104 developed SSI and 110 patients developed SSI in the CLA group. There was no significant difference in the two groups estimable ($P = 0.98$) (see **Supplementary Figures S2 and S3**).

Furthermore, randomized controlled trials were investigated separately. Nine trials were identified through database search (11, 12, 25, 27, 30, 34, 36, 37). The trial by Carter et al. reported

no SSIs in both study groups, therefore OR was not estimable (37). Overall 1143 patients were included in the analysis, 554 received SPA and 589 received CLA. A total of 72 patients developed SSI, 27 in the single-port group and 45 in the conventional group. No statistically significant difference was seen between the groups ($P = 0.06$) (see **Supplementary Figures S4 and S5**).

Secondary Outcome

Operation Time

Out of the studies that reported the incidence of SSI, 22 studies reported the duration of the performed surgery. Overall 4699 patients were included in the analysis on surgery time, 2223 received SPA and 2476 received CLA. One study did not report the standard deviation; therefore, OR was not estimable (22). There was a significant difference between the two groups with shorter operation time in the CLA group ($P < 0.00001$) (see **Supplementary Figures S6 and S7**).

The mean operation time was 53.52 min (SD 13.65) for SPA and 50.83 min (SD 15.75) for CLA.

Looking at randomized controlled trials only, 8 trials were identified that included 931 patients, 465 in the SPA group and 466 in the laparoscopic group. In line with the results of the analysis of all studies, there was a significantly longer surgery time in the single-port group ($P < 0.00001$) (see **Supplementary Figures S8 and S9**). The mean operation time was 55.67 min (SD 19.45) in the single-port group and 51.81 min (SD 23.06) in the CLA group.

Hospital Stay

Out of the studies that reported SSI in SPA and CLA, 23 investigated the length of hospital stay. 4735 patients were included in the analysis, 2235 in the single-port group and 2500 in the CLA group. In five studies, information was missing to perform further analysis (22, 27, 28, 38, 41). There was a significant difference between the two groups ($P < 0.00001$) favoring SPA (see **Supplementary Figures S10 and S11**). The mean length of stay was 2.93 days (SD 1.28) in the single-port group and 3.05 days (SD 1.17) in the CLA group.

Looking at only randomized controlled trials, there were eight studies found through a database search. Two studies did not provide enough information to perform further analysis (27, 28). Overall 852 patients were analyzed, 428 in the SPA group and 424 in the CLA group. There was no statistical significance in the two groups ($P = 0.29$) (see **Supplementary Figures S12 and S13**). The mean length of stay was 2.64 days (SD 0.92) in the single-port group and 2.6 days (SD 0.87) in the CLA group.

DISCUSSION

This systematic literature review and meta-analysis revealed no difference in the incidence of SSI for single-port appendectomy compared to CLA. Operation time was significantly shorter in the CLA group, while hospital length was significantly shorter in the SPA group.

On one hand, the updated guideline of the World Society of Emergency Surgery (WSES) on diagnosis and treatment of AA claims that SPA is equally safe and effective as CLA. On the other hand, the listed study in the guideline revealed longer operation time, higher rates of wound infection, and requirement for higher doses of pain medication while SPA does provide better wound cosmesis. Overall, the updated guideline does not recommend SPA over CLA due to the listed disadvantages (45). This meta-analysis did not investigate the use of pain medication, while first it can confirm longer operation time and second it did not show higher rates of SSI in the SPA group (46). Longer operation times and higher doses of pain medication (while the postoperative pain level did not reveal any difference) are socioeconomic factors that should not be the only aspects to be considered when deciding on one or the other procedure.

Duration of surgery varied broadly between the different studies, with means ranging from 32.6 to 84.8 min for SPA and 29.5 to 89 min in the CLA group. The difference between the means of the two groups is estimated at 3 min. When looking at the studies that had more than 100 patients in every group (23, 28, 42, 47), all of them were single-center studies and surgeries mostly performed by one surgeon. Operation time in these studies ranged from 34 to 43.8 in the SPA group and 29.8 to 42.28 min in the CLA group, which is a shorter duration than the median operation time if looking at all study types. Studies have revealed lower mortality for abdominal surgical procedures in high-volume centers (48) and furthermore a learning curve for laparoscopic skills (49). Therefore, it is likely that surgeons performing higher numbers of appendectomies (SPA and CLA) are able to do these procedures in a shorter duration. This should be considered when deciding between the two surgical procedures, as otherwise this review and meta-analysis were not able to reveal additional disadvantages for SPA compared to CLA and even show a shorter hospital stay for SPA.

A literature search revealed more than 5000 patients to be included through 25 studies in this analysis, which leads to one of the largest meta-analysis on this topic to date. Analyzation of randomized controlled trials and all studies did reveal matching results, except for the length of hospital stay in the overall analysis. Looking at only randomized controlled trials, which did not reveal a difference between SPA and CLA regarding the length of stay, the results of this meta-analysis are in line with the existing meta-analysis (9, 10).

Surgical techniques and instruments used in the studies included in the meta-analysis varied broadly, reaching from self-made incisional ports using surgical gloves to designated single-port trocars. This might be a risk of bias, as the procedure in itself varies and makes comparability difficult. The reason for the use of self-made single ports is mainly the higher costs of manufactured single-port trocars as well as availability in low-income countries (29). Studies investigating the self-made incisional ports reported a low complication rate and good postoperative cosmesis results (23, 43). However, there is still a lack of studies comparing self-made single ports with manufactured single-ports. Especially randomized

controlled trials focusing on cost-effectiveness and long-term outcomes are missing. Furthermore, contrary to the suspicion that SPA is associated with higher costs, the study by Goodman et al. revealed no difference in costs between SPA and CLA and Wieck et al. even reported significantly lower costs in the SPA group (50, 51).

In a high-quality meta-analysis by Zaman et al. who solemnly analyzed randomized controlled trials (and included pediatric patients in their analysis), a higher cosmetic score in the SPA group was reported (52). We did not analyze the cosmetic aspect in our analysis on SPA versus CLA, but it seems likely that one incision compared to three incisions results in a better cosmetic score.

This analysis has some limitations. First, all study types were included in the analysis. Therefore, it might be possible that low-quality studies were included in the analysis, which might affect the overall validity of this analysis, so we also performed an analysis on only randomized controlled trials that were found through the literature search. The analysis of randomized controlled trials alone included more than 1400 patients and the results are in line with the ones of the overall analysis except for the length of stay. On the other hand, the risk of bias assessment for all studies revealed rather high quality and low risk of bias for all studies (see **Table A1** in the appendix).

The influence of the surgical approach on hospital length of stay does show a statistical significance between the SPA and CLA groups. Nevertheless, the difference does add up to merely 3 h (171 min). Overall, this difference does not seem to be of clinical importance, as most patients are discharged after morning rounds, regardless if surgery took place in the morning or in the afternoon.

The aim of this analysis was to investigate only superficial and deep incisional surgical site infection and exclude deep/organ space infection. A number of studies divided SSI into superficial, deep, and organ/space according to the CDC classification. Some studies reported "wound infection" without further clarification. Therefore, it might be possible that to some extent deep SSIs are included in the analysis and distort the results.

Looking at the length of hospital stay, a limitation might be, that not all studies reported the overall hospital stay but described the postoperative hospital stay instead. We analyzed "postoperative hospital stay" and "hospital stay" under the same category. This might be an explanation for the differing results when analyzing all study types and randomized controlled trials separately and needs to be considered when interpreting the data.

CONCLUSION

SPA seems to be a safe alternative to CLA with equal risk for wound infection. It needs to be considered that SPA takes significantly longer operation time but leads to significantly shorter hospital length of stay, even if the latter is of questionable clinical importance.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

FK and AW designed the study; FK and LR performed the literature search; FK, AW, and SM performed the analysis; FK, AH, CK, and JFL compiled the graphs; FK, LR, CTG, and AW wrote the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This publication was supported by the Open Access Publication Fund of the University of Wuerzburg.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.919744/full#supplementary-material.

REFERENCES

1. Snyder MJ, Guthrie M, Cagle S. Acute appendicitis: efficient diagnosis and management. *Am Fam Physician*. (2018) 98(1):25–33. PMID: 30215950
2. Bhangu A, Søreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. *Lancet*. (2015) 386(10000):1278–87. doi: 10.1016/S0140-6736(15)00275-5
3. The Coda Collaborative. A randomized trial comparing antibiotics with appendectomy for appendicitis. *N Engl J Med*. (2020) 383(20):1907–19. doi: 10.1056/NEJMoa2014320
4. Poillucci G, Mortola L, Podda M, Di Saverio S, Casula L, Gerardi C, et al. Laparoscopic appendectomy vs antibiotic therapy for acute appendicitis: a propensity score-matched analysis from a multicenter cohort study. *Updates Surg*. (2017) 69(4):531–40. doi: 10.1007/s13304-017-0499-8
5. Harnoss JC, Zelienka I, Probst P, Grummich K, Müller-Lantzsch C, Harnoss JM, et al. Antibiotics versus surgical therapy for uncomplicated appendicitis: systematic review and meta-analysis of controlled trials (PROSPERO 2015: CRD42015016882). *Ann Surg*. (2017) 265(5):889–900. doi: 10.1097/SLA.0000000000002039
6. Wilms IM, de Hoog DE, de Visser DC, Janzing HM. Appendectomy versus antibiotic treatment for acute appendicitis. *Cochrane Database Syst Rev*. (2011) 11:CD008359. doi: 10.1002/14651858.CD008359.pub2
7. Köhler F, Hendricks A, Kastner C, Müller S, Boerner K, Wagner JC, et al. Laparoscopic appendectomy versus antibiotic treatment for acute appendicitis—a systematic review. *Int J Colorectal Dis*. (2021) 36(10):2283–6. doi: 10.1007/s00384-021-03927-5
8. St. Peter SD, Adibe OO, Juang D, Sharp SW, Garey CL, Laituri CA, et al. Single incision versus standard 3-port laparoscopic appendectomy: a

prospective randomized trial. *Ann Surg*. (2011) 254(4):586–90. doi: 10.1097/SLA.0b013e31823003b5
9. Feng J, Cui N, Wang Z, Duan J. Bayesian network meta-analysis of the effects of single-incision laparoscopic surgery, conventional laparoscopic appendectomy and open appendectomy for the treatment of acute appendicitis. *Exp Ther Med*. (2017) 14(6):5908–16. doi: 10.3892/etm.2017.5343
10. Gao J, Li P, Li Q, Tang D, Wang DR. Comparison between single-incision and conventional three-port laparoscopic appendectomy: a meta-analysis from eight RCTs. *Int J Colorectal Dis*. (2013) 28(10):1319–27. doi: 10.1007/s00384-013-1726-5
11. Ahmed I, Burr J, Castillo M, Collins D, Cook JA, Campbell M, et al. Single port/incision laparoscopic surgery compared with standard three-port laparoscopic surgery for appendicectomy: a randomized controlled trial. *Surg Endosc*. (2015) 29(1):77–85. doi: 10.1007/s00464-014-3416-y
12. Teoh AYB, Chiu PWY, Wong TCL, Poon MCM, Wong SKH, Leong HT, et al. A double-blinded randomized controlled trial of laparoendoscopic single-site access versus conventional 3-port appendectomy. *Ann Surg*. (2012) 256(6):909–14. doi: 10.1097/SLA.0b013e3182765fcf
13. Chow A, Purkayastha S, Nehme J, Darzi LA, Paraskeva P. Single incision laparoscopic surgery for appendicectomy: a retrospective comparative analysis. *Surg Endosc*. (2010) 24(10):2567–74. doi: 10.1007/s00464-010-1004-3
14. Mock K, Lu Y, Friedlander S, Kim DY, Lee SL. Misdiagnosing adult appendicitis: clinical, cost, and socioeconomic implications of negative appendectomy. *Am J Surg*. (2016) 212(6):1076–82. doi: 10.1016/j.amjsurg.2016.09.005
15. Andrade LAM, Muñoz FYP, Báez MVJ, Collazos SS, de los Angeles Martinez Ferretiz M, Ruiz B, et al. Appendectomy skin closure technique, randomized controlled trial: changing paradigms (ASC). *World J Surg*. (2016) 40 (11):2603–10. doi: 10.1007/s00268-016-3607-x
16. Horvath P, Lange J, Bachmann R, Struller F, Königsrainer A, Zdichavsky M. Comparison of clinical outcome of laparoscopic versus open appendectomy for complicated appendicitis. *Surg Endosc*. (2017) 31(1):199–205. doi: 10.1007/s00464-016-4957-z
17. Noorit P, Siribumrungwong B, Thakkinstian A. Clinical prediction score for superficial surgical site infection after appendectomy in adults with complicated appendicitis. *World J Emerg Surg*. (2018) 13(1):1–7. doi: 10.1186/s13017-018-0186-1
18. CDC. Surgical Site Infection Event (SSI). 2022;(January):1–39.
19. Onyekwelu I, Yakkanti R, Protzer L, Pinkston CM, Tucker C, Seligson D. Surgical wound classification and surgical site infections in the orthopaedic patient. *JAAOS Glob Res Rev*. (2017) 1(3):e022. doi: 10.5435/JAAOSGlobal-D-17-00022
20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Int J Surg*. (2021) 88(105906):1–11. doi: 10.1186/s13643-021-01626-4
21. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. (2016) 355:4–10. doi: 10.1136/bmj.i4919
22. Kim HO, Yoo CH, Lee SR, Son BH, Park YL, Shin JH, et al. Pain after laparoscopic appendectomy: a comparison of transumbilical single-port and conventional laparoscopic surgery. *J Korean Surg Soc*. (2012) 82 (3):172–8. doi: 10.4174/jkss.2012.82.3.172
23. Kim JH, Kim HY, Park SK, Lee JS, Heo DS, Park SW, et al. Single-incision laparoscopic appendectomy versus conventional laparoscopic appendectomy: experiences from 1208 cases of single-incision laparoscopic appendectomy. *Ann Surg*. (2015) 262(6):1054–8. doi: 10.1097/SLA.0000000000001064
24. Knott EM, Gasior AC, Holcomb GW, Ostlie DJ, St. Peter SD. Impact of body habitus on single-site laparoscopic appendectomy for nonperforated appendicitis: subset analysis from a prospective, randomized trial. *J Laparoendosc Adv Surg Tech*. (2012) 22(4):404–7. doi: 10.1089/lap.2012.0056
25. Kye B-H, Lee J, Kim W, Kim D, Lee D. Comparative study between single-incision and three-port laparoscopic appendectomy: a prospective randomized trial. *J Laparoendosc Adv Surg Tech*. (2013) 23(5):431–6. doi: 10.1089/lap.2012.0284
26. Lee YS, Kim JH, Moon EJ, Kim JJ, Lee KH, Oh SJ, et al. Comparative study on surgical outcomes and operative costs of transumbilical single-port laparoscopic appendectomy versus conventional laparoscopic appendectomy in adult patients. *Surg Laparosc Endosc Percutaneous Tech*. (2009) 19(6):493–6. doi: 10.1097/SLE.0b013e3181c15493
27. Park JH, Hyun KH, Park CH, Choi SY, Choi WH, Kim DJ, et al. Laparoscopic vs transumbilical single-port laparoscopic appendectomy; Results of prospective randomized trial. *J Korean Surg Soc*. (2010) 78 (4):213–8. doi: 10.4174/jkss.2010.78.4.213
28. Lee WS, Choi ST, Lee JN, Kim KK, Park YH, Lee WK, et al. Single-port laparoscopic appendectomy versus conventional laparoscopic appendectomy: a prospective randomized controlled study. *Ann Surg*. (2013) 257(2):214–8. doi: 10.1097/SLA.0b013e318273bde4
29. Lee SM, Hwang GS, Lee DS. Single-incision laparoscopic appendectomy using homemade glove port at low cost. *J Minim Access Surg*. (2016) 12 (2):124–8. doi: 10.4103/0972-9941.169979
30. Pan Z, Jiang X-H, Zhou J-H, Ji Z-L. Transumbilical single-incision laparoscopic appendectomy using conventional instruments the single working channel technique. *Surg Laparosc Endosc Percutaneous Tech*. (2013) 23(2):208–11. doi: 10.1097/SLE.0b013e3182827f5d
31. Park J, Kwak H, Kim SG, Lee S. Single-port laparoscopic appendectomy: comparison with conventional laparoscopic appendectomy. *J Laparoendosc Adv Surg Tech*. (2012) 22(2):142–5. doi: 10.1089/lap.2011.0253
32. Amos SE, Shuo-Dong W, Fan Y, Tian Y, Chen CC. Single-incision versus conventional three-incision laparoscopic appendectomy: a single centre experience. *Surg Today*. (2012) 42(6):542–6. doi: 10.1007/s00595-011-0110-8
33. Raakow R, Jacob DA. Initial experience in laparoscopic single-port appendectomy: a pilot study. *Dig Surg*. (2011) 28(1):74–9. doi: 10.1159/000322921
34. Sozutek A, Colak T, Dirlik M, Ocal K, Turkmenoglu O, Dag A. A prospective randomized comparison of single-port laparoscopic procedure with open and standard 3-port laparoscopic procedures in the treatment of acute appendicitis. *Surg Laparosc Endosc Percutaneous Tech*. (2013) 23(1):74–8. doi: 10.1097/SLE.0b013e3182754543
35. Vidal Ó, Valentini M, Ginestà C, Martí J, Espert JJ, Benarroch G, et al. Laparoendoscopic single-site surgery appendectomy. *Surg Endosc*. (2010) 24(3):686–91. doi: 10.1007/s00464-009-0661-6
36. Fatima-Tu-Zahara , Malik S, Ahmad I, Zia MI, Anum S. Outcome of single incision versus conventional laparoscopic appendectomy: a single institute based analysis. *Pakistan J Med Heal Sci*. 2020;14(4):1219–22.
37. Carter JT, Kaplan JA, Nguyen JN, Lin MYC, Rogers SJ, Harris HW. A prospective, randomized controlled trial of single-incision laparoscopic vs conventional 3-port laparoscopic appendectomy for treatment of acute appendicitis. *J Am Coll Surg*. (2014) 218(5):950–9. doi: 10.1016/j.jamcollsurg.2013.12.052
38. Ceci F, Orsini S, Tudisco A, Avallone M, Aiuti F, Di Girolamo V, et al. Single-incision laparoscopic appendectomy is comparable to conventional laparoscopic and laparotomic appendectomy: our single center single surgeon experience. *G Chir*. (2013) 34(7–8):216–9. doi: 10.11138/gchir/2013.34.7.216
39. Cho MS, Min BS, Hong YK, Lee WJ. Single-site versus conventional laparoscopic appendectomy: comparison of short-term operative outcomes. *Surg Endosc*. (2011) 25(1):36–40. doi: 10.1007/s00464-010-1124-9
40. Choi KW, Park BK, Suh SW, Lee ES, Lee SE, Park JM, et al. Risk factors for additional port insertion in single-port laparoscopic appendectomy. *Wideochir I Inne Tech Maloinwazyjne*. (2019) 14(2):223–8. doi: 10.5114/wiitm.2018.77714
41. Donmez T, Hut A, Avaroglu H, Uzman S, Yildirim D, Ferahman S, et al. Two-port laparoscopic appendectomy assisted with needle grasper comparison with conventional laparoscopic appendectomy. *Ann Surg Treat Res*. (2016) 91(2):59–65. doi: 10.4174/astr.2016.91.2.59
42. Jategaonkar PA, Yadav SP. Single site multiport umbilical laparoscopic appendicectomy versus conventional multiport laparoscopic appendicectomy in acute settings. *Ann R Coll Surg Engl*. (2014) 96 (6):452–7. doi: 10.1308/003588414X13946184901641
43. Kang KC, Lee SY, Kang DB, Kim SH, Oh JT, Choi DH, et al. Application of single incision laparoscopic surgery for appendectomies in patients with complicated appendicitis. *J Korean Soc Coloproctol*. (2010) 26(6):388–94. doi: 10.3393/jksc.2010.26.6.388
44. Lee J, Baek J, Kim W. Laparoscopic transumbilical single-port appendectomy: Initial experience and comparison with 3-port appendectomy. *Surg. Laparosc. Endosc. Percutaneous Tech*. (2010) 20:100–3. doi: 10.1097/SLE.0b013e31828dacde
45. Di Saverio S, Podda M, De Simone B, Ceresoli M, Augustin G, Gori A, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. *World J Emerg Surg*. (2020) 15(1):1–42. doi: 10.1186/s13017-020-00306-3

46. Xue C, Lin B, Huang Z, Chen Z. Single - incision laparoscopic appendectomy versus conventional 3 - port laparoscopic appendectomy for appendicitis : an updated meta-analysis of randomized controlled trials. *Surg Today*. (2015) 29:1179–86. doi: 10.1007/s00595-014-1094-y
47. O'Leary DP, Walsh SM, Bolger J, Baban C, Humphreys H, O'Grady S, et al. A randomized clinical trial evaluating the efficacy and quality of life of antibiotic-only treatment of acute uncomplicated appendicitis: results of the COMMA trial. *Ann Surg*. (2021) 274(2):240–7. doi: 10.1097/SLA.0000000000004785
48. Hendricks A, Diers J, Baum P, Weibel S, Kastner C, Müller S, et al. Systematic review and meta-analysis on volume-outcome relationship of abdominal surgical procedures in Germany. *Int J Surg*. (2021) 86:24–31. doi: 10.1016/j.ijsu.2020.12.010
49. Laubert T, Esnaashari H, Auerswald P, Höfer A, Thomaschewski M, Bruch HP, et al. Conception of the lübeck toolbox curriculum for basic minimally invasive surgery skills. *Langenbeck's Arch Surg*. (2018) 403(2):271–8. doi: 10.1007/s00423-017-1642-1
50. Goodman LF, Lin AC, Sacks MA, McRae JJLH, Radulescu A, Khan FA. Single site versus conventional laparoscopic appendectomy: some pain for no gain? *J Surg Res*. (2021) 264:321–6. doi: 10.1016/j.jss.2021.03.010
51. Wieck MM, Hamilton NA, Krishnaswami S. A cost and outcome analysis of pediatric single-incision appendectomy. *J Surg Res [Internet]*. (2016) 203(2):253–7. doi: 10.1016/j.jss.2016.04.033
52. Zaman S, Mohamedahmed AYY, Srinivasan A, Stonelake S, Sillah AK, Hajibandeh S, et al. Single-port laparoscopic appendicectomy versus conventional three-port approach for acute appendicitis: a systematic review, meta-analysis and trial sequential analysis of randomised controlled trials. *Surgeon*. (2021) 19(6):365–79. doi: 10.1016/j.surge.2021.01.018

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

APPENDIX

TABLE A1 | Assessment of risk of bias using the ROBINS-I Tool (Risk of Bias in Non-randomized Studies of Intervention).

	Baseline confounding	Selection of participants	Classification of intervention	Deviation from intended intervention	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Ahmed et al. (11)	Low	Low	Low	Low–moderate	Low–moderate	Low	Low	Low
Amos et al. (32)	Low	Moderate	Low	Low	Low	Low	Low	Low
Carter et al. (37)	Low	Low	Low	Low	Low	Low	Low	Low
Ceci et al. (38)	Moderate	High	Low	n/a	n/a	Low	Moderate	Moderate
Cho et al. (39)	Moderate	n/a	Low	n/a	Low	Low	Low	Low–moderate
Choi et al. (40)	Low	Low	Low	Moderate	Low	Low	Low	Low–moderate
Chow et al. (13)	Low	Low	Low	n/a	Low	Low	Low	Low
Donmez et al. (41)	Moderate	Moderate	Low	n/a	Low	Low	Low	Moderate
Fatima-Tu-Zahara et al. (36)	Low	Low	Low	Low	Low	Low	Low	Low
Jategaonkar et al. (42)	Low	Low	Low	n/a	Low	Low	Low	Low
Kang et al. (43)	Low	n/a	Low	Moderate	Low	Low	Low	Low–moderate
Kim et al. (22)	Low	Low	Moderate	Low	Low	Low	Low	Low–moderate
Kim et al. (23)	Low	Low	Low	Low	Low	Low	Low	Low
Kye et al. (25)	Low	Low	Low	Low	Low	Low	Low	Low
Lee et al. (26)	Low	Low	Low	Low	Low	Low	Low	Low
Lee et al. (44)	Low	Moderate	Low	Low	Low	Low	Low	Low–moderate
Lee et al. (28)	Low	Low	Low	Low	Low	Low	Low	Low

(*continued*)

TABLE A1 | Continued

	Baseline confounding	Selection of participants	Classification of intervention	Deviation from intended intervention	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Lee et al. (29)	Low	Moderate	Low	Moderate	Low	Low	Low	Moderate
Pan et al. (30)	Low	Low	Low	Low	Low	Low	Low	Low
Park et al. (27)	Low	Low	Low	Low	Low	Low	Low	Low
Park et al. (31)	Low	Low	Low	Low	Low	Low	Low	Low
Raakow et al. (33)	Low	Moderate	Low	Low	Low	Low	Low	Low–moderate
Sozutek et al. (34)	Low	Low	Low	Low	Low	Low	Low	Low
Teoh et al. (12)	Low	Low	Low	Low	Low	Low	Low	Low
Vidal et al. (35)	Low	Low	Low	Low	Low	Low	Low	Low

Low risk of bias, the study is comparable to a well-performed randomized trail; moderate risk of bias, the study appears to provide sound evidence for a non-randomized study but cannot be considered comparable to a well-performed randomized trial; high of bias, the study has some important problems; unclear risk, no information.

frontiers | Frontiers in Surgery

MINI REVIEW
published: 24 June 2022
doi: 10.3389/fsurg.2022.882625

Aspects Towards the Anastomotic Healing in Crohn's Disease: Clinical Approach and Current Gaps in Research

*F.H.M. Chaim, L.M.V. Negreiros, K.M. Steigleder, N.S.N. Siqueira, L.M. Genaro, P.S.P. Oliveira, C.A.R. Martinez, M.L.S. Ayrizono, J.J. Fagundes and R.F. Leal**

Inflammatory Bowel Disease Research Laboratory, Gastrocenter, Colorectal Surgery Unit, School of Medical Sciences, University of Campinas (Unicamp), São Paulo, Brazil

OPEN ACCESS

Edited by:
Sven Flemming, University Hospital of Wuerzburg, Germany

Reviewed by:
Matthias Kelm, University Hospital Würzburg, Germany

***Correspondence:**
Raquel Franco Leal
rafranco.unicamp@gmail.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *24 February 2022*
Accepted: *06 June 2022*
Published: *24 June 2022*

Citation:
Chaim F.H.M., Negreiros L.M.V., Steigleder K.M., Siqueira N.S.N., Genaro L.M., Oliveira P.S.P., Martinez C.A.R., Ayrizono M.L.S., Fagundes J.J. and Leal R.F. (2022) Aspects Towards the Anastomotic Healing in Crohn's Disease: Clinical Approach and Current Gaps in Research. Front. Surg. 9:882625. doi: 10.3389/fsurg.2022.882625

Anastomotic leakage is a major complication in gastrointestinal and colorectal surgery and its occurrence increases morbidity and mortality. Its incidence is even higher in Crohn's disease surgeries. Several authors have identified factors involved in the pathophysiology of anastomotic leak in the literature, aiming to reduce its occurrence and, therefore, improve its surgical treatment. Surgical technique is the most discussed topic in studies on guiding the performance of side-to-side stapled anastomosis. Preoperative nutritional therapy also has been shown to reduce the risk of anastomotic leakage. Other factors remain controversial – immunomodulator use and biologic therapy, antibiotics, and gut microbiota – with studies showing a reduction in the risk of complication while other studies show no correlation. Although mesenteric adipose tissue has been related to disease recurrence, there is no evidence in the literature that it is related to a higher risk of anastomotic leakage. Further exploration on this topic is necessary, including prospective research, to support the development of techniques to prevent anastomotic leakage, in this way benefiting the inflammatory bowel disease patients who have to undergo a surgical procedure.

Keywords: anastomotic healing, inflammatory bowel disease, surgical complications, Crohn's disease, anastomosis, mesenteric adipose tissue, postoperative complications/prevention & control, suture techniques

INTRODUCTION

The inflammatory bowel disease (IBD) therapeutic arsenal has broadened in the last decades due to pharmacological advances and the development of new drugs (1). Nevertheless a considerable percentage of patients need to undergo surgical treatment one or more times during their lifetime. From 50 to 90% of Crohn's disease (CD) patients, will require some type of surgical procedure along with medical follow-up and treatment period (2–4). The need to perform a surgical procedure is about 4 times lower (approximately 18%) among patients diagnosed with

ulcerative colitis (UC) (2). And yet, the performance of surgical propaedeutic requires the implementation of procedures with greater invasiveness and risk to the patients.

Implementation of surgical treatment incurs the risk of occurrence of postoperative inherent complications, including hemorrhage, intraperitoneal collection, wound infection and dehiscence, fistulas, pulmonary complications, and thromboembolic events. Among those complications, anastomotic leakage (AL) is a major complication in gastrointestinal and colorectal surgery and its occurrence contributes significantly to the increase in morbidity and mortality (5).

The pathophysiology of CD involves the occurrence of acute complications (e.g., bleeding, bowel obstruction, perforations; severe acute colitis) and chronic complications (e.g., strictures and stenosis, internal or external fistulas, adhesions, abdominal masses) as well as disease forms refractory to pharmacological therapy. Intestinal or colon resection is the required basis of surgery in CD and the consequent need to perform an anastomosis is a common fact during surgery. Anastomosis and reoperation are intrinsically related. The realization of an anastomosis increases the risk for urgent reintervention due to AL and in long term, postoperative recurrence typically occurs at the anastomotic site (3).

The surgically related incidence of anastomotic dehiscence in the literature varies widely. In a recent observational study involving more than 36.000 subjects who submitted to surgery due to colorectal carcinoma, AL incidence was 4.1% (6). Its incidence is even higher in CD surgeries. Recent studies enrolling CD patients showed AL occurrence in 6.4% up to 14% of patients submitted to surgical treatment (7–9). Therefore, surgeons are in constant pursuit of practices to prevent AL, in this way benefiting IBD patients who have to undergo a surgical procedure.

Mesenteric adipose tissue (MAT) and its mediators are increasingly more implicated in CD pathogenesis. Recent accumulating evidence also highlights the role of creeping fat in contributing to disease recurrence, to the point that it has become a well-known feature of CD (10, 11).

There is ample work in the literature concerning the healing process of anastomosis and AL after colorectal surgery in the context of neoplastic disease. However, the information on IBD and specifically in CD surgical treatment is sparse. This article aims to discuss and summarize the main topics present in the literature and identify potential areas for future research on the subject.

Despite recent advances in gastrointestinal/colorectal surgical technique and perioperative care, anastomotic healing is still a matter of concern in CD patients submitted to surgical treatment and AL remains a major complication. Its etiology is not yet completely understood. However, it is multifactorial and not only influenced by surgery-related factors but also by factors related to the disease and its behavior.

SURGICAL TECHNIQUE

The decision concerning anastomotic configuration depends on the surgical team's preference, the surgeon's experience, the availability of surgical materials (for example staplers and surgical threads), and the financial reality of each hospital.

Historically, hand-sewn anastomosis was the most common, and these produced variations related to the surgical thread and the type of stitches used. With the development and wide use of various types of staplers, even more, possible variations were added to this debate.

Side-to-side stapled anastomosis significantly reduces the incidence of short-term complications in surgical patients with CD when compared to end-to-end anastomosis (OR 0.54; 95% CI, 0.34 to 0.83). Specifically for the AL rate, side-to-side stapled anastomosis determines a decrease from 14.1 to 2% (95 percent confidence interval 1.7–22.2; $p = 0.02$). A reduction in mean postoperative hospital stays from 12.3 to 9.7 days ($p = 0.03$) was also observed (9, 12) (**Figure 1A**).

The technique chosen must consider the location of anastomotic performance (accessibility), the caliber of the intestinal segments (presence of edema may influence), surgical contamination, and the progress of the disease. According to the ECCO Consensus, the anastomotic diameter is an important discrimination factor that must be considered (13). Some authors suggest that for resections performed in the ileum, side-to-side anastomoses are indicated, in order to have a wider anastomotic lumen, while end-to-end anastomoses are performed in colonic segments, which have a larger caliber (14).

Due to the high recurrence rate characteristics of CD pathophysiology, repeat surgery is often required. In this sense, performing surgical procedures in CD patients with previous intestinal resection (reoperation) is an independent risk factor for AL and the number of previous resections is correlated with increased risk (8) (**Figure 1B**).

Recently, the laparoscopic approach has become more frequent and has become the standard of care in most situations. Robotic-assisted surgery also has been gaining acceptance in colorectal benignant and malignant surgery with intracorporeal anastomosis. Evidence on digital and robotic platform surgery applied to CD is scarce and recent, so it is still liable to selection bias. However, it seems to point to a lower occurrence of AL in patients undergoing robotic surgery (15). It has also already been verified that CD patients seem to be the most technically difficult group to apply the robotics procedures (16, 17). Despite the numerous benefits of these less invasive approaches, complications associated with stapled tissue continue to be a concern.

TIMING OF SURGERY

Considering that most CD patients will require surgical treatment over time (2–4), it becomes a persistent and recurrent dilemma in the daily practice of the surgeon: the decision between indicating an early surgery (incurring all the risks related to the surgical intervention) or continuing to try clinical treatments (at the risk of having to approach the patient later with an even more deteriorated clinical condition).

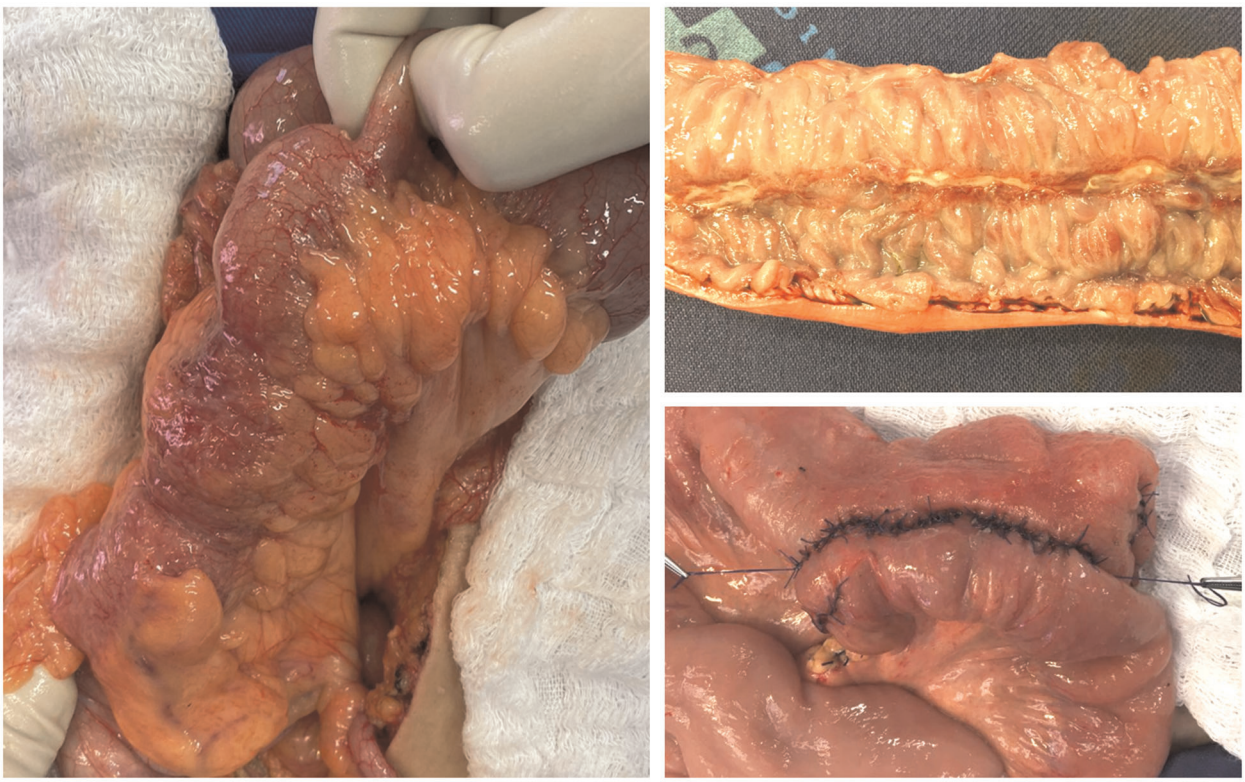

FIGURE 1 | Aspects of an anastomosis followed by an enterectomy for Crohn's disease (CD). (**A**) Surgical aspect of the ileum affected by CD. (**B**) Surgical specimen showing a longitudinal deep ulcer in the inflamed intestinal mucosa by the disease. (**C**) Side-to-side anastomosis. Source of the photographs: Colorectal Surgery Unit, Unicamp.

The literature is controversial regarding the optimal timing of surgery. Even the period that is taken into account to define a surgical intervention as early is inconstant, varying from 6 to 18 months after CD diagnosis (18, 19). Earlier surgical approaches would be related to the performance of technically easier procedures, smaller resections and consequently lower postoperative complications.

In a study performed by An et al., 31.3% of patients who were initially treated with drugs for ileocolonic CD required surgery within 5 years. In addition, patients in this cohort who underwent early surgery demonstrated a more benign course of the disease with fewer future surgical interventions and fewer hospitalizations (18). A prospective randomized controlled trial enrolling 134 localized ileocecal CD patients, demonstrated that both early and delayed resections are comparable in terms of their influence on the quality of life and that early resection is more cost-effective and associated with lower clinical recurrence (20).

Reliable predictors for the need for surgical interventions are yet to be established, to assist the surgical decision-making and individualize the treatment for each patient. Despite all the data that elucidate the advantages of performing early surgical interventions, the well-being of the patient should also be considered, especially in terms of the psychological aspects, such as anxiety, and also the consequences of surgeries such as the performance of stomas, the peri and postoperative risks, in addition to the possibility of CD recurrence even after surgical resection (21). Post-surgical complications such as infections, bleeding, anastomotic leakage, and mortality are questions that must be considered before choosing the intervention, in addition to factors such as the technical skills of the surgeons who will perform it. The final decision on the ideal moment of surgical therapy must be individualized for each patient, considering the characteristics of the disease, such as its phenotype, the risk factors involved in the process, and the patient's opinion regarding the procedure (22).

MEDICATIONS

The indication of surgical treatment for CD patients may occur in one of two different settings: emergent operations due to acute decompensating or life-threatening events in patients without a previous diagnosis, or elective operations which are indicated due to failure of clinical treatment. This distinction is relevant because in the latter situation, patients are in use of one or more drugs and it may influence the anastomotic healing process.

Conventional treatment has evolved to induce and maintain remission, thus avoiding complications, such as the need for surgical interventions. If this objective is not achieved, and the patient has to undergo surgical procedures, an evaluation of preoperative, perioperative, and postoperative medication uses is needed, and their implications for an increased risk of postoperative complications must be considered (23, 24).

Corticosteroids are anti-inflammatory drugs and have been widely used in the treatment of CD since 1950. Their use is only indicated for induction and not for maintenance of remission (25–28). However, they can have a negative influence, generating surgical complications and ineffective healing (29, 30). For elective surgeries, there is still no consensus regarding the recommendation to reduce the doses of corticosteroids before surgery, and in the studies that recommend doses reduction the preoperative interval varies from 3 to 6 weeks (13, 23, 31, 32).

Immunomodulators have been widely used for maintenance of remission or in conjunction with biological therapy to decrease surgical needs in CD patients. To date, studies have shown that its use does not adversely affect postoperative results (33, 34). Therefore, it is recommended to discontinue thiopurines on the day of surgery and reintroduce them along with all oral medications, if renal function remains normal. Methotrexate can be maintained pre-and post-operatively when the patient does not have an infection or renal failure (23, 35).

Biological medications, used in the treatment of various immune-mediated disorders, have revolutionized the treatment of CD. These medications are effective in containing inflammation and mucosal healing and reducing hospitalization and surgery rates (36–38). Despite the benefits established in the literature, this therapy has already been shown to be associated with an increased risk of postoperative septic complications in traditional abdominal surgeries for CD. Therefore, it is, recommended for elective surgeries to respect the longest possible interval between doses (e.g., 4 weeks for infliximab and a minimum of 2 weeks for adalimumab) (23, 39). Reintroduction is recommended approximately 3–4 weeks after definitive healing of the anastomosis (13).

Figure 2 summarizes the recommended management of immunosuppressors and biological therapy in CD patients who undergo abdominal surgery.

NUTRITIONAL ASPECTS

Aiming to reduce postoperative complications, surgeons have been making efforts to act beyond the surgical technique itself and control multidisciplinary perioperative issues to obtain better surgical results. In this sense, there is evidence that perioperative nutritional aspects are an important predictor of risks and complications (40).

Preoperative nutritional status is directly related to anastomotic healing since malnutrition directly interferes with collagen synthesis and fibroblast proliferation (40). Impaired preoperative nutritional status defined as anemia (hemoglobin ≤10.0 g/dL), or hypoproteinemia (albumin ≤3.2 g/dL) is significantly associated

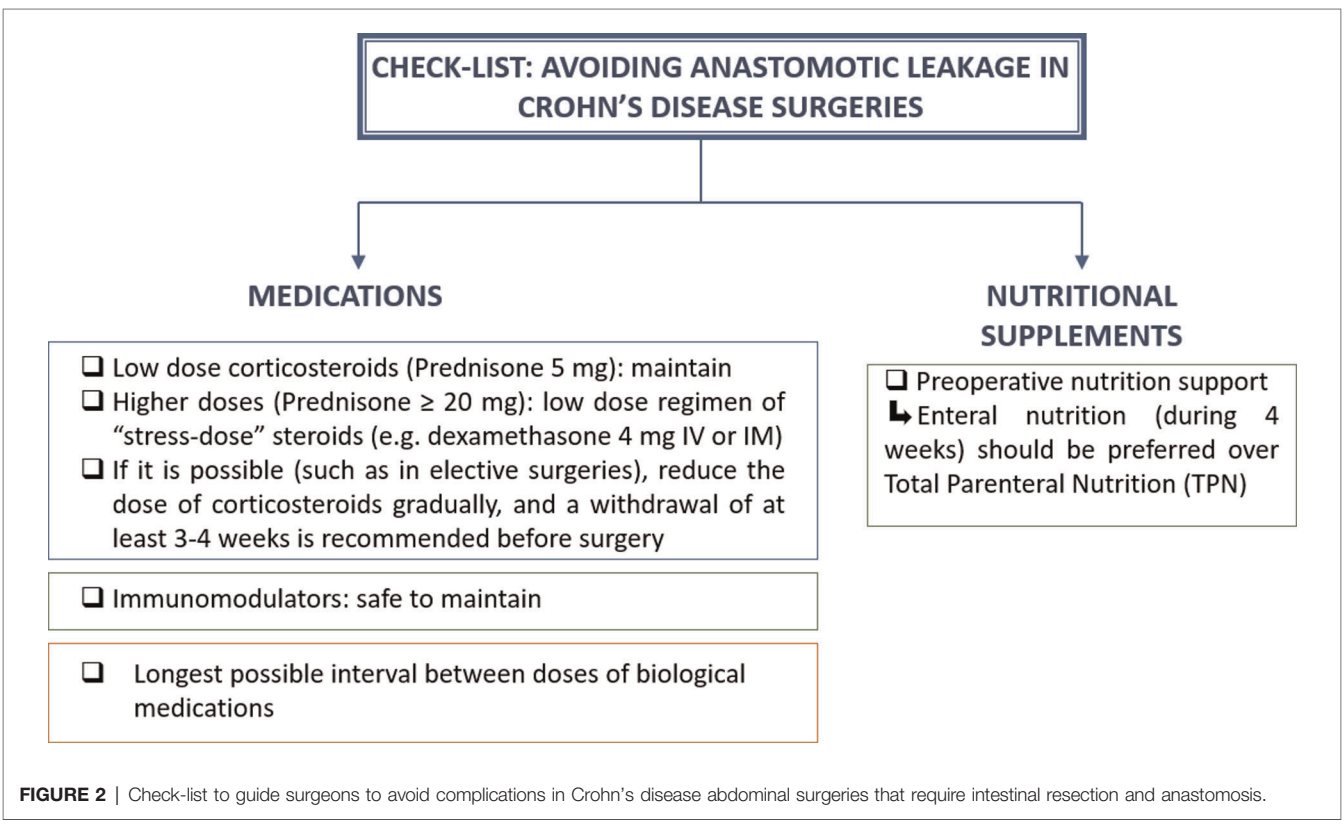

FIGURE 2 | Check-list to guide surgeons to avoid complications in Crohn's disease abdominal surgeries that require intestinal resection and anastomosis.

with complications (41). Preoperative hypoalbuminemia is an independent risk factor for intraabdominal septic complications after ileocolic resection (42, 43). These changes in perioperative albumin levels may reflect the severity of systemic inflammation, protein-losing enterocolopathy, malnutrition, or concurrent liver dysfunction (42).

In the postoperative period, malnutrition characterized by hypoalbuminemia can be a tool to identify patients at high risk of AL. Mean serum albumin levels on postoperative days 1 and 3 are significantly lower in patients that will present AL (44).

Even so, hypoalbuminemia is not a direct marker of preoperative nutritional status, nor is it the only biomarker that can be used for this purpose (42, 45). Several blood biomarkers, in addition to albumin, can be useful biochemical indicators to characterize malnutrition, even in the presence of chronic inflammation (e.g., pre-albumin, hemoglobin, total cholesterol, and total protein) (45). When malnutrition is detected in preoperative patients, nutritional optimization by enteral nutrition (EN) or total parenteral nutrition (TPN) is necessary to improve the surgical results reducing the overall rate of postoperative complications including AL (46). Nonetheless, further studies are needed to evaluate the best malnutrition biomarkers directly related to AL occurrence in CD surgeries.

The use of nutritional therapy (NT) has shown promise in modulating the inflammation in CD patients who required surgical resection, whether in exclusive or partial use (47, 48). Guo et al. evaluated the use of NT using exclusive EN with a polymeric formula that was infused continuously through a nasogastric tube (40). Two weeks of preoperative EN significantly increases albumin level, decreases C reactive protein, and also decreases AL incidence (48). Nutritional therapy in CD can reduce inflammation of intestinal and mesenteric fat, by reducing the expression of pro-inflammatory cytokines such as IL-1beta, IL-6, TNF-alpha, and leptin and increasing anti-inflammatory cytokines such as adiponectin (46, 49). This anti-inflammatory effect also may be able to improve wound healing ability (48).

The European Society for Parenteral and Enteral Nutrition has published guidelines addressing preoperative nutrition on IBD. Patients with severe nutritional risk (weight loss >10%–15% within six months; BMI <18.5 kg/m^2; serum albumin

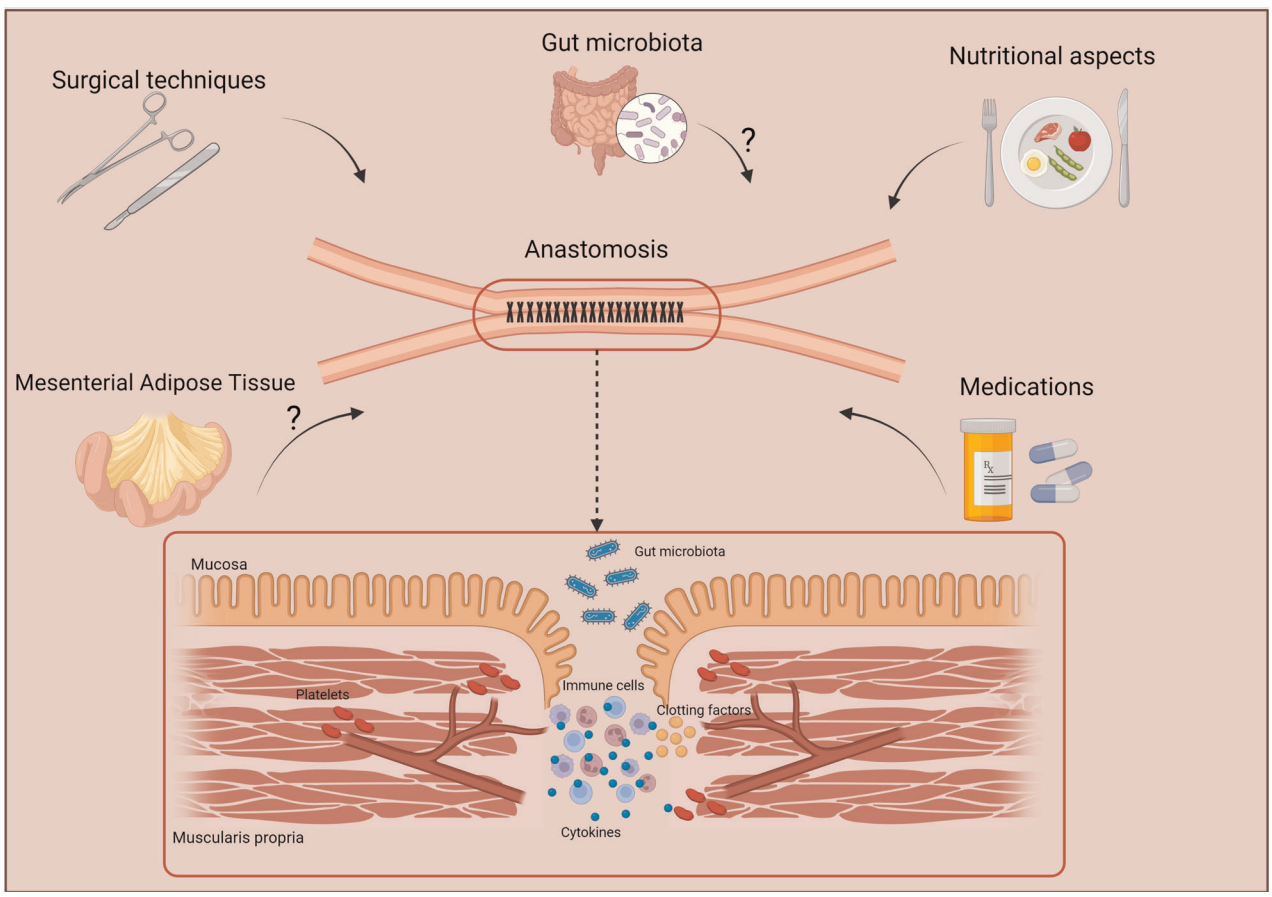

FIGURE 3 | Factors that may influence the effective healing of anastomosis. Several factors may act directly on the correct healing of anastomoses, such as nutritional factors, intestinal microbiota, medications, and the tissues nearby the intestinal affected area such as the mesenteric adipose tissue. Created with BioRender.com.

<3.0 g/dL with no evidence of liver or kidney dysfunction) should have surgery delayed for 7–14 days whenever possible (50). This period needs to be used for EN supplementation, and if there are any contraindications such as intestinal obstructions or ileum or high output fistulas, TPN should be indicated (51, 52). Although it does not specifically address only AL, a recent and comprehensive meta-analysis enrolling 1111 CD patients showed that preoperative nutritional supplementation through the use of EN is a positive prognostic factor and significantly reduced the overall rate of postoperative complications from 73.2% to 21.9% (OR = 0.09, 95% CI, 0.06–0.13, $p < 0.001$), when compared to the group that received standard nutritional care. However, a consensus about differences in specific nutrition formulations and the duration of enteral nutrition is yet to be achieved (52). Although the use of TPN did not reach statistical significance, it pointed to a trend in reducing postoperative complications.

Figure 2 also summarizes the recommended management of nutrition in CD patients who undergo abdominal surgery (**Figure 3**).

GUT MICROBIOTA

Gut microbiota has gained extensive importance in IBD pathophysiology and, thus, intraluminal microbes may also interact and have a significant influence on the anastomotic healing and consequently the risk of AL occurrence. An impaired permeable intestinal barrier can lead to exposure of the microbiota and its metabolites to various components, therefore becoming triggers for changes in physiology and the immune responses (53, 54).

Dysbiosis, a loss of balance of the intestinal microbiota, is associated with several diseases, including CD, presenting an increase in the number of pathogenic bacteria and reducing the proportion of the beneficial ones (55, 56). Thereby, CD patients have a reduction in bacteria of the genus *Firmicutes* (57), and an increase in specimens of the *Enterobacteriaceae* family (58) in their stool, when compared with healthy individuals.

Several studies have shown a relationship between intestinal microbiota and the healing process of anastomoses. In addition, external environmental factors such as comorbidities and surgeries directly impact the microbiota, being able to select and boost colonization by species considered more aggressive (59, 60). One of the products derived from the metabolism of intestinal bacteria is butyrate, a short-chain fatty acid, which acts as a source of energy for epithelial cells while decreasing their permeability and increasing the stiffness of junctions. In experimental studies, oral and rectal administration of butyrate during the perioperative period of intestinal resection demonstrated that the performed anastomoses were firmer (61). Similarly, it was demonstrated that the oral use of pectin in the rat model led to an increase in the production of short-chain fatty acid, thus contributing to accelerating the healing of the performed anastomoses (62). Although dietary factors are implicated in CD pathophysiology, the effects of dietary interventions based on fiber substrates with pectin supplementation are uncertain (63, 64).

Studies were also performed in humans to analyze the direct influence of the microbiota on the anastomoses. Comparing the microbiota of patients who had AL with that of patients whose anastomoses healed with no sign of leakage, it has been shown that patients with AL had lower microbial diversity and abundance in the *Lachnospiraceae* and *Bacteroidaceae* families, which may be directly related to AL due to its association with mucin-degrading bacteria (65).

Despite the availability of several approaches to modulation of gut microbiota for therapeutic benefit in CD patients (e.g., removal with antibiotics, replacement and reset with specific or multiple-bacteria probiotics), results to date have not found consistent evidence for the effectiveness of probiotics in these patients for the prevention of postoperative complications. Although it has been demonstrated that probiotics improve the bacterial variety, decrease the growth of pathogenic bacteria, and enhance the intestinal barrier, a detailed study demonstrating its benefit in clinical practice still lacking (66).

MESENTERIC ADIPOSE TISSUE

In recent years, MAT has gained increasing importance in the research of CD pathophysiology. Starting from the initial observation that chronic CD patients with transmural inflammation have MAT increasing nearby the affected intestinal area, alterations were found among the numerous functions of this tissue. It at least partially justifies the variations, the severity and contributes to the understanding of the disease.

Given the numerous mesentery intraoperative features found by surgeons (e.g., signs of inflammation, mesenteric thickening, edema extending circumferentially, presence of granulomata, increased mesenteric lymphatic vessel and lymph nodes density), it was postulated that inflammatory activity would result of the convergence of inflammatory inputs coming from both the submucosa and the mesentery. As a consequence, new mesenteric excision-based surgical strategies were formulated aiming to improve postoperative outcomes (67, 68).

Results from an international, multicenter, randomized controlled trial protocol comparing mesenteric excision or conservative limited resection in small intestine CD surgery, suggest that the inclusion of the mesentery during bowel resection improves the natural history of postoperative clinical and surgical recurrence of CD (11). Similarly, in another study, the mesentery resection technique was an independent determinant of postoperative recurrence rate in ileocolic resection for CD and the adoption of mesentery resection reduced the reoperation rate from 40% to 2.9% (69). Although mesenteric excision in CD may reduce postoperative disease recurrence, there is no robust data about the occurrence of morbidities, such as AL in cases that would require a larger resection of this tissue.

The extension of mesenteric resection has been evaluated to determine the effects of a more extensive or limited excision on

early postsurgical outcomes. Available data until now shows that extensive mesenteric resection is associated with a longer postoperative recurrence-free survival time (70). The involvement of MAT in CD is a fact. However, remains uncertain adequate excision extension and is still to be determined effects of MAT resection on the early postoperative period and AL rates.

A configuration of antimesenteric hand-sewn functional end-to-end anastomosis nominated "Kono-S" has been developed in 2003, based on cautious mesenteric excision, a stabilizing structure, and a wide anastomotic lumen. Since its introduction in Japan, its performance has spread around the world with cumulative evidence of favorable results. Kono-S technique is associated with a lower recurrence rate when compared to the standard hand-sewn end-to-end anastomosis (69, 71, 72). A recent meta-analysis enrolling 676 CD patients not only demonstrated a very low clinical and endoscopic recurrence rate (5% CI, 0.00–0.15) but also a small incidence of anastomotic leakage (1% CI, 0.00–0.03) (73). In addition, depending on the affected topography of the gastrointestinal tract, the surgical approach will involve the resection of specific intestinal segments and, consequently, the performance of the corresponding anastomosis. In this context, the literature data favors the Kono-S anastomosis even further when performing an ileocolic anastomosis (73, 74).

FINAL CONSIDERATIONS

The pursuit for the ideal anastomosis (technically easy, without the need for expensive materials, with a low rate of AL and low recurrence rate) is still ongoing. Based on data available until now, it is recommended to perform side-to-side anastomosis to obtain lower rates of AL. The benefits of pharmacological therapies to CD patients are irrefutable but in the perioperative setting, they may worsen the anastomotic healing process. In this sense, it is of extreme importance that the surgical team evaluate the medications that the patient uses in the context of elective surgeries to decide on their suspension or maintenance. Moreover, preoperative nutritional therapy impacts surgical outcomes by reducing AL rates. It is yet to be established whether there is a specific biomarker endpoint to be accomplished before performing elective surgeries to get lower AL rates.

Therefore, this review aimed to contribute to a better understanding of the anastomotic healing in CD patients and to highlight the factors that directly may affect it. CD is a chronic inflammatory disease that still has no cure, and many patients need surgical interventions at least once during the course of the disease. All these factors potentially involved with anastomotic healing are important and need to be analyzed carefully to provide a better outcome and avoid complications (**Figure 3**).

Concerning future developments on this topic, differences in intestinal microbiota have already been found between patients who develop AL and patients who suffered no complications in the postoperative period. This may become a future therapeutic topic. Another target worth exploring in future studies is the role of MAT in this whole process. MAT's resection demonstrably reduces disease recurrence and the need for reoperation in long-term follow-up. However, its influence on anastomotic healing and the relationship between the degree of mesenteric involvement and early postoperative complication rates in CD are two current research gaps that have yet to be addressed in the literature.

AUTHOR CONTRIBUTIONS

FHMC, LMVN, KMS, NSNS, LMG, and RFL were involved in drafting the manuscript. PSPO, CARM, MLSA, JJF, and RFL were involved in critical revision. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by National Council for Scientific and Technological Development (CNPq) [Grant no. #302557/2021-0 for R.F.L.]. K.M.S (co-author) received a doctoral scholarship from the National Council for Scientific and Technological Development (CNPq) [Grant number #140520/2019-8], N.S.N.S. (co-author) received a master's degree scholarship from the Brazilian Coordination for the Improvement of Higher Education Personnel, (CAPES - Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil), Finance Code 001, L.M.G. (co-author) received a Doctoral scholarship from the São Paulo Research Foundation (FAPESP) [Grant number #2020/01924-5].

ACKNOWLEDGMENTS

We thank Dr. Tristan Torriani for the English revision of our manuscript.

REFERENCES

1. Na SY, Moon W. Perspectives on current and novel treatments for inflammatory bowel disease. *Gut Liver*. (2019) 13(6):604–16. doi: 10.5009/gnl19019
2. Fucilini LMP, Genaro LM, Sousa DCE, Coy CSR, Leal RF, Ayrizono MLS. Epidemiological profile and clinical characteristics of inflammatory bowel diseases in a brazilian referral center. *Arq Gastroenterol*. (2021) 58(4): 483–90. doi: 10.1590/s0004-2803.202100000-87
3. Slavu I, Alecu L, Tulin A, Mihaila D, Braga V, Voiosu T, et al. Reintervention rate following emergency surgery for crohn disease. *Chirurgia (Bucur)*. (2018) 113(2):227–33. doi: 10.21614/chirurgia.113.2.227
4. Fichera A, Schlottmann F, Krane M, Bernier G, Lange E. Role of surgery in the management of Crohn's disease. *Curr Probl Surg*. (2018) 55(5):162–87. doi: 10.1067/j.cpsurg.2018.05.001
5. Group ESoCC. Predictors for anastomotic leak, postoperative complications, and mortality after right colectomy for cancer: results from an international

snapshot audit. *Dis Colon Rectum*. (2020) 63(5):606–18. doi: 10.1097/DCR.0000000000001590
6. Sparreboom CL, van Groningen JT, Lingsma HF, Wouters MWJM, Menon AG, Kleinrensink GJ, et al. Different risk factors for early and late colorectal anastomotic leakage in a nationwide audit. *Dis Colon Rectum*. (2018) 61(11):1258–66. doi: 10.1097/DCR.0000000000001202
7. Baelum JK, Qvist N, Ellebaek MB. Ileorectal anastomosis in patients with Crohn's disease. Postoperative complications and functional outcome-a systematic review. *Colorectal Dis*. (2021) 23(10):2501–14. doi: 10.1111/codi.15839
8. Johnston WF, Stafford C, Francone TD, Read TE, Marcello PW, Roberts PL, et al. What is the risk of anastomotic leak after repeat intestinal resection in patients with Crohn's disease? *Dis Colon Rectum*. (2017) 60(12):1299–306. doi: 10.1097/DCR.0000000000000946
9. Resegotti A, Astegiano M, Farina EC, Ciccone G, Avagnina G, Giustetto A, et al. Side-to-side stapled anastomosis strongly reduces anastomotic leak rates in Crohn's disease surgery. *Dis Colon Rectum*. (2005) 48(3):464–8. doi: 10.1007/s10350-004-0786-6
10. Eder P, Adler M, Dobrowolska A, Kamhieh-Milz J, Witowski J. The role of adipose tissue in the pathogenesis and therapeutic outcomes of inflammatory bowel disease. *Cells*. (2019) 8(6):628–46. doi: 10.3390/cells8060628
11. Li Y, Mohan H, Lan N, Wu X, Zhou W, Gong J, et al. Mesenteric excision surgery or conservative limited resection in Crohn's disease: study protocol for an international, multicenter, randomized controlled trial. *Trials*. (2020) 21(1):210. doi: 10.1186/s13063-020-4105-x
12. Feng JS, Li JY, Yang Z, Chen XY, Mo JJ, Li SH. Stapled side-to-side anastomosis might be benefit in intestinal resection for Crohn's disease: a systematic review and network meta-analysis. *Medicine (Baltimore)*. (2018) 97(15):e0315. doi: 10.1097/MD.0000000000010315
13. Bemelman WA, Warusavitarne J, Sampietro GM, Serclova Z, Zmora O, Luglio G, et al. ECCO-ESCP Consensus on Surgery for Crohn's Disease. *J Crohns Colitis*. (2018) 12(1):1–16. doi: 10.1093/ecco-jcc/jjx061
14. Diseases BSGoIB. Consensus guidelines for the management of inflammatory bowel disease. *Arq Gastroenterol*. (2010) 47(3):313–25. doi: 10.1590/S0004-28032010000300019
15. Hota S, Parascandola S, Smith S, Tampo MM, Amdur R, Obias V. Robotic and laparoscopic surgical techniques in patients with Crohn's disease. *Surg Endosc*. (2021) 35(8):4602–8. doi: 10.1007/s00464-020-07885-x
16. Johnson CS, Kassir A, Marx DS, Soliman MK. Performance of da Vinci Stapler during robotic-assisted right colectomy with intracorporeal anastomosis. *J Robot Surg*. (2019) 13(1):115–9. doi: 10.1007/s11701-018-0828-z
17. Crippa J, Carvello M, Kotze PG, Spinelli A. Robotic surgery in inflammatory bowel disease. *Curr Drug Targets*. (2021) 22(1):112–6. doi: 10.2174/1389450121999200820125918
18. 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(7):492–500. doi: 10.4240/wjgs.v8.i7.492
19. Zhu M, Feng Q, Xu X, Qiao Y, Cui Z, Yan Y, et al. Efficacy of early intervention on the bowel damage and intestinal surgery of Crohn's disease, based on the Lémann index. *BMC Gastroenterol*. (2020) 20(1):421. doi: 10.1186/s12876-020-01575-7
20. Stevens TW, Haasnoot ML, D'Haens GR, Buskens CJ, de Groof EJ, Eshuis EJ, et al. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: Retrospective long-term follow-up of the LIR!C trial. *Lancet Gastroenterol Hepatol*. (2020) 5(10):900–7. doi: 10.1016/S2468-1253(20)30117-5
21. Singh S, Al-Darmaki A, Frolkis AD, Seow CH, Leung Y, Novak KL, et al. Postoperative mortality among patients with inflammatory bowel diseases: a systematic review and eta-analysis of population-based studies. *Gastroenterology*. (2015) 149(4):928–37. doi: 10.1053/j.gastro.2015.06.001
22. 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(1):13–20. doi: 10.1159/000515959
23. Lightner AL, Shen B. Perioperative use of immunosuppressive medications in patients with Crohn's disease in the new "biological era". *Gastroenterol Rep (Oxf)*. (2017) 5(3):165–77. doi: 10.1093/gastro/gow046
24. Fleshner P. Expert commentary on perioperative management of biologic and immunosuppressive medications in Crohn's disease. *Dis Colon Rectum*. (2018) 61(4):431–2. doi: 10.1097/DCR.0000000000001073
25. Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. (2008) (2):CD006792. doi: 10.1002/14651858.CD006792.pub2
26. Rezaie A, Kuenzig ME, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH, et al. Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. (2015) (6):CD000296. doi: 10.1002/14651858.CD000296.pub4
27. Ford AC, Bernstein CN, Khan KJ, Abreu MT, Marshall JK, Talley NJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. (2011) 106(4):590–9, quiz 600. doi: 10.1038/ajg.2011.70
28. Steinhart AH, Ewe K, Griffiths AM, Modigliani R, Thomsen OO. Corticosteroids for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*. (2003) (4):CD000301. doi: 10.1002/14651858.CD000301
29. Subramanian V, Saxena S, Kang JY, Pollok RC. Preoperative steroid use and risk of postoperative complications in patients with inflammatory bowel disease undergoing abdominal surgery. *Am J Gastroenterol*. (2008) 103(9):2373–81. doi: 10.1111/j.1572-0241.2008.01942.x
30. Anstead GM. Steroids, retinoids, and wound healing. *Adv Wound Care*. (1998) 11(6):277–85.
31. Lightner AL. Perioperative management of biologic and immunosuppressive medications in patients with Crohn's disease. *Dis Colon Rectum*. (2018) 61(4):428–31. doi: 10.1097/DCR.0000000000001072
32. Preiß JC, Bokemeyer B, Buhr HJ, Dignaß A, Häuser W, Hartmann F, et al. [Updated German clinical practice guideline on "Diagnosis and treatment of Crohn's disease" 2014]. *Z Gastroenterol*. (2014) 52(12):1431–84. doi: 10.1055/s-0034-1385199
33. Colombel JF, Loftus EV, Tremaine WJ, Pemberton JH, Wolff BG, Young-Fadok T, et al. Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. *Am J Gastroenterol*. (2004) 99(5):878–83. doi: 10.1111/j.1572-0241.2004.04148.x
34. Aberra FN, Lewis JD, Hass D, Rombeau JL, Osborne B, Lichtenstein GR. Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. *Gastroenterology*. (2003) 125(2):320–7. doi: 10.1016/S0016-5085(03)00883-7
35. Afzali A, Park CJ, Zhu K, Hu JK, Sharma P, Sinanan MN, et al. Preoperative use of ethotrexate and the risk of early postoperative complications in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. (2016) 22(8):1887–95. doi: 10.1097/MIB.0000000000000780
36. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet*. (2017) 389(10080):1741–55. doi: 10.1016/S0140-6736(16)31711-1
37. Misselwitz B, Juillerat P, Sulz MC, Siegmund B, Brand S, Swiss IBDnet aowgotSSoG. Emerging treatment options in inflammatory bowel disease: Janus kinases, stem cells, and more. *Digestion*. (2020) 101(Suppl 1):69–82. doi: 10.1159/000507782
38. Scott FI. Infliximab versus biosimilars for IBD: is it better to fight than switch? *Dig Dis Sci*. (2020) 65(8):2158–60. doi: 10.1007/s10620-020-06283-6
39. Kienle P. Impact of modern drug therapy on surgery: Crohn's disease. *Visc Med*. (2018) 34(6):422–5. doi: 10.1159/000495127
40. Sciuto A, Merola G, De Palma GD, Sodo M, Pirozzi F, Bracale UM, et al. Predictive factors for anastomotic leakage after laparoscopic colorectal surgery. *World J Gastroenterol*. (2018) 24(21):2247–60. doi: 10.3748/wjg.v24.i21.2247
41. Zhu QL, Feng B, Lu AG, Wang ML, Hu WG, Li JW, et al. Laparoscopic low anterior resection for rectal carcinoma: Complications and management in 132 consecutive patients. *World J Gastroenterol*. (2010) 16(36):4605–10. doi: 10.3748/wjg.v16.i36.4605
42. Shah RS, Bachour S, Jia X, Holubar SD, Hull TL, Achkar JP, et al. Hypoalbuminaemia, not biologic exposure, is associated with postoperative complications in Crohn's disease patients undergoing ileocolic resection. *J Crohns Colitis*. (2021) 15(7):1142–51. doi: 10.1093/ecco-jcc/jjaa268
43. Cambi MPC, Yamamoto T, Kotze PG. Importance of nutrition and hypoalbuminaemia in postoperative morbidity in Crohn's disease: thinking

outside of the box on biologics as single risk factors. *J Crohns Colitis*. (2021) 15(8):1401–2. doi: 10.1093/ecco-jcc/jjab019
44. Shimura T, Toiyama Y, Hiro J, Imaoka H, Fujikawa H, Kobayashi M, et al. Monitoring perioperative serum albumin can identify anastomotic leakage in colorectal cancer patients with curative intent. *Asian J Surg*. (2018) 41(1): 30–8. doi: 10.1016/j.asjsur.2016.07.009
45. Zhang Z, Pereira SL, Luo M, Matheson EM. Evaluation of blood biomarkers associated with risk of malnutrition in older adults: a systematic review and meta-analysis. *Nutrients*. (2017) 9(8):829–48. doi: 10.3390/nu9080829
46. Feng Y, Li Y, Mei S, Zhang L, Gong J, Gu L, et al. Exclusive enteral nutrition ameliorates mesenteric adipose tissue alterations in patients with active Crohn's disease. *Clin Nutr*. (2014) 33(5):850–8. doi: 10.1016/j.clnu.2013.10.009
47. Levine A, Wine E, Assa A, Sigall Boneh R, Shaoul R, Kori M, et al. Crohn's disease exclusion diet plus partial enteral nutrition induces sustained remission in a randomized controlled trial. *Gastroenterology*. (2019) 157(2): 440–50.e8. doi: 10.1053/j.gastro.2019.04.021
48. Guo Z, Guo D, Gong J, Zhu W, Zuo L, Sun J, et al. Preoperative Nutritional Therapy Reduces the Risk of Anastomotic Leakage in Patients with Crohn's Disease Requiring Resections. *Gastroenterol Res Pract*. (2016) 2016:5017856. doi: 10.1155/2016/5017856
49. Yamamoto T, Nakahigashi M, Saniabadi AR, Iwata T, Maruyama Y, Umegae S, et al. Impacts of long-term enteral nutrition on clinical and endoscopic disease activities and mucosal cytokines during remission in patients with Crohn's disease: a prospective study. *Inflamm Bowel Dis*. (2007) 13(12): 1493–501. doi: 10.1002/ibd.20238
50. Bischoff SC, Escher J, Hébuterne X, Kłęk S, Krznaric Z, Schneider S, et al. ESPEN practical guideline: clinical Nutrition in inflammatory bowel disease. *Clin Nutr*. (2020) 39(3):632–53. doi: 10.1016/j.clnu.2019.11.002
51. Adamina M, Bonovas S, Raine T, Spinelli A, Warusavitarne J, Armuzzi A, et al. ECCO guidelines on therapeutics in Crohn's disease: surgical treatment. *J Crohns Colitis*. (2020) 14(2):155–68. doi: 10.1093/ecco-jcc/jjz187
52. Brennan GT, Ha I, Hogan C, Nguyen E, Jamal MM, Bechtold ML, et al. Does preoperative enteral or parenteral nutrition reduce postoperative complications in Crohn's disease patients: a meta-analysis. *Eur J Gastroenterol Hepatol*. (2018) 30(9):997–1002. doi: 10.1097/MEG.0000000000001162
53. Zulian A, Cancello R, Ruocco C, Gentilini D, Di Blasio AM, Danelli P, et al. Differences in visceral fat and fat bacterial colonization between ulcerative colitis and Crohn's disease. An in vivo and in vitro study. *PLoS One*. (2013) 8(10):e78495. doi: 10.1371/journal.pone.0078495
54. Amar J, Chabo C, Waget A, Klopp P, Vachoux C, Bermúdez-Humarán LG, et al. Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes: molecular mechanisms and probiotic treatment. *EMBO Mol Med*. (2011) 3(9):559–72. doi: 10.1002/emmm.201100159
55. Thursby E, Juge N. Introduction to the human gut microbiota. *Biochem J*. (2017) 474(11):1823–36. doi: 10.1042/BCJ20160510
56. Elson CO, Alexander KL. Host-microbiota interactions in the intestine. *Dig Dis*. (2015) 33(2):131–6. doi: 10.1159/000369534
57. Manichanh C, Rigottier-Gois L, Bonnaud E, Gloux K, Pelletier E, Frangeul L, et al. Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. *Gut*. (2006) 55(2):205–11. doi: 10.1136/gut.2005.073817
58. Seksik P, Rigottier-Gois L, Gramet G, Sutren M, Pochart P, Marteau P, et al. Alterations of the dominant faecal bacterial groups in patients with Crohn's disease of the colon. *Gut*. (2003) 52(2):237–42. doi: 10.1136/gut.52.2.237
59. Yu YN, Fang JY. Gut Microbiota and Colorectal Cancer. *Gastrointest Tumors*. (2015) 2(1):26–32. doi: 10.1159/000380892
60. Lucke K, Miehlke S, Jacobs E, Schuppler M. Prevalence of Bacteroides and Prevotella spp. in ulcerative colitis. *J Med Microbiol*. (2006) 55(Pt 5): 617–24. doi: 10.1099/jmm.0.46198-0
61. Bosmans JW, Jongen AC, Boonen BT, van Rijn S, Scognamiglio F, Stucchi L, et al. Comparison of three different application routes of butyrate to improve colonic anastomotic strength in rats. *Int J Colorectal Dis*. (2017) 32(3): 305–13. doi: 10.1007/s00384-016-2718-z
62. Yamada F, Endo N, Miyatake S, Ebisu G, Hino K. Enteral feeding with low-methoxyl pectin accelerates colonic anastomosis healing in rats. *Nutrition*. (2018) 45:94–8. doi: 10.1016/j.nut.2017.07.013
63. Limketkai BN, Iheozor-Ejiofor Z, Gjuladin-Hellon T, Parian A, Matarese LE, Bracewell K, et al. Dietary interventions for induction and maintenance of remission in inflammatory bowel disease. *Cochrane Database Syst Rev*. (2019) 2:CD012839. doi: 10.1002/14651858.CD012839.pub2
64. Gerasimidis K, Nichols B, McGowan M, Svolos V, Papadopoulou R, Kokkorou M, et al. The effects of commonly consumed dietary fibres on the gut microbiome and its fibre fermentative capacity in adults with inflammatory bowel disease in remission. *Nutrients*. (2022) 14(5):1053–67. doi: 10.3390/nu14051053
65. van Praagh JB, de Goffau MC, Bakker IS, Harmsen HJ, Olinga P, Havenga K. Intestinal microbiota and anastomotic leakage of stapled colorectal anastomoses: a pilot study. *Surg Endosc*. (2016) 30(6):2259–65. doi: 10.1007/s00464-015-4508-z
66. Glassner KL, Abraham BP, Quigley EMM. The microbiome and inflammatory bowel disease. *J Allergy Clin Immunol*. (2020) 145(1):16–27. doi: 10.1016/j.jaci.2019.11.003
67. Coffey JC, O'Leary DP, Kiernan MG, Faul P. The mesentery in Crohn's disease: friend or foe? *Curr Opin Gastroenterol*. (2016) 32(4):267–73. doi: 10.1097/MOG.0000000000000280
68. Peltrini R, Bucci L. "Mesentery-based surgery" to prevent surgical recurrence in Crohn's disease: from basics to surgical practice. *Int J Colorectal Dis*. (2019) 34(2):353–4. doi: 10.1007/s00384-018-3197-1
69. Coffey CJ, Kiernan MG, Sahebally SM, Jarrar A, Burke JP, Kiely PA, et al. Inclusion of the mesentery in ileocolic resection for crohn's disease is associated with reduced surgical recurrence. *J Crohns Colitis*. (2018) 12(10): 1139–50. doi: 10.1093/ecco-jcc/jjx187
70. Zhu Y, Qian W, Huang L, Xu Y, Guo Z, Cao L, et al. Role of extended mesenteric excision in postoperative recurrence of Crohn's colitis: a single-center study. *Clin Transl Gastroenterol*. (2021) 12(10):e00407. doi: 10.14309/ctg.0000000000000407
71. Alshantti A, Hind D, Hancock L, Brown SR. The role of Kono-S anastomosis and mesenteric resection in reducing recurrence after surgery for Crohn's disease: a systematic review. *Colorectal Dis*. (2021) 23(1):7–17. doi: 10.1111/codi.15136
72. Kono T, Fichera A. Surgical treatment for Crohn's disease: a role of Kono-S Anastomosis in the West. *Clin Colon Rectal Surg*. (2020) 33(6):335–43. doi: 10.1055/s-0040-1714236
73. Ng CH, Chin YH, Lin SY, Koh JWH, Lieske B, Koh FH, et al. Kono-S anastomosis for Crohn's disease: a systemic review, meta-analysis, and meta-regression. *Surg Today*. (2021) 51(4):493–501. doi: 10.1007/s00595-020-02130-3
74. Luglio G, Rispo A, Imperatore N, Giglio MC, Amendola A, Tropeano FP, et al. Surgical prevention of anastomotic recurrence by excluding mesentery in Crohn's disease: the SuPREMe-CD study - a randomized clinical trial. *Ann Surg*. (2020) 272(2):210–7. doi: 10.1097/SLA.0000000000003821

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Surgery

TYPE Review
PUBLISHED 22 July 2022
DOI 10.3389/fsurg.2022.905049

OPEN ACCESS

EDITED BY
Hans Martin Schardey,
Agatharied Hospital GmbH, Germany

REVIEWED BY
Cihangir Akyol,
Ankara University, Turkey
Qingsen Shang,
Ocean University of China, China
Shima Hadifar,
Pasteur Institute of Iran (PII), Iran

*CORRESPONDENCE
Matthias Kelm
Kelm_M@ukw.de

SPECIALTY SECTION
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

RECEIVED 26 March 2022
ACCEPTED 06 July 2022
PUBLISHED 22 July 2022

CITATION
Kelm M and Anger F (2022) Mucosa and microbiota – the role of intrinsic parameters on intestinal wound healing.
Front. Surg. 9:905049.
doi: 10.3389/fsurg.2022.905049

Mucosa and microbiota – the role of intrinsic parameters on intestinal wound healing

Matthias Kelm* and Friedrich Anger

Department of General, Visceral, Transplant, Vascular and Pediatric Surgery, University Hospital of Wuerzburg, Wuerzburg, Germany

Mucosal healing in the gut is an essential process when it comes to chronic inflammatory disorders such as inflammatory bowel diseases (IBD) but also to the creation of intestinal anastomosis. Despite an improvement of surgical techniques, the rates of anastomotic leakage remain substantial and represent a significant health-care and socio-economic burden. Recent research has focused on intrinsic factors such as mucosal linings and differences in the intestinal microbiota and identified specific endoluminal bacteria and epithelial proteins which influence intestinal wound healing and re-establishment of mucosal homeostasis. Despite the lack of large clinical studies, previous data indicate that the identified bacteria such as aerotolerant lactobacilli or wound-associated Akkermansia muciniphila as well as epithelial-expressed sialyl Lewis glycans or CD47 might be critical for wound and anastomotic healing in the gut, thus, providing a potential novel approach for future treatment strategies in colorectal surgery and IBD therapy. Since microbiota and mucosa are interacting closely, we outline the current discoveries about both subsets in this review together to demonstrate the significant interplay

KEYWORDS
epithelial cells, mucosal healing (MH), microbiota, inflammatory bowel disease, anastomotic leakage

Introduction

Impaired intestinal mucosal healing is a hallmark of inflammatory bowel diseases (IBD) and anastomotic leakage. Current IBD treatment mainly focuses on the immune system but the numbers of patients who still require surgery or suffer from side effects remain high (1). Since the incidence of IBD is increasing worldwide and numbers of anastomotic leakage remain significant (2, 3), insufficient mucosal healing represents a major socioeconomic burden making the development of novel therapeutic approaches urgently necessary to improve patient care. While endoscopic assessment of mucosal healing represents an established parameter to evaluate disease development (4, 5), specific treatment strategies to enhance wound healing are lacking. Therefore, an improved understanding of interactions between various gut-specific factors on wound healing and reconstitution of mucosal homeostasis is crucial.

The selectively and dynamically permeable barrier between luminal components and the basolateral membrane is established and maintained by the epithelium consisting of enterocytes and goblet cells. Intercellular connections between the epithelial cells are

formed by intercellular junctions, namely the tight junctions, adherence junctions, desmosomes and gap junctions (6, 7). The goblet cells cover the intestinal epithelium with a mucus layer, which varies in terms of thickness, organization and composition. The small intestine is coated with a single thin, loose and penetrable layer, probably due to the rather sparse colonization and the antimicrobial peptides secreted from Paneth cells (8, 9). In the colon, the mucus consists of two layers, a loose outer layer and a dense inner layer attached to the epithelium (10). The inner layer serves as a physical barrier, while the outer layer provides a habitat and food source for certain commensal microbe populations. Due to this complexity, adequate reconstitution of the intestinal mucosa is crucial to maintain homeostasis of epithelial linings.

The increasing relevance of intestinal wound healing given and the significance of its dysregulation on patients (11), future therapeutic strategies will broaden the focus on aspects to improve mucosal repair. While this approach offers great potential, further research is necessary to enhance our knowledge about interactions between mucosal and luminal factors. In this review, we address the current roles of epithelial cells and microbiota in intestinal wound healing and discuss potential therapeutic strategies.

Mucosal healing in the gut

Dysfunctional healing of the intestinal mucosa affects a large spectrum of patients resulting in a significant clinical relevance (12). Importantly, mucosal healing remains to be a double-edged sword since it has to be taken into account that persistent inflammation can result in uncontrolled overstimulation of proliferative pathways leading to the formation of neoplastic lesion and subsequent carcinogenesis. While reasons for the initial mucosal damage can be inflammation- or mechanical-related, mechanisms of wound repair are largely independent of the cause and consist of a multi-step process with various factors and cell types being involved (13). The complex process of mucosal healing, which needs to be clearly distinguished from the daily perpetual epithelial renewal driven by progenitor and stem cells, is well-regulated but dysregulation at any stage might result in insufficient wound closure with compromised gastrointestinal function or leakage. Importantly, maintaining adequate mucosal homeostasis consists of more than just closure of the epithelial lining since the intestinal mucosa is responsible to preserve barrier function but also to transport nutrients (14, 15). While factors such as environmental aspects or vascular insufficiency due to atherosclerosis, diabetes, aging or smoking are also relevant for wound healing in the gut, they are characterized by a different pathobiology and need to be addressed systemically. In contrast, factors which can be addressed locally and contribute to mucosal homeostasis and wound repair are epithelial cells and microbiota. Both sites are interacting closely and demonstrate a significant impact on the multi-step process of mucosal healing but despite that fact, they have no role in current treatment concepts. While clinicians and scientists mainly focused on interactions between microbiota and the local immune system in the past, recent studies have addressed the role of mucosa-associated microbiota with the relationship between epithelial cells and luminal bacteria being crucial for health and disease (16, 17).

The role of epithelial cells and junctional proteins on intestinal wound healing

The coordination of the multi-step process of intestinal wound repair depends on the complex interplay between epithelial cells, immune cells and microbiota (18, 19). It consists of several overlapping stages which result in the re-establishment of the epithelial barrier through successful wound closure. After initial homeostasis, the inflammatory stage is driven by mucosal injury and mainly defined by the infiltration of neutrophils followed by macrophages and monocytes (20). In parallel and partially triggered by inflammation, epithelial cells remodel their cytoskeleton and start migrating and proliferating to achieve epithelial restitution. Finally, the restoration of mucosal homeostasis is completed by the differentiation of wound-associated epithelial cells (18).

Epithelial cells have an important role in segregating the intestinal microbiota from mucosal and submucosal linings but they are also participating in different pathways resulting in adequate mucosal healing. Various chemokines and growth factors are involved in the complex process of intestinal wound repair. For instance, small GTPases of the Rho family such as Rho and Rac contribute to the remodeling of the cytoskeleton with epidermal growth factor (EGF) and hepatocyte growth factor (HGF) and their signaling pathways leading to mucosal restitution and cell proliferation (21, 22). While the role of those factors and proteins is well established, recent studies have focused on the role of epithelial cells and their junctional proteins in regard to intestinal wound repair. In line with the relevance of GTPases mentioned before, Flemming et al. showed that loss of Desmocollin-2 (Dsc-2), a desmosomal cadherin, significantly delays epithelial cell migration in the gut due to the altered activity of GTPase Rap1 (23). While it remains to be confirmed that Dsc-2 controls Rap1 *via* Pkp3, the authors also demonstrated a functional interplay between Dsc-2 and integrin $\beta 1$ and $\beta 4$, thus, arguing for Dsc-2 as a key contributor in intestinal mucosal healing. In contrast, Desmoglein-2, another desmosomal cadherin which interacts closely with Dsc-2, is required for intestinal barrier integrity

(24), but no effect on mucosal healing has been demonstrated to date, thus, underlining the complex interplays and functions of junctional proteins.

In line with the important role of epithelial cells and its junctions for intestinal wound repair, Reed et al. demonstrated that epithelial-expressed CD47 significantly effects mucosal healing *in vitro* and *in vivo* (25). While selective intestinal knockout of CD47 resulted in decreased mucosal healing following DSS colitis and biopsy wounding, it was shown that CD47 regulates mucosal repair again through a β1 integrin-dependent FAK-Src-p130Cas pathway. Similarly, other studies provide additional evidence for a direct effect of CD47 expression through that signaling pathway on intestinal wound closure. CD47 might be linked to FAK *via* TSP-1 and TGF-β1 but the mechanistic connection of CD47 to TSP-1 and TGF-β1 is currently missing and needs to be proven in the future (26, 27). Interestingly, while CD47 is a glycoprotein, the functional role of glycans located at the intestinal epithelium in general and its effect on wound repair in particular receives increasing attention in recent years. We could show that targeting of sialyl Lewis glycans located on Cd44v6 on the apical site of intestinal epithelial cells positively effect intestinal wound healing *in vitro* and *in vivo* (28). While sialyl Lewis glycans are highly upregulated during chronic inflammatory bowel diseases such as Crohn's Disease and Ulcerative Colitis, antibody-mediated ligation of epithelial expressed sialyl Lewis glycans significantly enhances epithelial cell proliferation and migration by activating a signaling pathway downstream of CD44v6 including Src-FAK (28). In line with that, there is an increasing focus on glycolisation of cells such as intestinal epithelial cells and its functional aspect while the relevance of glycans in wound repair has been addressed in other studies as well (29–31).

Based on the evidence presented above, the role of junctional proteins connecting epithelial cells in the gut might have been understated in the past. Future studies will demonstrate if other proteins related to tight and adhesion junctions are not only contributing to epithelial barrier stabilization but also to signaling pathways resulting in adequate mucosal healing. Following that, it might not be surprising that wound repair and barrier function are closely related and should be addressed collectively. However and regardless of future studies, intestinal epithelial cells and its junctional proteins can already be seen as major players in mucosal healing in the gut.

The role of microbiota on intestinal wound healing

Born sterile, the neonatal intestinal tract is soon colonized with commensal enteric bacteria. Although the temporal patterns of colonization and the formation of a complex and dynamic ecosystem are unique to each infant, the composition and functional capabilities of the microbiota resemble those of an adult at the age of around 2.5 years (32–34). The total number of commensal bacteria vary greatly between the different sections of the gastrointestinal tract and reach their peak in the ascending colon. About 2,100 species classified into 12 different phyla were identified in humans, but 90% of the species belong to one of the four following phyla: *Proteobacterio, Actinobacteria, Firmicutes and Bacteroidetes* (35). The symbiosis between microbiota and host is part of an ongoing evolutionary process that established a barrier function with a separation the colonized microbes from the systemic tissues on the one hand, but providing a gateway for a physiologically relevant cross-talk on the other hand.

In case of an intestinal wound due to physical trauma, infection or inflammatory conditions, the intestinal barrier is dysfunctional, changing the interplay of microbiota and systemic tissue. Depending on the composition of the microbiota prior or even immediately after wounding, healing might be promoted or disturbed. Commensal bacteria seem to promote the initial stage of epithelial restitution as studies in germ-free mice showed impaired rates of epithelial cell migration (36, 37). Cell migration is critically dependent upon the formation of focal adhesions (38), a link between the extracellular matrix and the cytoplasmic cytoskeleton of the migrating cell which is controlled by an enzyme called focal adhesion kinase. Several studies were able to show that enteric microbiota activate focal adhesion kinase, thereby enhance epithelial restitution and promote repair of mucosal wounds in a redox-dependent manner (39–42). The commensal microbiota also influences the development and training of the innate and adaptive immune system (43). This process is modulated by pattern recognition receptor (PPR) expressed on intestinal epithelial cells (44). They include Toll-like receptors (TLR) amongst others and recognize microbe-associated molecular patterns (MAMPs) from commensal microbiota (45). The TLR signaling regulates the production of antimicrobial peptides, which in turn are required to prevent microbial encroachments towards the intestinal mucosa and thereby preserve gut homeostasis (46). However, TLR was found to be expressed on intestinal stem cells as well, inhibiting cellular proliferation in the intestinal crypts by microbial ligand-mediated activation (47). Moreover, enterocyte-specific TLR4 activation *via* LPS resulted in an increase of intestinal stem cell apoptosis, following the pathogenic pathway of necrotizing enterocolitis. On the other hand, there are studies providing evidence, that the cytosolic bacterial sensor Nod2 stimulates stem cell survival of intestinal organoids upon activation by peptidoglycan motifs (48). These muramyl dipeptides (MDP) is common on all bacteria, but crypt resident bacteria have been identified (49) and the released MDP may have a protective effect on intestinal stem cells (48). The close crosstalk between microbiota and intestinal epithelial cells seems to affect

proliferation of enterocytes and consecutively the repair of intestinal wound healing. However, the course for regenerative capacity of the intestinal epithelial might be set early in life and dependent on the microbial colonization. Germ-free born mice co-housed with specific-pathogen free mice during weaning, showed endured changes in gene expression, especially erythroid differentiation regulator-1 (Erdr1). It localizes to intestinal stem and transit amplifying cells, which differentiate into all epithelial lineages including Paneth cells, tuft cells, enteroendocrine cells, goblet cells, and enterocytes along crypt-villus axis. As a consequence, mice would show increased intestinal epithelial proliferation and regeneration in response to mucosal damage (50).

Infiltrating immune cells, such as macrophages, are important components of the intestinal wound healing. Microbial metabolites or cell wall components affect the polarization of macrophaghes to a M2 state in a mouse model of colitis, augmenting intestinal wound healing (51). In case of inflammation or wounding of the gut, transmigrating neutrophils accumulate in the injured mucosa, altering the physiological parameters of the local microenvironment, which is mostly due to a decrease in oxygen levels resulting from the formation of reactive oxygen species (52). In addition, the amount of mucins, as a relevant food supply to the microbiota, is shortened in mucosal wounds (53), thus, affecting local microbial composition and maybe to some extent individual wound healing. On the contrary, Wrzosek et al. reported an increase in goblet cell differentiation and mucus production when *Bacteroides thetaiotaomicron* and *Faecalibacterium prausnitzii*, two short-chain fatty acids-producing bacteria, were introduced to germ-free mice and colonized their guts (54). Microbial metabolites seem to have various effects on the architecture and functions of the intestinal barrier. Short-chain fatty acids were shown to enhance epithelial proliferation and differentiation and support the restauration of the epithelial barrier upon tissue damage (55, 56). In mice, *Bacteroides ovatus* alleviated lipopolysaccharide-induced inflammation (57). Furthermore, *Bacteroides ovatus* produces indole-3-acetic acid that most likely promotes IL-22 production by immune cells, yielding beneficial effects in a mice colitis model (58). In a mouse endoscope-wounding model, creating uniform lesion in the colonic mucosa of wild type mice, the abundance of anaerobic bacteria (*Akkermansia spp.*) increased substantially in early regenerative mucosa. In this study *Akkermansia muciniphilia* was applied intrarectally and mice showed superior wound closure and increased proliferation of enterocytes compared to mice that received inert control. However, this effect was dependent on the presence of the Fpr1 gene, which encodes for a necessary protein for respiratory burst in neutrophils (52).

However, despite the great potential of the microbiota and mucosal healing, another important aspect of microbiota-associated wound healing is the potential association between microbial composition and inflammation-associated carcinogenesis. Due to the great effects on cell proliferation and barrier integration, specific microbial species have also been demonstrated to facilitate the formation of pre-neoplastic lesions with one study showing a different microbial diversity in patients with IBD-related colorectal cancer. The importance is further underlined by different incidences between IBD-related colon and small bowel cancers which might be related to differences in microbial compositions. Therefore, further research is necessary to address this issue to evaluate the impact of the microbial diversity on the overall IBD-cancer prognosis as well as to identify the potential of probiotics to limit the overgrowth of pathogenic microbial species.

In a nutshell, there is consistently increasing evidence that intestinal wound healing is orchestrated by the microbial-epithelial interface (**Figure 1**). However, due to the inter-individual differences in the composition of the enteric microbiota, potential dysbiosis in commensal and pathogenic microbes and the circumstances under which the mucosal wounding occurs will challenge the results of this fundamental research in a bench-to-bedside translation. In addition, the enteric microbiota generates a vast variety of metabolites of largely unknown functions in the modulation of host cellular events.

Future aspects

While the medical history teaches the pathophysiological misleading thesis of monomicrobial infections (59), the results on the fundamental research of the microbial-epithelial interface make it hard to believe that a single pathogenic microbe is causative for the underlying disease. While the mere presence of a pathogen will not cause the disease, it is a multifactorial disorder that leads to dysbiosis and ultimately the abundance of the microbe which meanwhile gained or activated virulence genes turning into a harmful aggressor for the host. In surgically created intestinal wounds, the use of antimicrobial or immunosuppressive drugs, extent and length of surgery, and early recovery pathways including nutritional aspects will have a relevant impact on the changes in enteric microbiota and thus on the healing of intestinal wounds. In endogenously developed intestinal wounds, e.g. due to inflammatory bowel disease, changes in microbiota might be a consequence of previous intestinal barrier breakdown as a function of dysfunctional intercellular adhesions or misguided inflammation. While there is data suggesting that Collagenase-producing and antibiotic-resistant organisms are more prevalent in anastomotic leak infections, precise adjustments in clinical management to prevent the local dysbiosis remain to be found (60). A promising approach seems to be a dietary change prior to surgery showing a preventive effect in developing anastomotic leakage after colostomy in mice (61).

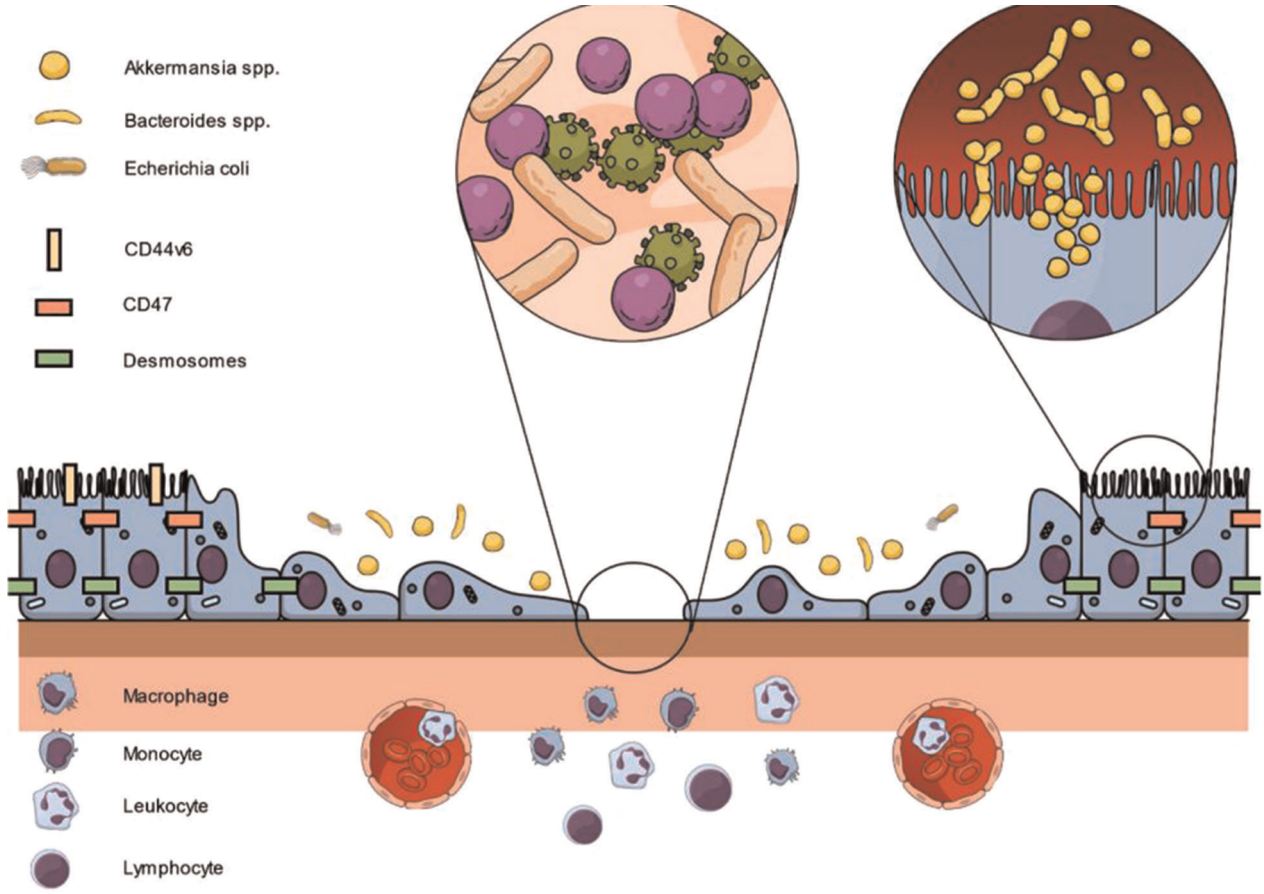

FIGURE 1
Interaction between epithelial cells, junctional proteins and microbiota on intestinal wound healing to restore mucosal homeostasis. Following epithelial injury, proteins such as CD44v6 or CD47 are upregulated at epithelial cells adjacent to the wound. In addition, luminal microbes are in close contact with intact epithelial cells. As a result, cell proliferation and migration is controlled and supported by the presented pathways to restore epithelial linings.

In addition, the transfer of living microorganisms, mostly Lactobacillus phyla, has exerted benefical effects on mucosal healing in murine models of DSS-colitis and gastric ulcera (62).

Besides addressing the microbiota, targeting proteins on intestinal epithelial cells such as desmosomes, CD47 or sialyl Lewis glycans relevant for epithelial migration and proliferation with novel medication has great potential as well and offers another target to improve intestinal mucosal healing (23–25, 28). To date, current research demonstrates great effects on wound healing but the promising results are limited to *in vivo* experiments, thus, translation to clinical studies is necessary to evaluate the disease-specific relevance in detail. Based on the postulated results, the innovative approach of targeting mucosal healing for therapy of IBD or to support anastomotic healing looks to be particularly promising. However, relevant questions such as how to obtain adequate local levels of the applicated substance by either oral or intravenous administration remain to be answered. In case of anastomotic healing, local application or injection could be an interesting approach which needs to be evaluated as well. Moreover, while for sialyl Lewis glycans antibody-targeting by GM35 to block shedding of the v6 domain from CD44v6 is necessary to support wound healing (28), for desmosomes and CD47 upregulation is aspired (23–25). Promising mechanisms for protein upregulation in humans are lacking, thus, more research is necessary to develop a realistic strategy for the latter proteins. In line with that, targeting and enhancing the involved pathways such as the β1 integrin-dependent FAK-Src-p130Cas pathway is an alternative which can be translated to clinical aspects more easily. Importantly, striving for a limited local effect of the administered agent is particularly relevant for CD47 since it is an ubiquitously expressed protein and a systemic impact of medical targeting of CD47 cannot be completely estimated upfront.

Finally, and most importantly, further development of treatment strategies does not mean to leave established aspects

and concepts such as anti-inflammatory and immunosuppressive medication behind but to complement the current therapeutic regimen. Therefore, optimal disease-specific therapy should consider all aspect of the pathophysiology including epithelial cells, immune cells and microbiota in the future and will combine different targets to address mucosal healing better and to improve patient outcome.

Conclusion

Recent research has demonstrated a major role of intestinal epithelial cells as well as microbiota on adequate mucosal healing in the gut with a close interaction between both sites. All targets involve the key intrinsic parameters of intestinal wound healing: The systemic condition of the patient, the mucosal cells, resident and transmigrating immune cells, and the enteric microbiota, both commensal and pathogenic (**Figure 1**). However, mucosal healing remains a double-edged sword since overstimulation of proliferative pathways can results in neoplastic lesions. Based on the postulated results, a repetitive re-evaluation of established principles for adequate wound repair in the gut is necessary to improve patient outcomes and disease control in the short- and long-term. To date, therapies of IBD and anastomotic healing mainly focus on immunosuppression and surgical aspects. However, the complex interplay not only of immune cells but also of junctional proteins and microbiota needs to be addressed in future studies and novel therapeutic protocols. Therefore, future investigators will need to consider all parameters in trying to piece this complex puzzle together. For clinicians, protection or restoration of the intestinal homeostasis should be the ultimate goal in the treatment of intestinal wounds.

Author contributions

MK and FA contributed to conception and design of the study and wrote the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Burisch J, Kiudelis G, Kupcinskas L, Kievit HAL, Andersen KW, Andersen V, et al. Natural disease course of Crohn's Disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study. *Gut*. (2019) 68(3):423–33. doi: 10.1136/gutjnl-2017-315568

2. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. *Br J Surg*. (2015) 102(5):462–79. doi: 10.1002/bjs.9697

3. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet*. (2017) 390 (10114):2769–78. doi: 10.1016/S0140-6736(17)32448-0

4. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm Bowel Dis*. (2009) 15(9):1295–301. doi: 10.1002/ibd.20927

5. Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. 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(1):3–25. doi: 10.1093/ecco-jcc/jjw168

6. Farkas AE, Nusrat A. Pharmacological targeting of the inflamed intestinal barrier. *Curr Pharm Des*. (2016) 22(35):5400–14. doi: 10.2174/1381612822666160726123857

7. Laukoetter MG, Bruewer M, Nusrat A. Regulation of the intestinal epithelial barrier by the apical junctional complex. *Curr Opin Gastroenterol*. (2006) 22 (2):85–9. doi: 10.1097/01.mog.0000203864.48255.4f

8. Ermund A, Gustafsson JK, Hansson GC, Keita AV. Mucus properties and goblet cell quantification in mouse, rat and human ileal Peyer's Patches. *PLoS One*. (2013) 8(12):e83688. doi: 10.1371/journal.pone.0083688

9. Ermund A, Schutte A, Johansson ME, Gustafsson JK, Hansson GC. Studies of mucus in mouse stomach, small intestine, and colon. I. Gastrointestinal mucus layers have different properties depending on location as well as over the Peyer's Patches. *Am J Physiol Gastrointest Liver Physiol*. (2013) 305(5):G341–7. doi: 10.1152/ajpgi.00046.2013

10. Johansson ME, Larsson JM, Hansson GC. The two mucus layers of colon are organized by the MUC2 mucin, whereas the outer layer is a legislator of host-microbial interactions. *Proc Natl Acad Sci USA*. (2011) 108(Suppl 1):4659–65. doi: 10.1073/pnas.1006451107

11. Neurath MF. New targets for mucosal healing and therapy in inflammatory bowel diseases. *Mucosal Immunol*. (2014) 7(1):6–19. doi: 10.1038/mi.2013.73

12. Pineton de Chambrun G, Peyrin-Biroulet L, Lémann M, Colombel JF. Clinical implications of mucosal healing for the management of IBD. *Nat Rev Gastroenterol Hepatol*. (2010) 7(1):15–29. doi: 10.1038/nrgastro.2009.203

13. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. *Gut*. (2012) 61(11):1619–35. doi: 10.1136/gutjnl-2012-302830

14. Luissint AC, Parkos CA, Nusrat A. Inflammation and the intestinal barrier: leukocyte-epithelial cell interactions, cell junction remodeling, and mucosal repair. *Gastroenterology*. (2016) 151(4):616–32. doi: 10.1053/j.gastro.2016.07.008

15. Abraham C, Medzhitov R. Interactions between the host innate immune system and microbes in inflammatory bowel disease. *Gastroenterology*. (2011) 140(6):1729–37. doi: 10.1053/j.gastro.2011.02.012

16. Daniel N, Lécuyer E, Chassaing B. Host/microbiota interactions in health and diseases-time for mucosal microbiology!. *Mucosal Immunol*. (2021) 14 (5):1006–16. doi: 10.1038/s41385-021-00383-w

17. Kayama H, Okumura R, Takeda K. Interaction between the microbiota, epithelia, and immune cells in the intestine. *Annu Rev Immunol*. (2020) 38:23–48. doi: 10.1146/annurev-immunol-070119-115104

18. Sommer K, Wiendl M, Müller TM, Heidbreder K, Voskens C, Neurath MF, et al. Intestinal mucosal wound healing and barrier integrity in IBD-crosstalk and trafficking of cellular players. *Front Med (Lausanne)*. (2021) 8:643973. doi: 10.3389/fmed.2021.643973

19. Chang JT. Pathophysiology of inflammatory bowel diseases. *N Engl J Med*. (2020) 383(27):2652–64. doi: 10.1056/NEJMra2002697

20. Brazil JC, Quiros M, Nusrat A, Parkos CA. Innate immune cell-epithelial crosstalk during wound repair. *J Clin Invest*. (2019) 129(8):2983–93. doi: 10.1172/JCI124618

21. Okamoto R, Watanabe M. Molecular and clinical basis for the regeneration of human gastrointestinal epithelia. *J Gastroenterol*. (2004) 39(1):1–6. doi: 10.1007/s00535-003-1259-8

22. Yamaguchi N, Mizutani T, Kawabata K, Haga H. Leader cells regulate collective cell migration via Rac activation in the downstream signaling of integrin β1 and PI3K. *Sci Rep*. (2015) 5:7656. doi: 10.1038/srep07656

23. Flemming S, Luissint AC, Kusters DHM, Raya-Sandino A, Fan S, Zhou DW, et al. Desmocollin-2 promotes intestinal mucosal repair by controlling integrin-dependent cell adhesion and migration. *Mol Biol Cell*. (2020) 31(6):407–18. doi: 10.1091/mbc.E19-12-0692

24. Gross A, Pack LAP, Schacht GM, Kant S, Ungewiss H, Meir M, et al. Desmoglein 2, but not desmocollin 2, protects intestinal epithelia from injury. *Mucosal Immunol*. (2018) 11(6):1630–9. doi: 10.1038/s41385-018-0062-z

25. Reed M, Luissint AC, Azcutia V, Fan S, O'Leary MN, Quiros M, et al. Epithelial CD47 is critical for mucosal repair in the murine intestine in vivo. *Nat Commun*. (2019) 10(1):5004. doi: 10.1038/s41467-019-12968-y

26. Horowitz JC, Rogers DS, Sharma V, Vittal R, White ES, Cui Z, et al. Combinatorial activation of FAK and AKT by transforming growth factor-beta1 confers an anoikis-resistant phenotype to myofibroblasts. *Cell Signal*. (2007) 19 (4):761–71. doi: 10.1016/j.cellsig.2006.10.001

27. Gao AG, Lindberg FP, Dimitry JM, Brown EJ, Frazier WA. Thrombospondin modulates alpha v beta 3 function through integrin-associated protein. *J Cell Biol*. (1996) 135(2):533–44. doi: 10.1083/jcb.135.2.533

28. Kelm M, Quiros M, Azcutia V, Boerner K, Cummings RD, Nusrat A, et al. Targeting epithelium-expressed sialyl Lewis glycans improves colonic mucosal wound healing and protects against colitis. *JCI Insight*. (2020) 5(12):e135843. doi: 10.1172/jci.insight.135843

29. Zhao B, Zhang X, Han W, Cheng J, Qin Y. Wound healing effect of an Astragalus membranaceus polysaccharide and its mechanism. *Mol Med Rep*. (2017) 15(6):4077–83. doi: 10.3892/mmr.2017.6488

30. Fusté NP, Guasch M, Guillen P, Anerillas C, Cemeli T, Pedraza N, et al. Barley β-glucan accelerates wound healing by favoring migration versus proliferation of human dermal fibroblasts. *Carbohydr Polym*. (2019) 210:389–98. doi: 10.1016/j.carbpol.2019.01.090

31. Wang XY, Lin SQ, Li JW, Kemmner W, Ding YQ. Effect of cell surface sialic acid and their linkages on adhesion of mammary carcinoma cells. *Nan Fang Yi Ke Da Xue Xue Bao*. (2006) 26(6):742–6. PMID: 16793589

32. Cong X, Xu W, Janton S, Henderson WA, Matson A, McGrath JM, et al. Gut microbiome developmental patterns in early life of preterm infants: impacts of feeding and gender. *PLoS One*. (2016) 11(4):e0152751. doi: 10.1371/journal.pone.0152751

33. Kundu P, Blacher E, Elinav E, Pettersson S. Our gut microbiome: the evolving inner self. *Cell*. (2017) 171(7):1481–93. doi: 10.1016/j.cell.2017.11.024

34. Mehta RS, Abu-Ali GS, Drew DA, Lloyd-Price J, Subramanian A, Lochhead P, et al. Stability of the human faecal microbiome in a cohort of adult men. *Nat Microbiol*. (2018) 3(3):347–55. doi: 10.1038/s41564-017-0096-0

35. Lloyd-Price J, Mahurkar A, Rahnavard G, Crabtree J, Orvis J, Hall AB, et al. Strains, functions and dynamics in the expanded human microbiome project. *Nature*. (2017) 550(7674):61–6. doi: 10.1038/nature23889

36. Abrams GD, Bauer H, Sprinz H. Influence of the normal flora on mucosal morphology and cellular renewal in the ileum. A comparison of germ-free and conventional mice. *Lab Invest*. (1963) 12:355–64. PMID: 14010768

37. Pull SL, Doherty JM, Mills JC, Gordon JI, Stappenbeck TS. Activated macrophages are an adaptive element of the colonic epithelial progenitor niche necessary for regenerative responses to injury. *Proc Natl Acad Sci USA*. (2005) 102(1):99–104. doi: 10.1073/pnas.0405979102

38. Leoni G, Neumann PA, Sumagin R, Denning TL, Nusrat A. Wound repair: role of immune-epithelial interactions. *Mucosal Immunol*. (2015) 8(5):959–68. doi: 10.1038/mi.2015.63

39. Alam A, Leoni G, Wentworth CC, Kwal JM, Wu H, Ardita CS, et al. Redox signaling regulates commensal-mediated mucosal homeostasis and restitution and requires formyl peptide receptor 1. *Mucosal Immunol*. (2014) 7(3):645–55. doi: 10.1038/mi.2013.84

40. Jones RM, Mercante JW, Neish AS. Reactive oxygen production induced by the gut microbiota: pharmacotherapeutic implications. *Curr Med Chem*. (2012) 19 (10):1519–29. doi: 10.2174/092986712799828283

41. Leoni G, Alam A, Neumann PA, Lambeth JD, Cheng G, McCoy J, et al. Annexin A1, formyl peptide receptor, and NOX1 orchestrate epithelial repair. *J Clin Invest*. (2013) 123(1):443–54. doi: 10.1172/JCI65831

42. Swanson 2nd PA, Kumar A, Samarin S, Vijay-Kumar M, Kundu K, Murthy N, et al. Enteric commensal bacteria potentiate epithelial restitution via reactive oxygen species-mediated inactivation of focal adhesion kinase phosphatases. *Proc Natl Acad Sci USA*. (2011) 108(21):8803–8. doi: 10.1073/pnas.1010042108

43. Sansonetti PJ, Medzhitov R. Learning tolerance while fighting ignorance. *Cell*. (2009) 138(3):416–20. doi: 10.1016/j.cell.2009.07.024

44. Chung H, Kasper DL. Microbiota-stimulated immune mechanisms to maintain gut homeostasis. *Curr Opin Immunol*. (2010) 22(4):455–60. doi: 10.1016/j.coi.2010.06.008

45. Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R. Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. *Cell*. (2004) 118(2):229–41. doi: 10.1016/j.cell.2004.07.002

46. Vaishnava S, Yamamoto M, Severson KM, Ruhn KA, Yu X, Koren O, et al. The antibacterial lectin RegIIIgamma promotes the spatial segregation of microbiota and host in the intestine. *Science*. (2011) 334(6053):255–8. doi: 10.1126/science.1209791

47. Hou Q, Ye L, Huang L, Yu Q. The research progress on intestinal stem cells and its relationship with intestinal microbiota. *Front Immunol*. (2017) 8:599. doi: 10.3389/fimmu.2017.00599

48. Nigro G, Rossi R, Commere PH, Jay P, Sansonetti PJ. The cytosolic bacterial peptidoglycan sensor Nod2 affords stem cell protection and links microbes to gut epithelial regeneration. *Cell Host Microbe*. (2014) 15(6):792–8. doi: 10.1016/j.chom.2014.05.003

49. Pedron T, Mulet C, Dauga C, Frangeul L, Chervaux C, Grompone G, et al. A crypt-specific core microbiota resides in the mouse colon. *mBio*. (2012) 3(3): e00116–12. doi: 10.1128/mBio.00116-12

50. Abo H, Chassaing B, Harusato A, Quiros M, Brazil JC, Ngo VL, et al. Erythroid differentiation regulator-1 induced by microbiota in early life drives intestinal stem cell proliferation and regeneration. *Nat Commun*. (2020) 11 (1):513. doi: 10.1038/s41467-019-14258-z

51. Vannella KM, Wynn TA. Mechanisms of organ injury and repair by macrophages. *Annu Rev Physiol*. (2017) 79:593–617. doi: 10.1146/annurev-physiol-022516-034356

52. Alam A, Leoni G, Quiros M, Wu H, Desai C, Nishio H, et al. The microenvironment of injured murine gut elicits a local pro-restitutive microbiota. *Nat Microbiol*. (2016) 1:15021. doi: 10.1038/nmicrobiol.2015.21

53. Smithson JE, Campbell A, Andrews JM, Milton JD, Pigott R, Jewell DP. Altered expression of mucins throughout the colon in ulcerative colitis. *Gut*. (1997) 40(2):234–40. doi: 10.1136/gut.40.2.234

54. Wrzosek L, Miquel S, Noordine ML, Bouet S, Joncquel Chevalier-Curt M, Robert V, et al. Bacteroides thetaiotaomicron and Faecalibacterium prausnitzii influence the production of mucus glycans and the development of goblet cells in the colonic epithelium of a gnotobiotic model rodent. *BMC Biol*. (2013) 11:61. doi: 10.1186/1741-7007-11-61

55. Kelly CJ, Zheng L, Campbell EL, Saeedi B, Scholz CC, Bayless AJ, et al. Crosstalk between microbiota-derived short-chain fatty acids and intestinal epithelial HIF augments tissue barrier function. *Cell Host Microbe*. (2015) 17 (5):662–71. doi: 10.1016/j.chom.2015.03.005

56. Park JH, Kotani T, Konno T, Setiawan J, Kitamura Y, Imada S, et al. Promotion of intestinal epithelial cell turnover by commensal bacteria: role of short-chain fatty acids. *PLoS One*. (2016) 11(5):e0156334. doi: 10.1371/journal.pone.0156334

57. Tan H, Zhao J, Zhang H, Zhai Q, Chen W. Novel strains of Bacteroides fragilis and Bacteroides ovatus alleviate the LPS-induced inflammation in mice. *Appl Microbiol Biotechnol*. (2019) 103(5):2353–65. doi: 10.1007/s00253-019-09617-1

58. Ihekweazu FD, Engevik MA, Ruan W, Shi Z, Fultz R, Engevik KA, et al. Bacteroides ovatus promotes IL-22 production and reduces trinitrobenzene sulfonic acid-driven colonic inflammation. *Am J Pathol*. (2021) 191(4):704–19. doi: 10.1016/j.ajpath.2021.01.009

59. Alverdy JC, Hyoju SK, Weigerinck M, Gilbert JA. The gut microbiome and the mechanism of surgical infection. *Br J Surg*. (2017) 104(2):e14–e23. doi: 10.1002/bjs.10405

60. Anderson DI, Keskey R, Ackerman MT, Zaborina O, Hyman N, Alverdy JC, et al. Enterococcus faecalis is associated with anastomotic leak in patients undergoing colorectal surgery. *Surg Infect (Larchmt)*. (2021) 22(10):1047–51. doi: 10.1089/sur.2021.147

61. Hyoju SK, Adriaansens C, Wienholts K, Sharma A, Keskey R, Arnold W, et al. Low-fat/high-fibre diet prehabilitation improves anastomotic healing via the microbiome: an experimental model. *Br J Surg*. (2020) 107(6):743–55. doi: 10.1002/bjs.11388

62. Filidou E, Kolios G. Probiotics in intestinal mucosal healing: a new therapy or an old friend? *Pharmaceuticals (Basel)*. (2021) 14(11):1181. doi: 10.3390/ph14111181

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership