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Advances in proctology and colorectal surgery

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Advances in proctology and colorectal surgery

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Editorial: Advances in proctology and colorectal surgery

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Editorial on the Research Topic
Advances in proctology and colorectal surgery

Proctology and colorectal surgery for benign disorders and neoplasia represent a broad field of general surgery. Their relevance is well known, on the one hand because of the still extremely high frequency in Western countries of colon-rectal cancer (currently estimated as the third most frequent cancer in the world), and on the other hand because of the serious impact on the quality of life (QoL) of patients suffering from benign, inflammatory, and functional diseases of the lower gastrointestinal tract. This Research Topic of Frontiers in Surgery, composed by forty-five original articles on colorectal surgery and proctology addresses several topics including non-surgical solutions, diagnostic aspects, translational research, and specific scenarios.

Rectal cancer, which accounts for about 30% of all colorectal malignancies, has been studied from several perspectives. The routine use of the LARS score after rectal surgery to assess the bowel function and QoL of patients is highly recommended (De Simone et al.).

Pacevicius et al. conducted a case-control study to investigate the differences in terms of overall survival and surgical outcome between the invasive surgical approach with TME and local excision (LE) ± chemotherapy of early rectal cancer. The authors identified that approximately 85.2% of the patients had no Low Anterior Rectal Resection Syndrome (LARS) in LE group compared with 54.5% in TME group ($p = 0.018$); furthermore, they reported comparable survival outcomes in the two groups, thus favoring a less invasive surgical approach in early stages such as LE for better QoL outcomes. Herzberg et al. as well investigated the QoL in terms of LARS in patients who underwent rectal resection and End-to End primary anastomosis in favor of the first one using a standardized perioperative pathway. An interesting radiological study was conducted using innovative imaging techniques to correlate the oncological outcome to inadvertent residual pelvic diaphragm on postoperative MRI after extralevator abdominoperineal excision (ELAPE) or the conventional abdominoperineal excision (c-APE) demonstrating that anterior tumor orientation was a risk factor for circumferential resection margin (CRM) involvement regardless of surgical approach (Oerskov et al.). Tumour downsizing of rectal cancer to allow a R0 resectablility is a long-standing problem, especially for those patients who do not tolerate neoadjuvant conventional chemoradiation (CRT). A research group from Germany proposes short-term neoadjuvant radiotherapy (5 × 5 Gy)

followed by an interval before surgery (SRT- delay) as a valid alternative to CRT with comparable results in those patients who cannot tolerate CRT (Albrecht et al.).

In this regard of personalized medicine, Coletta et al. published a state of the art focused on the de-functioning ileostomy techniques highlighting the relevance of a tailored surgical approach in those patients.

In fact, this editorial has given numerous authors the opportunity to highlight and report unique cases in lower GI abdominal surgery in which the patient-specific surgical approach has demonstrated successful results (Zhang et al.).

Concerning colon cancer surgery, a current debate on the management of synchronous and metachronous metastasis is ongoing. The selection of a surgical approach for liver resection (SLR) should take into account various factors, including the tumor's location, size, and resectability, the overall health of the patient (including age, comorbidities, and prior treatments), and the surgeon's experience. SLR represents a safe and effective option for patients with primary liver metastases of limited extent. It offers advantages such as reduced intraoperative bleeding, quicker recovery of intestinal function, shorter postoperative hospital stays, and lower rates of surgical complications compared to open laparotomy. Importantly, there are no significant differences in long-term outcomes between the two approaches. It is worth noting that there is currently insufficient high-quality evidence to establish the superiority of one approach over the other. Therefore, future studies should involve larger patient cohorts and randomized controlled trials to provide more definitive insights into the most appropriate strategy (Sena et al.). Also, synchronous liver resection (LR), cytoreductive surgery (CRS), and hyperthermic intraperitoneal chemotherapy for colorectal liver and peritoneal metastases have been investigated. However, the role of combined surgical strategy extensive surgical approach including CRS with hyperthermic intraperitoneal chemotherapy (HIPEC) and LR is still controversial. (Di Carlo et al.)

The standardized surgical procedure techniques are also evolving and being studied towards modern surgery in continuous progress. For example, Xu et al. studied a novel knotless hand-sewn end-to-end anastomosis using V-loc barbed suture vs. stapled anastomosis in laparoscopic left colonic surgery and demonstrated that this technique can reduce operating time and costs for the hospital when compared to the technique using staplers. The authors therefore propose it as a safe and feasible technique. Anastomotic leak prevention has also been investigated by the group of Baeza-Murcia with a propensity score-matched study on bowel mechanical preparation and oral antibiotics use. They confirmed that oral antibiotics, mechanical bowel preparation and inflammatory markers, significantly reduces morbidity adjusted to severity of complications, the anastomotic leakage rate, hospital stay and readmissions (Baeza-Murcia et al.). A multicenter study by Admasu et al. instead, demonstrated the need to increase the level of alertness regarding blood disorders such as coagulopathy even in the presence of colorectal polyps with a prevalence of 76 (50.7%; 95% CI: 45.66, 54.34). As well as associations of advanced age with comorbidity, stage and primary subsite as contributors to mortality from colorectal cancer are currently still in force (Gheybi et al.).

Moreover, the use of alternative procedures in the postoperative period that can prevent postoperative complications and promote the recovery of patients after major abdominal surgery is also making incredible progress. A recent paper by Zhao et al. investigated the effects of acupuncture and electroacupuncture in postoperative ileus prevention with promising results with shorter time to the first flatus [stand mean difference (SMD), −0.57; 95% CI, −0.73 to −0.41, $p < 0.00001$], shorter time to the first defecation [mean difference (MD), −4.92 h, 95% CI −8.10 to −1.74 h, $p = 0.002$] than the control group.

Another super topical subject in colorectal surgery is the use of indocyanine green, not only for the evaluation of tissue perfusion but also for the assessment of the risk of anastomotic dehiscence. Image guided surgery in fact represents the most modern frontier of technology development in surgery. Maione et al. were able to demonstrate that the intraoperative use of Near-Infrared Fluorescence-Indocyanine Green in colorectal surgery is safe, feasible, and associated with a substantial reduction in postoperative anastomotic leakage rate. As well as, ICG has shown promising results as a safe and reproducible technique for the preoperative tumour marking prior of robotic resections (Konstantinidis et al.).

In addition, some less frequent but complex medical and hospital management pathologies, with a huge impact on the patient's life and with huge consequences also on the inpatient ward in terms of nursing support, complications, costs for the company, are also the responsibility of the emergency surgeon and have been analyzed in this editorial. For example, Fournier's gangrene is a pathology that places the patient's life at a very high risk and whose only treatment at present is surgical debridement with great loss of tissue associated with antibiotic therapy with the need for long hospitalization. Tutino et al. retrospectively analyzed a series of cases in which the hyperbolic chamber was used in support of surgical therapy to see whether hyperbolic therapy was associated with a better prognosis. The authors showed, however, that the hospital stay was longer in patients treated with hyperbaric oxygen therapy [mean 11 (C.I. 0.50–21.89) vs. mean 25 (C.I. 18.02–31.97); $p = 0.02$] without an improvement in survival ($p = 1.00$), while the delay in treatment was associated with a higher risk of mortality in their case series. Another peculiar and rare pathological condition that has to be known form is the diagnosis of rectal cancer in a patient symptomatic for rectal prolapse (Jurić et al.). Similarly, also appendiceal tumors represent a rare but relevant incidental finding (0.5%) after appendicectomy that challenge the physicians that deserves further investigations starting from the work of Viel et al.

Likewise, certain measures in clinical practice have been identified and proven effective. For example, the recently published propensity score by Jiang et al. stated regarding surgical infections that the clichéd incisional press after suturing is a simple, costless, and effective intervention in reducing superficial incisional SSI. Furthermore, the current knowledge on C. difficile infection after colorectal surgery was also re-evaluated, confirming that fresh faecal bacteria are the best treatment, but frozen and freeze-dried faecal bacteria can achieve the same effect (Yang et al.). Another extremely frequent condition routinely dealt with by the emergency surgeon is incarcerated

inguinal hernia for which Chen et al. proposed a predictive model of bowel resection based on the systemic immune-inflammation index. Indeed, they demonstrated that the increased risk of bowel resection is highly correlated among the elderly (≥70 years) and for persons with elevated temperature (≥37.3°C), high systemic immuno-inflammation index (SII) values (≥1,230.13), presence of bowel obstruction, and signs of peritonitis.

The Covid-19 pandemic has posed a great challenge for medical and surgical personnel and also for residents' education especially concerning surgical training. Both the maintenance of oncological surgical activity, tending to implement extraordinary measures to limit contagion, and the management of all benign chronic and acute diseases of the colorectal and proctological spheres put a great strain on healthcare personnel (1). Despite this, some of the strategies implemented during the pandemic period showed surprising results under emergency conditions, which were also proposed afterwards with promising improvements in clinical practice. Among these, the use of telemedicine, but also the development of scores to stratify the population according to priority of need for treatment have been useful. In addition, new strategies of anesthesiologic and surgical approaches to limit infections have been formulated. 'Awake surgery' for example is a term borrowed from Neurosurgery, meaning major abdominal surgery performed on an awake patient in spontaneous breathing. During the coronavirus pandemic, the awake surgery technique was also introduced in general surgery. The advantages of awake surgery include reduced airway manipulation, reduced risk of infection in the operating room during the pandemic period, patient awake and spontaneously breathing during surgery, minimal nausea and vomiting, effective postoperative analgesia, early recovery after the surgical procedure, and reduced need for intensive care (Romanzi et al., Pietroletti et al.). Concerning the residency program however, a nationwide survey on the Italian scenario reported worrisome information on the training program of future surgeons during pandemic which deserves attention and planning of improvements to guarantee an adequate education (Gallo et al.). Those results were consistent with a previous survey concerning the first wave of the pandemic (2).

Surgery of the colon, rectum and anus, however, does not only concern neoplastic pathologies or major surgical treatments; in fact, in terms of frequency, benign surgery, proctology and functional pelvic floor disorders are by far the largest and sometimes, although benign, the most disabling. For example, about 40% of pregnant and post-partum women are affected by hemorrhoids and anal fissures, the treatment of which is often delayed for reasons of pregnancy or breastfeeding. These pathologies have such an impact on the patient's quality of life that they require the outmost attention for their prevention, management in the acute phase and their conservative or bridge-to-surgery treatment (Bužinskienė et al., Snopkova et al.).

In any case, anal fissure and proctological pathologies represent a challenging field for the surgeon, especially for the use of new products and technologies and also because of the heterogeneity in the choice of the correct surgical assessment (3). Giani et al. first proposed the Scanner-Assisted CO2 Laser Fissurectomy technique as a pilot study. Scanner-assisted CO2 laser showed great results in terms of pain control and wound healing, secondary to an extremely precise ablation, vaporization, and debridement procedures with minimal lateral thermal damage. Similarly, Alyanak et al. reported results on the comparison of botulinum toxin injection (BoNT) and left lateral sphincterotomy for the treatment of recurrent anal fissures, showing during the 3-month post-surgery follow-up period, that there was statistically significant difference ($p < 0.01$) between groups by pain and that neither technique was associated with deterioration in the incontinence scores during the 6-month post-surgery period. They therefore propose the traditional lateral internal sphincterotomy (LIS) technique as the most suitable and best in terms of pain and postoperative outcomes. Moreover, other authors investigated the complex treatment of perianal fistulas with preservation of the sphincter complex, concluding that the incidence rate of complications after fistulectomy treatment was higher than the others ($P < 0.05$) and that ligation of the intersphincteric fistula tract (imLIFT) may be the surgical method with the lowest incidence of postoperative complications (Huang et al.). Taking a step back towards the use of topical products for the conservative treatment of anal fissure, Tomasicchio et al. proposed the use of a topical gel for the treatment of the first uncomplicated presentation of fissure with an overall decrease in the VAS scale decreased significantly from 7 (IQR 4.7–8) at baseline to 1 (IQR 0–3.2, $p = 0.05$) after 20 days and a rate.

Promising results for the future have been published on the attempt of performing a pelvic floor transplant on rat models. Their microsurgical technique for pelvic floor transplantation in rats achieved an early survival rate of 81.82% that might open future scenarios on management of severe pelvic floor dysfunction with fecal and urinary incontinence, extensive perineal trauma, or congenital disorders (Galvao et al.).

However, especially for functional pathologies, there are multiple aspects ranging from conservative medical treatment, lifestyle, the gastroenterological aspect, pain management, surgical technique, the postoperative course, and the psychological aspect that all play a fundamental role in the successful management and treatment of the pathology that can be defined as multifactorial (4).

Hemorrhoidal prolapse is another benign extremely common condition that poses a treatment challenge to the surgeon. In recent years, several new techniques with increasingly stringent indications have been introduced. The challenge for the surgeon today is to find an algorithm to identify the best procedure for the patient's pathology and to acquire the necessary expertise to perform it best. Some studies have investigated the role and relevance of Goligher's classification, demonstrating the impossibility of providing today an adequate treatment algorithm. Consequently, it is important to emphasize the fundamental role of symptoms and clinical examination in assessing the pathology (5).

On this regard, numerous strategies have been implemented to study the best conservative treatment for early cases or bridge to surgery for more severe ones with the use of 3% polidocanol foam sclerotherapy or the better management of acute manifestations of hemorrhoidal prolapse such as hemorrhoid thrombosis. [Picciariello et al., Goglia et al., Lisi et al., Lobascio et al. (6, 7),]

Even THD for hemorroidal prolapse reported to be another safe and reproducible technique, both as a first intervention and on recurrence. Physician and patient need to understand each other's expectations, weight the risks and benefits, and customize the treatment (Verre et al.). Anal stenosis after conventional treatment of hemorrhoidal disease has been investigated too, concluding that both complications and recurrence were significantly lower after house flap compared with rhomboid/diamond and Y-V flap (8–10).

Concerning the treatment of postoperative pain from haemorrhoidectomy, one of the well-established therapies is the subcutaneous injection of methylene blue (11). Studies on doses have been conducted concluding that the injection of 0.1% methylene blue has been shown to be equally effective at higher doses and safer (Long et al.).

However, medical management is pivotal in these patients both in the preoperative and in the postoperative phase. Beyond hemorrhoidal disease, a gastroenterological disorder associated with chronic constipation or obstructed defecation syndrome is frequently identified and it is usually responsible of the worsening of symptoms and the recurrency of the pathology after surgical treatment (Li et al.).

Moreover, psychological support is of paramount importance in proctological pathologies. In fact, the symptoms of such pathologies are frequently extremely disabling in daily activities and the patient feels ashamed when dealing with the doctor. The doctor-patient relationship is definitely to be improved with specialized communication techniques, but a clear association and need for psychological support has been demonstrated. Furthermore, certain psychiatric disorders have been associated with the specific recurrence of rectal prolapse as well as psychological support for postoperative pain management have been investigated. [Brochard et al., Wang et al. (12),]

The present editorial offered the opportunity to range from the hottest current topics in oncological medicine and surgery to minor but relevant adjustments. "Small major" changes are routinely done in major abdominal surgery. However, innovations and technologies are constantly growing and expanding, and the general surgeon must be ready to embrace and make the most of them in order to achieve the best outcome for patient care from the presentation of symptoms to the best and least painful and long-lasting postoperative care.

Author contributions

MG: Project administration, Writing – original draft, Writing – review & editing. MT: Supervision, Validation, Writing – review & editing. AR: Supervision, Validation, Writing – review & editing. GC: Supervision, Validation, Writing – review & editing. GG: Conceptualization, Data curation, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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.

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BRIEF RESEARCH REPORT
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Pain Distraction During Awake Major Colorectal Surgery: Supporting Patients Beyond the COVID-19 Era. Preliminary Findings

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Introduction: During the coronavirus disease 2019 (COVID-19) pandemic, hospitals rapidly ran out of intensive care beds. Because minimally invasive surgery and general anaesthesia are both aerosol-generating procedures, their use has become controversial. We report a case series of awake undelayable colorectal surgeries which, innovatively, took advantage of intraoperative pain distraction. Moreover, we describe our frugal solution to social distancing in psychological support of inpatients.

Methods: Between October 2020 and February 2021, five patients underwent acute-care colorectal surgery under locoregional anaesthesia in our department. A 3D mobile theatre (3DMT) was used during the operation to distract the patients from pain. Vital signs, pain intensity, ergonomic comfort/discomfort, sense of presence and distress were intraoperatively monitored. A postoperative "cuddle delivery" service was instituted: video messages from relatives and close friends were delivered daily to the patient through the 3DMT. Emotional effects were investigated through clinical interviews conducted by a psychologist at our hospital.

Results: Both intraoperative and postoperative pain were always well controlled. Conversion to general anaesthesia and postoperative intensive support/monitoring were never necessary. The "cuddle delivery" initiative helped patients fill the emotional gap created by the strict containment measures implemented inside the hospital, distracting them from emotional anxiety and physical pain.

Conclusions: During the next phase of the COVID-19 pandemic and even after the COVID-19 era, awake laparotomy under locoregional anaesthesia may be a crucial option for delivering acute-care surgery to selected patients when intensive care beds are unavailable and postponing surgery is unacceptable. We also introduce a new modality for the provision of emotional support during postoperative inpatient care as a countermeasure to the restrictions imposed by social distancing measures.

Keywords: awake surgery, pain distraction, loco-regional anaesthesia, combined spinal-epidural anaesthesia, mobile theatres, colorectal surgery, case report, COVID-19

INTRODUCTION

During the coronavirus disease 2019 (COVID-19) pandemic, allocating intensive care beds to patients needing acute-care surgery became very difficult. After the first lockdown, innovative COVID-19 preoperative triage protocols allowed a gradual reopening and the ramping up of elective surgeries (1).

Major abdominal surgeries are generally carried out with minimally invasive surgery (MIS) under general anaesthesia (GA). MIS and GA are both aerosol-generating medical procedures (AGMPs), and their use has become controversial during the pandemic because they could contribute to the spread of pathogens inside operating theatres (2, 3). In addition, frail patients may require intensive postoperative monitoring/support, which cannot be provided when resources are scarce (4). In such a unique context, performing open abdominal surgery under locoregional anaesthesia (LA) helped us perform acute-care surgery in selected patients during the COVID-19 pandemic.

LA (spinal, epidural or combined spinal-epidural) reduces the exposure of medical staff to patients' respiratory secretions and the risk of perioperative viral transmission and preserves patients' cardiorespiratory function.

Besides this, the implementation of containment measures and social distancing resulted in serious consequences for our inpatients: the impossibility of being visited by their loved ones (sometimes for longer than a week) clearly increased the sense of solitude, discouragement, and depression in almost all our inpatients, especially the elderly patients. This negatively influenced their postoperative course.

The aim of this study was to investigate the possibility of distracting patients from pain through the use of a 3D mobile theatre (3DMT) as a means of improving the approach to performing awake major abdominal surgeries. Moreover, because we believe emotional care is fundamental (especially for the elderly population), we report the use of a functional countermeasure to the effects of social distancing to support the emotional needs of inpatients.

METHODS AND RESULTS

Five patients needing acute-care surgery for colorectal disease were treated at our Department between October 2020 and February 2021 (**Table 1**).

One week prior to each surgery, on the day on which the preadmission tests were performed, both the surgical procedure and approach to anaesthesia were explained to the patients during a multidisciplinary meeting. On that occasion, each patient underwent nasopharyngeal swab sampling to test for COVID-19 (all were negative), and the 3DMT was shown to the patient. Each patient had the opportunity to wear the device, learn how to adjust it, and express his/her approval of its use during surgery after being fully informed of the risks and benefits.

Awake Laparotomy

Surgery was performed under combined spinal-epidural (CSE) anaesthesia. Continuous epidural analgesia was administered with an elastomeric pump. The protocols for the administration of CSE anaesthesia and the elastomeric pump settings adhered to the routine clinical practice in our institution (5, 6).

Vital signs, intraoperative pain intensity, ergonomic comfort/discomfort level, sense of presence and distress were continuously monitored. Only light sedation was administered (midazolam 5 mg) to two patients. No other drugs were administered to the patients during surgery. Intraoperative pain was always well-controlled (VAS $\leq$ 3), and conversion to GA was unnecessary.

Postoperative pain was assessed daily, and pain control was satisfactory (VAS $\leq$3). Intensive postoperative monitoring/support was never necessary. A separate COVID-19-free ward was established for postoperative recovery to ensure that COVID-negative patients remained isolated from all other patients. The epidural elastomeric pump was removed on postoperative day (POD) 3 for all patients. Patients were discharged free from complications on POD 5 (mean value).

3D Mobile Theatre

During surgery, patients wore Royole's Moon (RM) (Royole®, Shenzhen, China). RM is an all-in-one 3DMT headset. It uses two AMOLED displays that deliver 3D or 2D content in full HD 1080p resolution. The optics are independent and can be adjusted from −7.0 D to +2.0 D. An immersion mask is mounted on the device to ensure a close fit around the eyes. Active noise cancellation was used. The right ear pad contains flexible sensor technology that can be used to navigate the menu and adjust the volume by swiping or tapping a finger on it.

Internal flash storage allowed the storage of several 4K ultra HD videos. Some videos offered immersion in a natural setting from an aerial perspective, and other videos simulated walking through a specific scenario.

After the patient was positioned on the operating table, the patient's dominant hand was freed to enable the patient to adjust the device in case of displacement. Patients wore the 3DMT two times during surgery (**Figures 1**, **2**). The first time started before the surgical incision was made and lasted 40 min. After a pause of 20 min, they wore the 3DMT again for 20 min. Patient #1 wore the 3DMT longer because he underwent a prolonged surgery: the second time, he wore the 3DMT for 50 min.

A questionnaire was designed to investigate critical factors that may have affected patients during or after the use of the device. The questionnaire was completed by each patient before discharge. Questionnaires were then analysed (**Table 2**).

Cuddle Delivery Initiative

Before admission, we contacted the relatives and close friends of each patient and gave them the opportunity to send us homemade videos addressed to their loved one with the aim of cheering the patient. The video messages were delivered daily to the patients through RM during their postoperative stay. The day before discharge, patients underwent clinical interviews with the psychologist in our department.

TABLE 1 | Patients' clinico-pathological characteristics and intraoperative results.

Pt (#)	Age	Sex	Diagnosis	ASA score	Surgery	OT (min)	S	CGA	3DMT (min)	PO ICU
1	64	♂	RCa (nCRT)	II	LAR (sanCRT)	170	–	–	90	–
2	84	♀	CD	III	SR	85	yes	–	60	–
3	76	♂	CCa	III	RC	90	yes	–	60	–
4	67	♂	CCa	III	RC	105	–	–	60	–
5	92	♀	RCCa	III	RC	75	–	–	60	–

FIGURE 1 | Patient wearing the device (preoperative snapshot).

FIGURE 2 | Intraoperative use of the device.

DISCUSSION

Multiple authors have described awake laparotomy as a feasible and safe approach to major surgical procedures; hence, this solution has been considered a valid option when gradually making surgery available again after its temporary cessation during the COVID-19 pandemic (2, 5–7). Some colleagues even reported that awake laparoscopy is adequate and safe for minor laparoscopic surgeries in healthy patients (8). Nevertheless, the recent identification of SARS-CoV-2 in the peritoneal fluid of COVID-19 patients likely makes this impossible at the current time (9).

The use of head-mounted displays or portable virtual reality (VR) devices in medicine, surgery and behavioural healthcare is not new (10). In all cases, head-mounted displays without earphones were used. The effective use of these displays to distract patients from pain during prolonged and invasive surgeries has thus far only been hypothetical (10).

To the best of our knowledge, this is the first case series focusing on distraction from pain through the use of an immersive audio-visual device during awake major colorectal surgeries.

Several 3DMT units are commercially available. We selected this specific device because of some specific characteristics. First, RM is an audio-visual all-in-one headset. If immediate anaesthesiological support is required during surgery, the device can be quickly removed. Second, other popular head-mounted devices come with an elastic band that goes around the head. This can be a source of discomfort during prolonged supine positioning. Third, independent optics allow patients to view it without prescription glasses even if they have mild optical defects that differ between their eyes.

Intraoperatively, the large, curved, full-HD screen helped deliver videos with compelling stereoscopic depth perception. The noise-cancelling headphones together with the immersion mask blocked out the ambient sources of distraction and created an immersive experience. The optimised viewing angle and the combination of ultra-high resolution pictures with a fast image response rate contributed to providing relaxation during prolonged viewing by reducing eye strain. The ergonomic design ensured a comfortable fit: the patients never complained of a sense of constriction or breathing restriction. The analysis of the questionnaires revealed that, despite being initially discouraged by the weight of the device and hesitant during the first attempt to focus the device, after proper training, patients did not encounter any difficulties in its use or discomfort during or after its use (**Table 2**).

Additionally, on the basis of our experience, the use of 3DMT as a countermeasure to the negative effects of social distancing on patients appears to be a promising approach and represents

TABLE 2 | Sample of the evaluation sheet showing the mean mark for each aspect.

		1–4	5–6	7–10
First impression	1. lightness of the device	■	□	□
	2. comfort	□	□	■
	3. ease to focus	■	□	□
	4. video quality	□	□	■
	5. audio quality	□	□	■
	6. ease to wear the device	□	□	■
	7. ease to use the device (in general)	□	■	□
While watching	8. sense of constriction	■	□	□
	9. discomfort (□ nasal ■ ocular □ auricular)	□	■	□
	10. pain (□ nasal □ ocular □ auricular)	■	□	□
	11. steadiness of the device on the face	□	□	■
At removal	12. memory of the weight of the device	■	□	□
	13. discomfort (□ nasal □ ocular □ auricular)	■	□	□
	14. pain (□ nasal □ ocular □ auricular)	■	□	□
	15. eye strain	■	□	□
	16. eye dryness	■	□	□
	17. headache	■	□	□
	18. dizziness	■	□	□
	19. nausea	■	□	□
	20. tinnitus	■	□	□

Patients expressed their personal evaluation from 1 (completely negative evaluation or absence of the sensation in question) to 10 (completely positive evaluation or presence of the sensation in question). Scores were interpreted inversely based on the positive or negative nature of the factor in question: scores from 1 to 4 were considered indicators of a negative impression if the question pertained to a positive factor (or a positive impression in the case of a negative factor); scores of 5 and 6 were considered indicators of a neutral impression; and scores from 7 to 10 were considered indicators of a positive impression if the question pertained to a positive factor (or a negative impression in the case of a negative factor).

an example of the positive application of technology (11). It is well-known that older patients affected by dementia can develop postoperative confusion, disorientation, depression and fear (3). Social distancing made it impossible for patients to have visitors, exacerbating their feelings of solitude and discouragement. We have also noted psychological issues in the elderly patients without dementia and younger patients.

The psychological interviews revealed that every patient appreciated the initiative, reporting that it helped reduce their sense of loneliness and increased their desire to return home. The patients also reported that the video messages distracted them from physical pain. None of our patients showed signs of depression. None of our patients required the administration of benzodiazepines or other anti-anxiety medications during hospitalisation. These elements lead us to believe that postoperative emotional services may have marked positive effects on the postoperative course.

Our study has some limitations. It was a single-centre study based on a small group of patients. Nevertheless, we believe our preliminary data may allow to make valuable observations and to raise useful questions. The effects of emotional and psychological postoperative support were only investigated through a clinical interview; further studies including a tailored psychological questionnaire are needed to standardise the evaluation and objectively assess the impact of emotional support on the postoperative course.

During the pandemic, open surgery under LA is a crucial option for delivering acute-care surgery when ICU beds are unavailable and postponing surgery is unacceptable. After the COVID-19 era, methods of distracting patients from pain may make awake surgery (whether open or minimally invasive) more pleasant for the patient. Moreover, the use of a 3DMT can help deliver postoperative psychological care when social distancing measures are in place.

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 Valduce Hospital IRB. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

AR, AV, and SD designed the study and analysed and interpreted the patient data. AR, GG, and BV performed the

review of the manuscript and were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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During pandemic we contacted Royole Corporation to present our project. Royole Corporation donated three 3D mobile theatres to Valduce Hospital for the use described in the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.754059/full#supplementary-material

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Local Excision ± Chemoradiotherapy vs. Total Mesorectal Excision for Early Rectal Cancer: Case-Matched Analysis of Long-Term Results

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Background: Our aim was to compare the bowel function and oncologic outcomes following these two treatment modalities.

Materials and methods: This was a single-center study with 67 patients included between 2009 and 2018. A total of 32 patients underwent total mesorectal excision (TME) group and 35 transanal local excisions (LE) ± chemoradiation. We performed a case-matched analysis: we matched the patients by age, cancer stage, and comorbidities. Duration of operation, postoperative complications, length of hospital stay, and long-term functional and oncological outcomes were compared. We calculated oncological outcomes using *Kaplan–Meier* Cox diagrams. In addition, we used a low anterior resection syndrome (LARS) score for the bowel function assessment.

Results: Mean operation time in the LE group was 58.8 ± 45 min compared with the TME group that was 121.1 ± 42 min ($p = 0.032$). Complications were seen in 5.7% in LE group and 15.62% in TME group ($p = 0.043$). ∼85.2% of the patients had no LARS in LE group compared with 54.5% in TME group ($p = 0.018$). Minor LARS was 7.4% in LE group compared with 31.8% in TME group ($p = 0.018$); major LARS was 7.4 and 13.7%, respectively ($p = 0.474$). Hospital stay was 2.77 days in LE group compared with 9.21 days in TME group ($p = 0.036$). The overall survival was 68.78 months in LE group compared with 74.81 months in TME group ($p = 0.964$).

Conclusion: Our results of a small sample size showed that local excision ± chemoradiation is a rather safe method for early rectal cancer compared with gold standard treatment. In addition, better bowel function is preserved with less postoperative complications and shorter hospital stays.

Keywords: early rectal cancer, local excision, total mesorectal excision, chemoradiotherapy, survival, functional outcome

INTRODUCTION

Colorectal cancer is common cancer worldwide with rectal cancer accounting for approximately 30% of all colorectal malignancies (1). Due to its location and dissemination, treatment of rectal cancer remains challenging. Over the last three decades, the gold standard treatment was total mesorectal excision (TME) with or without neoadjuvant chemoradiotherapy, which has shown significant improvements with respect to local disease control (2). However, this treatment is associated with certain numbers of mortality (4%) and morbidity (from 6 to 35%) (3, 4). Up to 75% of these patients eventually will experience bowel, urogenital dysfunction seriously affecting the quality of life (5).

Recently, thanks to cancer screening programs, the proportion of rectal cancers diagnosed at an early stage are increasing in Western countries, which gives the capability of reducing the size of the operation and minimizing negative effects on low anterior resection with TME (6). Now, minimally invasive local excision (LE) techniques, in addition to standard transanal excision (TE) with chemoradiation, can be used as an alternative to radical excision (7). LE plus chemoradiotherapy approach possibly decreases the risk of bowel dysfunction and gives acceptable local/distant recurrence rates by decontaminating the mesorectal lymph nodes and the excision bed. It is later translated to lower morbidity and comparable long-term survival results (7–9). Nevertheless, there is limited knowledge on the long-term functional and oncological results of TME vs. LE ± chemoradiotherapy for early rectal cancer.

We aimed to compare the long-term bowel function and oncologic outcomes following these two treatment modalities.

METHODS

Patients and Groups

The National Cancer Institute Review Board has approved the study (approval number NCI 2019.129AK). All the patients signed the written informed consent.

Data from the consecutively recruited patients who were treated at the National Cancer Institute between 2009 and 2018 were investigated. Patients who had T1-T2 rectal cancer with no lymph node or distant metastases (staging was done by using CT scan of the chest and abdomen and MRI of the pelvis) and with final pathology were included. We excluded patients with more than pT2 cancers and patients with positive lymph nodes (either on staging MRI or on final pathology). During the study period, more than 1,600 rectal cancer surgeries were performed (see in **Figure 1**). All the surgeries were performed by the five surgeons with experience of at least 5 years. The type of operation was determined by considering age of the patient, comorbidities, preference of the patient, and the size of the tumor. In total, there were 67 cases: 32 cases with TME group and 35 cases with transanal LE ± chemoradiation – LE group. All the patients in the TME group underwent straight radical open surgery with stapled coloanal anastomosis without previous LE techniques. Patients in the LE group underwent either transanal endoscopic microsurgery (TEM) or transphincteric excision. We matched both groups by age, cancer stage, and comorbidities. The mean follow-up duration of the patients was more than 3 years. Patients every 3 months for 2 years underwent carcinoembryonic antigen (CEA) evaluation, chest X-ray, ultrasound of the abdomen, or CT scan of the abdomen/chest, later every 6 months and then once a year. A mass in the pelvis around or in anastomosis site found by clinical, endoscopic, radiologic, pathologic examination, or autopsy was defined as local recurrence (or in pelvic lymph nodes in cases when LE was performed). Similarly, distant recurrence was defined as tumor growth in any lymph node outside the pelvis or in any other organ.

We used a low anterior resection syndrome (LARS) score for bowel function assessment for at least 2 years following the procedure (10, 11). Complications were graded by using *Clavien–Dindo* classification (12).

If the final pathology report following local excision was T2 cancer (10 patients) or T1 cancer with poor prognostic factors (seven patients) (such as positive margin, lymphovascular invasion, poor differentiation—G3 and Sm3), the patient was offered completion of TME or adjuvant chemoradiotherapy, if the patient was unfit or unwilling for the surgery. Patients received 50.4–54.0 Gy of radiation to the pelvis concomitant to 5-fluorouracil-based chemotherapy for 5 weeks (1.8–2 Gy per day). Seventeen patients underwent chemoradiotherapy. We have excluded nine patients who had poor prognostic factors and underwent completion of TME (13).

We have also performed a subgroup analysis and compared the survival and bowel function in three groups: LE only, LE + chemoradiotherapy, and TME group.

Statistical Analysis

We performed statistical analysis using SPSS Statistics 23.0 (IBM Corporation, released 2015, IBM SPSS Statistics for Windows, Version 23.0. Armonk, New York). The *Kaplan–Meier* Cox diagrams were calculated for oncologic outcomes.

The sample size was calculated by using G*Power 3.1.9.4 sample size calculator and the free version was available from https://stats.idre.ucla.edu/other/gpower/ (accessed on August 31, 2021). The value of alpha—the probability of a false positive was set at 5% and, hence, the familiar $p < 0.05$. Power is 1-beta, so in percentage terms, these were expressed as 80%. The effect size was set at 0.15 (the expected difference of patients having major LARS between the two groups of 15%). For 1:1 randomization, it showed that 44 patients (22 in each arm) would provide 80% power for a two-sample proportion test. There are likely to be patients lost to follow-up, so the target recruitment was set at 50.

RESULTS

The demographics of the patient are highlighted in **Table 1**. The mean duration of operation in the LE group was 58.8 ± 45 min compared with the TME group that was 121.1 ±

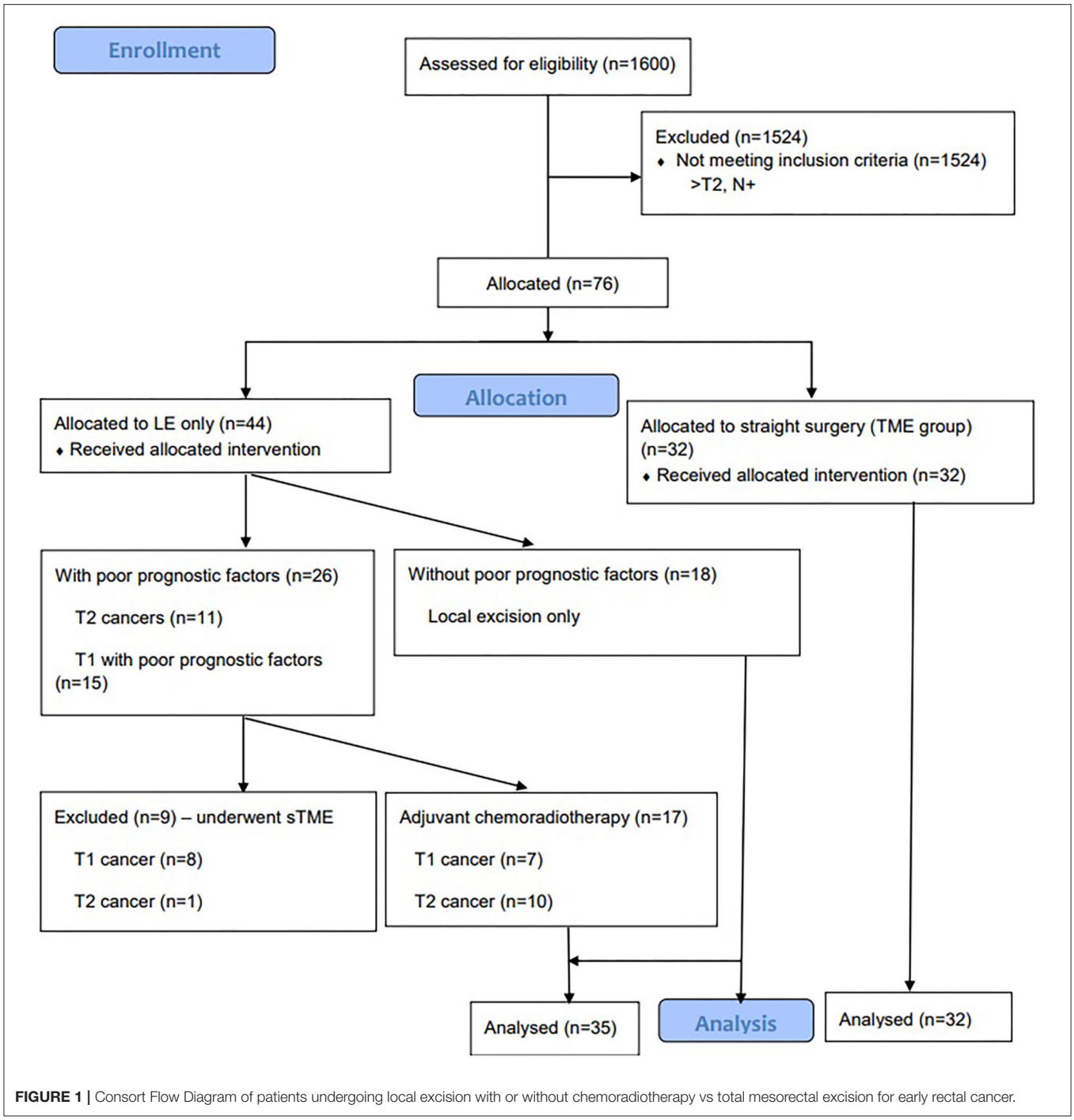

FIGURE 1 | Consort Flow Diagram of patients undergoing local excision with or without chemoradiotherapy vs total mesorectal excision for early rectal cancer.

42 min ($p = 0.032$). Two patients (5.7%) in the LE group had complications: one patient was treated conservatively, one had grade IIIB complication—fistula, which required additional surgical intervention and five patients in TME group (15.62%) ($p = 0.043$) had grade II-IIIA complications. The length of hospital stay in LE group was 2.77 days and 9.21 days in the TME group (**Table 2**). In the LE group, 17 (49%) patients received adjuvant chemoradiotherapy.

In LE group, out of 35 patients, 25 patients (71.4%) underwent TME.

No LARS was found in 85.2% of the patients in LE group compared to 54.5% of the patients in the TME group ($p = 0.018$). Minor LARS was 7.4% in LE group compared to 31.8% in TME group ($p = 0.018$); major LARS was 7.4 and 13.7%, respectively ($p = 0.474$) (**Table 3**). There was no statistically significant difference in overall survival between the

TABLE 1 | Patient and tumor characteristics of both the study groups.

Category, data ($n = 67$)	Groups	
	LE ($n = 35$)	TME ($n = 32$)
Age range (average), years	69 ± 11 (from 51 to 88)	66 ± 8 (from 45 to 75)
Sex, *n* (%) • Male ($n = 45$) • Female ($n = 22$)	23 (51.11%) 12 (54.54%)	22 (48.89%)10 (45.46%)
T stage, *n* (%) • T1 ($n = 47$) • T2 ($n = 20$)	25 (53.19%) 10 (50%)	22 (46.81%)10 (50%)
Tumor height from anus, *n* (%) • <6 cm ($n = 25$) • 6–12 cm ($n = 42$)	17 (68%) 18 (43%)	8 (32%)24 (57%)

LE, local excision; TME, total mesorectal excision.

TABLE 2 | Comparison of two groups included in our study (LE, local excision group and TME, radical surgery group).

Groups	LE	TME	*p*-value
Patient number, *n* (%)	35 (52%)	32 (48%)	
Operating time (average), min	58.8 ± 45(from 15 to 300)	121.1 ± 42(from 45 to 225)	0.032
Complications, *n* (%)	2 (5.7%)	5 (15.62%)	0.043
Hospital stay, days	2.77 ± 2.5 (from 1 to 15)	9.21 ± 4.2 (from 5 to 14)	0.036
Oncological recurrence, *n* (%)	1 (2.9%)	0 (0%)	
Survival, months	68.78	74.81	0.964
Follow-up, months	34 ± 21 (from 25 to 82)	37 ± 20 (from 24 to 85)	0.870

TME, total mesorectal excision.

TABLE 3 | Low anterior resection syndrome (LARS) comparison between the two groups.

Groups	LE ($n = 27$)	TME ($n = 22$)	*p*-value
No LARS, *n* (%)	23 (85.2%)	12 (54.5%)	0.018
Minor LARS, *n* (%)	2 (7.4%)	7 (31.8%)	0.028
Major LARS, *n* (%)	2 (7.4%)	3 (13.7%)	0.474
LARS	4 (14.8%)	10 (45.5%)	0.043

LE, local excision; TME, total mesorectal excision.

two groups: 68.78 months in the LE group and 74.81 months in the TME group ($p = 0.964$) (**Figure 2**). Local recurrence was detected in one (2.9%) patient in the LE group 6 years following the treatment compared to the TME group 0 year. The patient underwent abdominoperineal excision with a final pT3N0 pathology.

In addition, in a subgroup analysis, we found no LARS in 12 (54.5%) patients who underwent TME, in 12 (92.3%) patients with LE ± chemoradiation, and in 11 (78.6%) patients with LE only ($p = 0.045$). Accordingly, major LARS was present in three (13.6%) patients, one (7.7%) patient, and one (7.1%) patient ($p = 0.7330$). Moreover, we found no survival difference between the three groups ($p = 0.236$) (**Figure 3**).

In both groups, 13 patients (seven patients in the LE group and six patients in the TME group) had poor prognostic factors. However, as the numbers are very small, no further analysis was performed.

DISCUSSION

We found that LE with or without chemoradiation can provide good oncological and functional outcomes compared with radical surgery (TME). LE remains an evolving area in the management of rectal cancer, requiring comprehensive screening and selection of patients. Nevertheless, the right choice of treatment can significantly improve quality of life of the patient without compromising survival. However, LE for high-risk T1 or T2 rectal carcinomas is a relative contraindication because it is associated with a high risk of local or distant recurrence compared to radical surgery (7, 14).

Cancer recurrence is one of the most important indicators when talking about alternative treatment modalities compared to gold standard treatment—TME. In a large meta-analysis, *Borstlap et al.* found the overall local recurrence after LE following adjuvant chemoradiotherapy that was 5% for pT1 rectal cancer and 14.3% for pT2 rectal cancer. Distant recurrence for pT1/pT2 rectal cancer was 8.2% (7). Furthermore, a large Norwegian national observational study including more than 2,000 patients showed that transanal endoscopic microsurgery (TEM) had similar 5-year survival rates to the TME group in T1 rectal cancer, but lower 5-year relative survival in T2 rectal cancer. TEM also had higher local recurrence rates for T1 and T2 cancers (15).

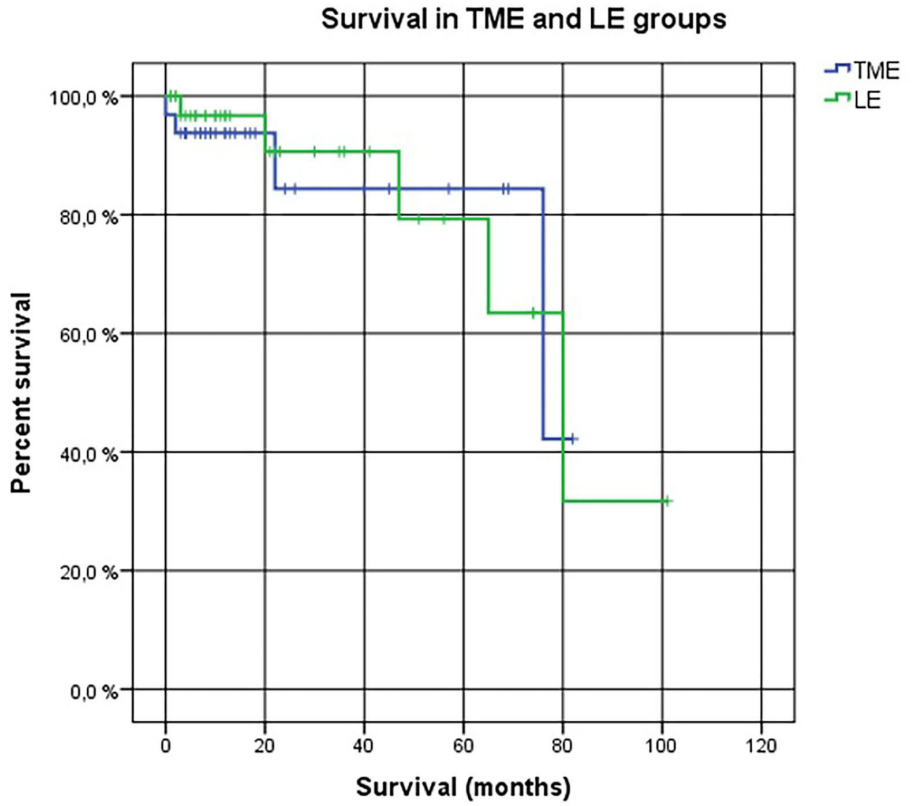

FIGURE 2 | The *Kaplan–Meier* Cox diagrams for evaluating survival in two groups. Log Rank (Mantel-Cox) *p*-value = 0.964. LE, local excision. TME, total mesorectal excision.

In a recent systematic review by *You et al.* including about 800 patients, the local recurrence rate after LE ± chemoradiotherapy was 5.8% for pT1, 13.8% for pT2, and 33.7% for pT3 tumors (16). Some studies show that the recurrence rate is relatively higher after LE alone compared with TME (15, 17, 18).

In this study, not all the patients underwent chemoradiotherapy after surgery, so it raises a question—how chemoradiotherapy additionally affects oncological outcomes. *Cutting et al.* in their systematic review draw attention that the evidence addressing the outcomes of the patients receiving adjuvant therapy after LE is lacking. Despite these limitations, the patients following LE and adjuvant treatment for high-risk early rectal cancer can sustain an acceptable long-term outcome (16). Documented data suggest that LE for pT1 tumor can recur locally in 8.2 to 23% and in pT2 tumor up to 30% (19). Our study results are corresponding to those mentioned above with 2.9%—although we observed a better recurrence rate, it must be considered that we had a smaller amount of the patients. Other authors suggest that in T1 rectal cancer, LE with additional chemoradiotherapy gives sufficient local control making it an acceptable treatment possibility in unfit patients or refusing radical surgery (20). *Rackley et al.* showed that early-stage cancer additionally affected with chemoradiotherapy has a 5-year local control of 92.5% (84.3–100%) for T1 cancer and 78.2% (65.5–90.9%) for T2 cancer. In addition, they stated that the LE and chemoradiotherapy were not recommended to be used in advanced disease (high-risk T2/T3 cancer). Interestingly, they found no local recurrence in the patients with T3 cancer. It is possible because these patients were typically very friable and died even before the development of recurrence with a 5-year overall survival rate of just 20 (21).

It is important to recognize that chemoradiotherapy is not so harmless. It is known that pelvic organ function worsens the following chemoradiotherapy with surgery compared to those who underwent surgery alone (22). Chemoradiotherapy has a significant negative effect and may lead to a spectrum of acute and late toxicities such as ulceration, bleeding, diarrhea, or problems of the skin. According to literature, 30–40% of the patients had chronic diarrhea, about 15% of the patients had obstructions, and even half of the patients had anorectal dysfunction after chemoradiotherapy (23–25). However, chemoradiotherapy is improving in areas warranting future research, such as advanced chemoradiation delivery techniques and risk-stratified patient management approaches are evolving and hopefully, it will cause a less negative effect in the future.

Furthermore, the importance of the quality of life of the patient after surgery should also be taken into consideration because often intervention has a negative impact on long-term

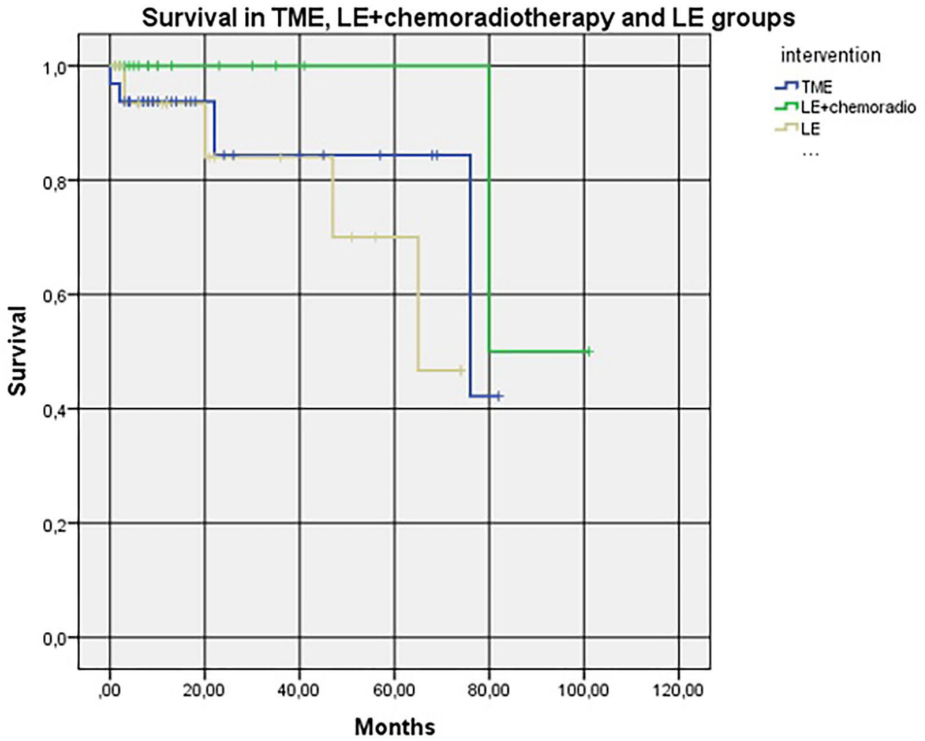

FIGURE 3 | *Kaplan–Meier* Cox diagrams evaluating survival in three groups (subgroup analysis). Log Rank (Mantel-Cox) *p*-value = 0.236. LE+chemoradio-local excision + chemoradiotheraphy. LE, local excision. TME, total mesorectal excision.

bowel function and urogenital function. A study by *Pucciarelli et al.* states that when bowel function and quality of life after LE and TME were compared, LE revealed better results in all the bowel functions such as increased stool frequency (LE−12.8% vs. TME−25.8%), developed fecal incontinence (LE−9.9% vs. TME−24.8%), pain (LE−3.6% vs. TME−15.3%), and impotence (LE−33.3% vs. TME−62.3%) (26). Similar to these results, in our study, we found that LARS occurred in 14.8% of the patients in the LE group vs. 45.5% of the patients in the TME group. As already mentioned before, radiotherapy has a considerable negative effect—not only causes the development of complications but generally also affects anorectal function. Therefore, the need to evaluate LARS score occurs—several randomized controlled trials have demonstrated an almost 2-fold higher LARS prevalence in patients undergoing chemoradiotherapy with surgery compared to surgery alone (27, 28). In a recent study by *Ihnát et al.*, authors compared LARS score following the surgery with or without radiotherapy and found that in the surgery alone group, 14.8% of the patients had major LARS and 37.0% of the patients had minor LARS compared to surgery plus radiotherapy group−53.6% of the patients with major LARS and 31.6% of the patients with minor LARS (29). In this study, the effect of chemoradiotherapy was not investigated, which could be added in future research.

Recently, the issue of treatment of early rectal cancer brought even more attention. Two systematic reviews and meta-analyses have been just published (30, 31). In both, the authors concluded that LE is safe for the treatment of early rectal cancer (this is T1 without poor prognostic factors). For T1 cancer with poor prognostic factors, chemoradiotherapy is a possible alternative to surgery and for T2 cancer—completion of TME should be the standard of care. This is in line with our results. However, because of a relatively small number of cases, we could not show the benefit of surgery in T2 cancers. Moreover, a group of experts from the STAR-TREC trial proposed limited irradiation volume for early rectal cancer to reduce toxicity and pelvic organ dysfunction (32, 33). However, this is the only theoretical proposal and the results of this trial should be awaited.

Our study is limited by the small sample size and retrospective approach. However, previous studies had very similar numbers of included patients. Moreover, in the LE group, there might have been more fragile older patients with the inability to survive the radical surgery. In addition, the follow-up of our last patients included is only 3 years—this weakens our statement on equal survival rates. As only one patient within the surveillance period had local recurrence, counting disease-free survival or local recurrence-free survival becomes irrelevant. Finally, the lack of endoanal ultrasound for preoperative examination is another limitation. The strength of our study is the assessment of bowel function in two selected groups by using a validated questionnaire.

CONCLUSION

According to our small group, LE ± chemoradiation probably gives comparable results to TME in survival rates. On the contrary, it has better bowel function, causes fewer postoperative complications, and helps to shorten the length of hospital stay. However, patients with T2 cancer should be warned of the high risk of recurrence.

DATA AVAILABILITY STATEMENT

The data are available upon reasonable request from the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Cancer Institute review board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AD, JP, and LP contributed to the study design and edition, patient enrollment, follow-up, data collection, final statistical analysis, text creation, and final text supervision. VP contributed with statistical analysis, text creation, and final text supervision. All authors listed have made a substantial, direct, intellectual contribution to the work, and approved it for publication.

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Postoperative MRI Findings Following Conventional and Extralevator Abdominoperineal Excision in Low Rectal Cancer

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Aim: The disparity in outcomes for low rectal cancer may reflect differences in operative approach and quality. The extralevator abdominoperineal excision (ELAPE) was developed to reduce margin involvement in low rectal cancers by widening the excision of the conventional abdominoperineal excision (c-APE) to include the posterior pelvic diaphragm. This study aimed to determine the prevalence and localization of inadvertent residual pelvic diaphragm on postoperative MRI after intended ELAPE and c-APE.

Methods: A total of 147 patients treated with c-APE or ELAPE for rectal cancer were included. Postoperative MRI was performed on 51% of the cohort ($n = 75$) and evaluated with regard to the residual pelvic diaphragm by a radiologist trained in pelvic MRI. Patient records, histopathological reports, and standardized photographs were assessed. Pathology and MRI findings were evaluated independently in a blinded fashion. Additionally, preoperative MRIs were evaluated for possible risk factors for margin involvement.

Results: Magnetic resonance imaging-detected residual pelvic diaphragm was identified in 45 (75.4%) of 61 patients who underwent ELAPE and in 14 (100%) of 14 patients who underwent c-APE. An increased risk of margin involvement was observed in anteriorly oriented tumors with 16 (22%) of 73 anteriorly oriented tumors presenting with margin involvement vs. 7 (9%) of 74 non-anteriorly oriented tumors ($p = 0.038$).

Conclusion: Residual pelvic diaphragm following abdominoperineal excision can be depicted by postoperative MRI. Inadvertent residual pelvic diaphragm (RPD) was commonly found in the series of patients treated with the ELAPE technique. Anterior tumor orientation was a risk factor for circumferential resection margin (CRM) involvement regardless of surgical approach.

Keywords: rectal cancer, magnetic resonance imaging, extralevator abdominoperineal excision, ELAPE, APE

INTRODUCTION

Treatment of patients with rectal cancer has improved dramatically with the adoption of mesorectal excision surgery (1–4), the introduction of MRI for preoperative tumor staging (5–7), multidisciplinary team (MDT) conferences for the planning of treatment (8), and use of preoperative chemoradiotherapy (CRT). However, outcomes for patients with locally advanced low rectal cancers, which necessitate abdominoperineal excision (APE), have been inferior to those following sphincter-preserving surgery for mid- or upper rectal cancer with poorer survival and a higher risk of local recurrence (9–11). The observed inferior outcomes in low rectal cancer are most likely multifactorial, including high rates of positive circumferential resection margin (CRM) involvement and specimen perforation. These outcomes may in part be explained on the basis of the surgical planes during resection when conventional APE (c-APE) is performed (4, 6, 7, 9–11). This aspect of APE specimens was first identified in 2002 (9) and subsequently verified in a joint study of APE specimens in the Dutch total mesorectal excision (TME) trial (10).

To reduce margin involvement and specimen perforation, the "extralevator APE" (ELAPE) was promoted by Holm et al. (12). The ELAPE involves removing the levators attached to the lower mesorectum and the entire anal canal with internal and external sphincters and a greater or lesser volume of ischioanal fat. The procedure is performed under direct vision, leaving only the most anterior parts of the levator ani *in situ*, and may provide the critical extra margin of protection around a locally advanced low rectal tumor.

In 2008, West et al. compared ELAPE specimens to c-APE specimens and demonstrated markedly reduced rates of CRM involvement and specimen perforation. Consistent with this finding, an increased amount of tissue was removed by the ELAPE technique compared with the c-APE technique (13). Standardization and quality assurance by training and pathological audit were implemented in the major trials to ensure that optimal surgery was performed (4, 14, 15). Thus, data on the problems of c-APE seemed abundant, and evidence of the superiority of the ELAPE was accumulating.

However, in 2014, Ortiz et al. published a multicenter study comparing ELAPE to c-APE, finding that ELAPE did not improve the rates of involved CRM, tumor perforation, local recurrence rates, or mortality (16). Others have proclaimed that ELAPE should not be the surgery of choice for low rectal cancers, although advocating that the selective use of the procedure might be warranted (17–21). However, patients may more often suffer from wound complications and perineal pain after ELAPE than after c-APE (22–24).

Thus, opinions range from authors advocating the widespread implementation of ELAPE for the treatment of low rectal cancers to the proposition that the procedure be filed under "nunquam iterum" —never again (25).

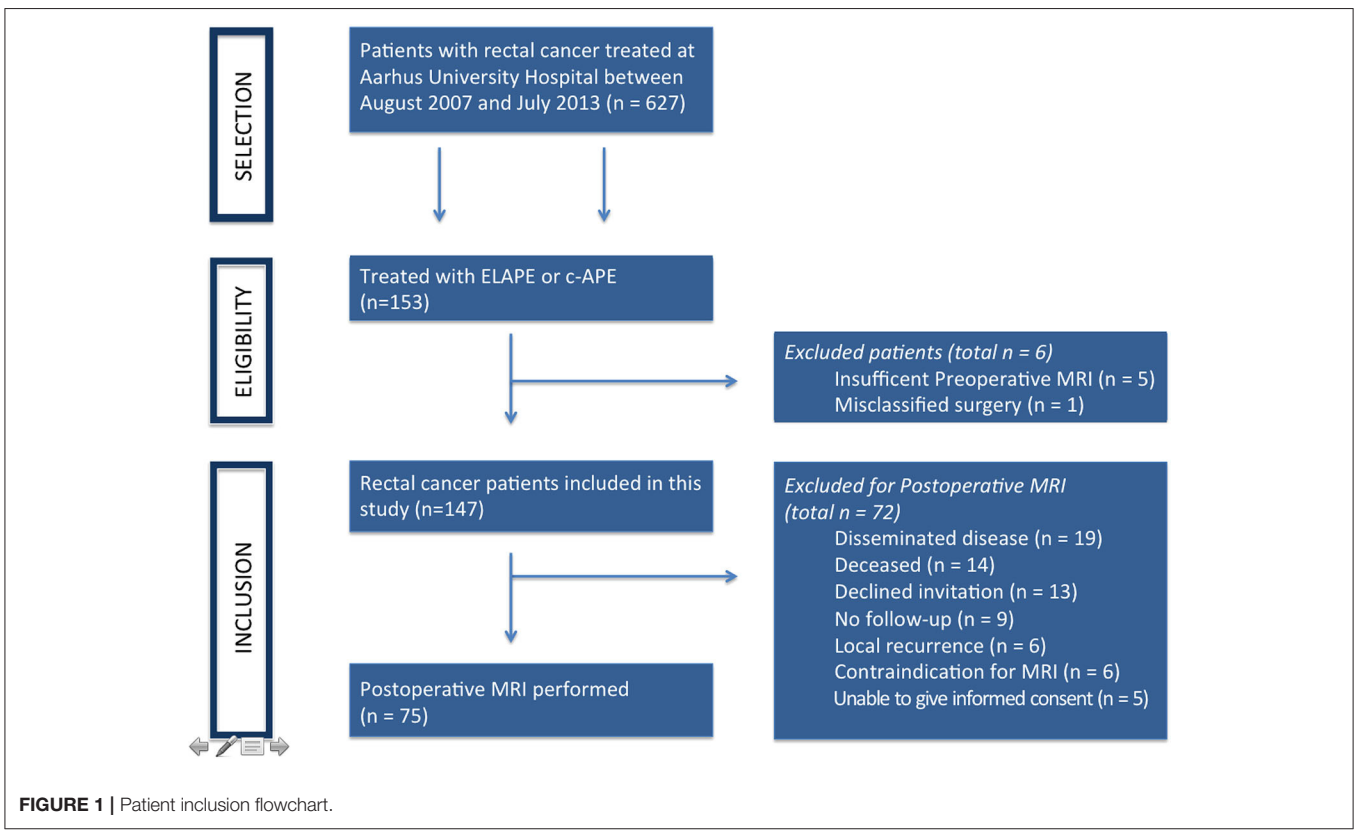

FIGURE 1 | Patient inclusion flowchart.

TABLE 1 | Demographic and clinical data.

	N = 147
Sex ratio, M:F	91:56 (38.1% F)
Median age in years (range)	67 (40–89)
Distance of primary tumor to anal verge by rigid proctoscopy in centimeters	
→ 0–1.9	10 (6.8)
→ 2–3.9	54 (36.7)
→ 4–5.9	42 (28.6)
→ ≥6	12 (8.2)
→ Missing	29 (19.7)
Neoadjuvant therapy	
→ None	54 (36.7)
→ CRT	93 (63.3)
T-category on MRI	
→ T2	36 (24.5)
→ T3	78 (53.1)
→ T4	32 (21.7)
→ Tx	1 (0.7)
Tumor orientation on MRI	
→ Anterior	73 (49.3)
→ Other	74 (50.7)
Surgery	
→ ELAPE	125 (85.0)
→ c-APE	22 (15.0)
Pathological T-category*	
→ pT0	10 (6.8)
→ pT1	5 (3.4)
→ pT2	48 (32.7)
→ pT3	71 (48.3)
→ pT4	13 (8.8)
Circumferential resection margin	
→ Not involved	124 (84.4)
→ Involved	23 (15.6)
Venous invasion	
→ V0	106 (72.1)
→ V1-V2	41 (27.9)
Lymph node involvement	
→ N0	113 (76.9)
→ N1-N2	33 (22.4)
→ Missing	1 (0.7)
Mesorectal plane of surgery	
→ Mesorectal	39 (26.5)
→ Intramesorectal	43 (29.3)
→ Musc. Propria	64 (43.5)
→ Not reported	1 (0.7)
Perineal plane of surgery	
→ Extralevator plane	19 (12.9)
→ Sphincteric plane	59 (40.1)
→ Intramuscular/submucosal plane	60 (40.8)
→ Not reported	9 (6.2)
Local recurrence	
→ Yes	11 (7.5)
→ No	136 (92.5)

Values in parentheses are percentages unless indicated otherwise.
**Based on pathological evaluation of excised specimen (the pathological tumor category for the 94 patients who had preoperative adjuvant therapy (ypT) was: T0, 10; T1, 4; T2, 24; T3, 43; T4, 11).*
CRM, circumferential resection margin; MRI, magnetic resonance imaging.

The disparity in outcomes may reflect differences in operative approach and quality. In 2018, Holm argued that since no formal standardization of the c-APE exists, the procedure has gradually taken on characteristics of the ELAPE, thus explaining why rates of involved CRM and local recurrence in c-APE have improved (26). Using postoperative MRI allows the assessment of the extent and completeness of mesorectal excision after surgery for rectal cancer (27, 28). This makes postoperative MRI an expedient method for quality assessment of both surgery and pathological assessment of the specimen.

In this study, we aimed to investigate the prevalence and localization of inadvertent residual pelvic diaphragm (RPD) on postoperative MRI after ELAPE and c-APE. Clinical data were analyzed for potential risk factors for having RPD at postoperative MRI, and for the involvement of the CRM at pathological evaluation.

METHODS

In 2007, an audit on the quality of rectal cancer treatment and surgery was implemented at Aarhus University Hospital, Denmark. The audit was part of a large regional audit with a focus on postgraduate training of colorectal MDTs in the North and Central Denmark Region. This study was approved as a quality assurance project by the local ethics committee with no need for oral or written consent required by Danish law.

Population

The Department of Surgery at Aarhus University Hospital had a primary catchment population of 400.000 inhabitants during the study period, during which approx. one hundred and twenty patients with rectal cancer were treated annually. The department serves as a secondary referral center for advanced low rectal cancer in the region (population 1.25 million) and as the tertiary referral center for very advanced as well as locally recurrent rectal cancer in Denmark (population 5.8 million). Patients with low rectal adenocarcinoma who underwent ELAPE or c-APE between October 2007 and July 2013 were included (**Figure 1**). Consecutive patients were invited for postoperative MRI of the pelvis. Excluded were patients with disseminated disease, previous diagnosis of local recurrence, contraindication for MRI, unable to give informed consent, or deceased.

A total of 147 patients treated with ELAPE or c-APE between 2007 and 2013 were included. Patient and

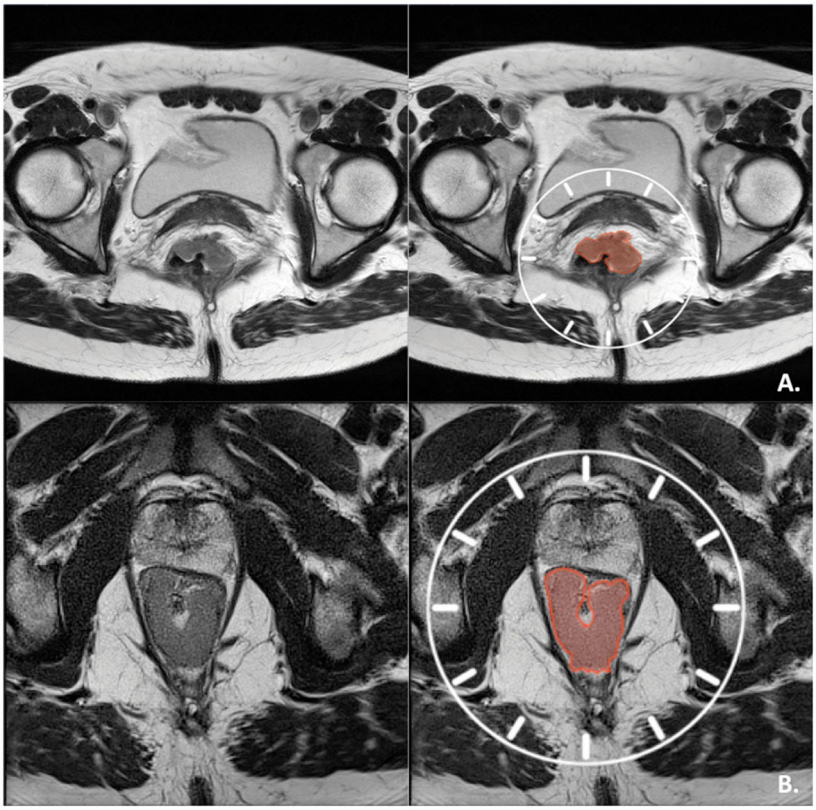

FIGURE 2 | Tumor orientation. **(A)** Axial T2-weighted view of an anterior mrT3 tumor with center and invasive component between 11 and 1 o'clock. **(B)** Axial T2-weighted view of a non-anterior, early mrT3 tumor with center and invasive component between 5 and 7 o'clock.

treatment characteristics are shown in **Table 1**. Of the 147 patients, 75 (51%) had postoperative MRI performed. Postoperative MRI was performed a median of 12 months after primary surgery.

Data on patient characteristics and clinical information were obtained from clinical records. Throughout the study period, the preferred and standard surgical approach for low rectal cancer at Aarhus University Hospital was the ELAPE performed with the intent of removing all posterior muscular pelvic diaphragm (29). Professor Holm introduced and supervised the procedure at the hospital while appointed there.

Low rectal cancer was defined as tumors located between 0 and 5 cm from the anal verge, measured by rigid proctoscopy. Topographical relations of the tumor were weighted over standardized measurements, and thus, selected patients with tumors above 5 cm from the anal verge but within a short distance of the levators at preoperative MRI were treated with ELAPE or c-APE and consequently included in this study.

In accordance with Danish guidelines, patients with low rectal and UICC TNM category T3 or T4 tumors were referred for long-course neoadjuvant CRT. Treatment planning including the decision of surgical approach was made at a multidisciplinary conference.

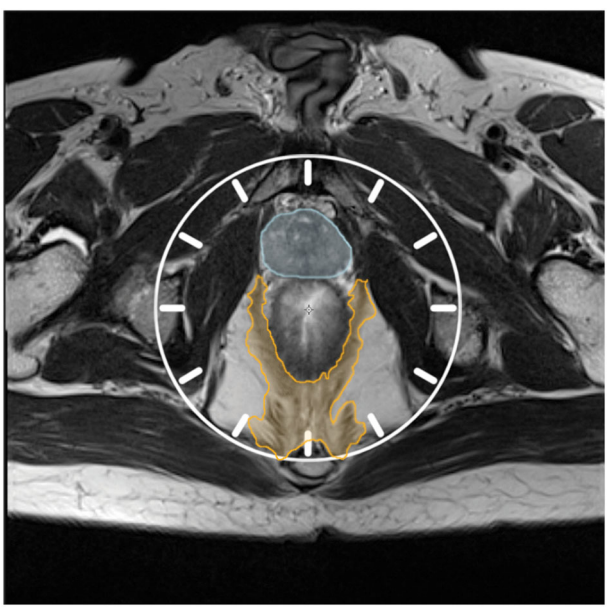

FIGURE 3 | Visualizing the axial plane of T2w MRI as the face of a clock. Orange hatching: Pelvic diaphragm. Blue hatching: Prostate.

Postoperative MRI

A dedicated MRI protocol was developed, including sagittal, axial, and coronal T2-weighted turbo spin echo images, slice thickness of 4 mm, in addition to a sagittal, short T1 inversion recovery (STIR) sequence of the bony pelvis and a sagittal T2 3D sequence of the pelvis. Postoperative MRIs were performed a minimum of 6 months after surgery to avoid confusion with postoperative changes.

Tumor Location and Orientation in the Axial Plane

Tumor center and location(s) of invasive growth (if applicable) were determined on the preoperative MRIs. Tumors with a center or invasive growth between 10 o'clock and 2 o'clock were classified as "anterior," while tumors with a center or invasive growth between 2 and 10 o'clock were classified as "non-anterior" (**Figure 2**).

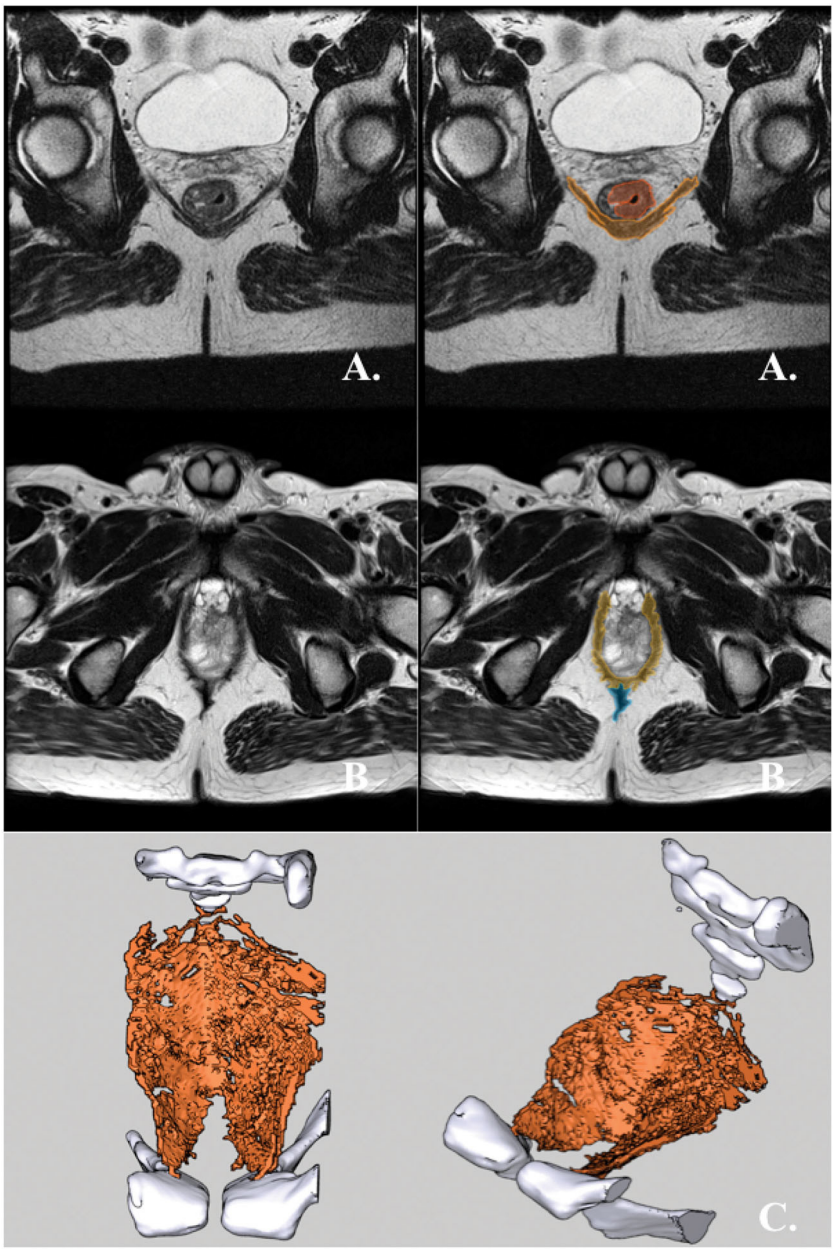

FIGURE 4 | c-APE. **(A)** Preoperative axial T2-weighted MRI of a rectal cancer patient with an mrT3-tumor with invasive growth between 2 and 4 o'clock. RPD is hatched in orange. The tumor is hatched in red. **(B)** Postoperative axial T2-weighted MRI of the same patient after cAPE. RPD is hatched in orange. Cicatrice is hatched in blue. **(C)** The RPD of the same patient, 3D-rendered and shown in superior and antero-lateral superior views. The rendering is made from the above postoperative MRI. The bony pelvis is rendered in white, while RPD is rendered in orange. No bio-mesh was used for supporting the closure of the defect in the pelvic diaphragm.

Residual Pelvic Diaphragm

The residual pelvic diaphragm was defined as any remaining levator ani and/or coccygeal muscle visible on postoperative MRI in the two posterior quadrants of the pelvis [from 3 to 6 and 6 to 9 o'clock if visualizing the axial plane of an MRI of the mesorectum and pelvic diaphragm as the face of a clock (**Figure 3**)]. The MRI examinations were all evaluated by a dedicated multidisciplinary team radiologist subspecialized in pelvic MRI and reviewed together with co-author PB for consensus. The multidisciplinary team radiologist was blinded to all clinical data with the exception of the preoperative MRI examination.

Pathology

The pathological evaluation followed a standardized protocol with the assessment of the surgical plane achieved in the mesorectal and the perineal segments (30, 31). The CRM was considered involved if a distance of 1 mm or less was observed between any vital tumor cell and the resection margin. Inspecting standardized photo documentation, an experienced colorectal pathologist retrospectively evaluated the specimens for surgical plane and volume defects in the pelvic diaphragm. The pathological assessment was blinded to the clinical data and MRI findings.

3D Rendering of MRI

Three-dimensional renders of the pelvic diaphragm at T2w images were made to ensure a better spatial understanding of the anatomy of the pelvic diaphragm and for aiding visualization of the surgical planes before and after ELAPE or c-APE surgery (32). Amira version 5.6 (Thermo Fischer Scientific, Waltham, MA, United States) at a Windows platform was used for image segmentation and 3D rendering. Segmentation was done semi-automatically and reviewed by an experienced radiologist with more than 10 years of experience with pelvic MRI.

Statistical Analysis

For comparison of categorical data distributions, $\chi 2$-test, Fisher's exact test, or the Fisher–Freeman–Halton test was used. $P < 0.05$ were considered statistically significant. The programming language "R" (R Foundation for Statistical Computing, Vienna, Austria) and the coding program "RStudio" (RStudio, Inc., Boston, MA) were used for statistical analysis.

RESULTS

Detection of RPD on Postoperative MRI

Of the 147 patients, 75 (51%) had postoperative MRI performed. Upon the evaluation of postoperative MRIs, RPD was present in 60 (80%) of 75 patients. Sixty-one (81%) of the 75 patients had an ELAPE performed. All 14 patients treated with c-APE had RPD in both posterior quadrants of the pelvis on postoperative MRI (**Figure 4**). Thus, in the included c-APEs, the muscular pelvic diaphragm was retained as intended.

The residual pelvic diaphragm in any posterior quadrant of the pelvis was identified on postoperative MRI in 46 of 61 ELAPEs (75%, **Table 2**). Of 46, 13 had RPD in one posterior quadrant (3-6 o'clock OR 6-9 o'clock, as per **Figure 3**), while 33 had RPD in both posterior quadrants (**Figure 5**). The remaining 15 had no visible RPD in either posterior quadrant (**Figure 6**). Although performed with the intent to completely excise the

TABLE 2 | RPD on postoperative MRI, ELAPE-subgroup.

	N = 61	Residual pelvic diaphragm (*n* = 46)	No residual pelvic diaphragm (*n* = 15)	*p* value
Sex ratio (M:F)		29:17	8:7	0.504
Distance of primary tumor to anal verge by rigid proctoscopy (cm)€				0.455
→ 0–1.9	4	2 (50)	2 (50)	
→ 2–3.9	27	22 (81)	5 (19)	
→ 4–5.9	17	12 (70)	5 (30)	
→ >6	4	3 (75)	1 (25)	
→ Missing	9	7 (78)	2 (22)	
Neoadjuvant therapy				0.061
→ None	28	18 (64)	10 (36)	
→ CRT	33	28 (85)	5 (15)	
CRM$				>0.999
→ Involved	7	5 (71)	2 (29)	
→ Not Involved	54	41 (76)	13 (24)	
Tumor location on MRI				0.266
→ Anterior	29	20 (69)	9 (31)	
→ Other	32	26 (81)	6 (19)	
Pathological T-category§,€				0.194
→ pT0	5	4 (80)	1 (20)	
→ pT1	5	5 (100)	0 (0)	
→ pT2	23	16 (70)	7 (30)	
→ pT3	25	20 (80)	5 (20)	
→ pT4	3	1 (33)	2 (67)	
Mesorectal plane of surgery€				0.867
→ Mesorectal	17	13 (76)	4 (24)	
→ Intramesorectal	16	13 (81)	3 (19)	
→ Musc. Propria	28	20 (71)	8 (29)	
Perineal plane of surgery				0.981
→ Extralevator plane	8	6 (75)	2 (25)	
→ Sphincteric plane	27	21 (78)	6 (22)	
→ Intramuscular/ submucosal plane	25	19 (76)	6 (24)	
→ Not reported	1	0 (0)	1 (100)	
Local Recurrence				>0.999
→ Yes	6	5 (83)	1 (17)	
→ No	55	41 (75)	14 (25)	

Values in parentheses are percentages unless indicated otherwise.
Residual levator was defined as any muscular pelvic diaphragm visible on MRI in the two posterior quadrants of the pelvis, i.e., between 3 and 9 o'clock.
§ Based on pathological evaluation of excised specimen (the pathological tumor category for the 33 patients who had preoperative adjuvant therapy (ypT) was: T0, 5; T1, 4; T2, 9; T3, 13; T4, 2).
$: Fischer's exact test.
€: Freeman–Halton test.
CRM, circumferential resection margin; MRI, magnetic resonance imaging.

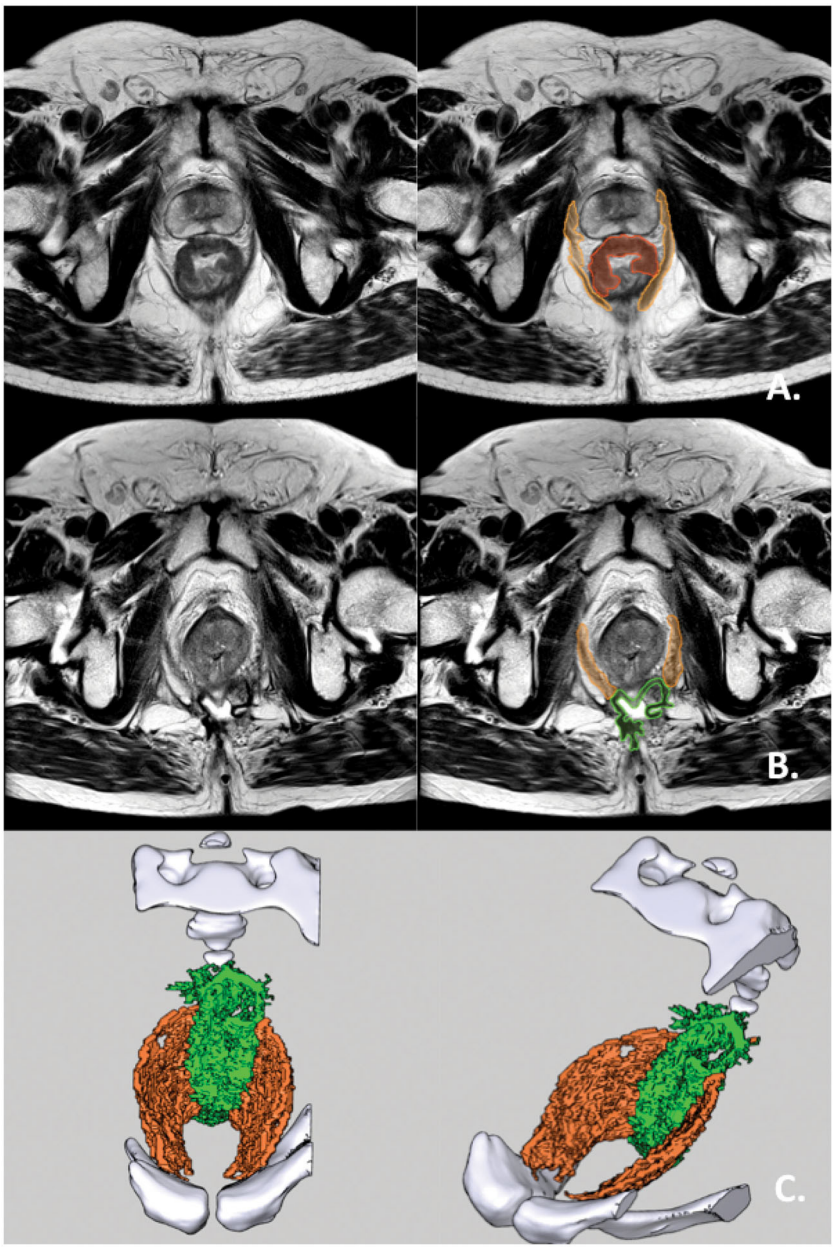

FIGURE 5 | ELAPE with RPD in both posterior quadrants. **(A)** Preoperative axial T2-weighted MRI of a rectal cancer patient with an mrT3 tumor with invasive growth from 9 o'clock to 2 o'clock. The pelvic diaphragm is hatched in orange. The tumor is hatched in red. **(B)** Postoperative axial T2-weighted MRI of the same patient. RPD hatched in orange while supporting mesh hatched in green. **(C)** The pelvic diaphragm of the same patient, 3D-rendered and shown in superior and antero-lateral superior views. The rendering is made from the above postoperative MRI. The bony pelvis is rendered in white. RPD is rendered in orange. Supporting mesh is rendered in bright green.

pelvic diaphragm in the posterior quadrants, this was not achieved in 75% of ELAPEs.

In those treated with ELAPE, male sex, neoadjuvant therapy, the distance of primary tumor to the anal verge, involved CRM, tumor orientation, pathological T-category, surgical planes, and local recurrence were not found to be univariate risk factors of RPD (**Table 2**).

Circumferential Resection Margin Involvement

Twenty-three (16%) of 147 patients had an involved CRM at pathological evaluation. An increased risk of involved CRM after surgery was observed in anteriorly oriented tumors with 16 (22%) of 73 after surgery compared with 7 (9%) of 74 non-anteriorly oriented tumors ($p = 0.038$). The increased

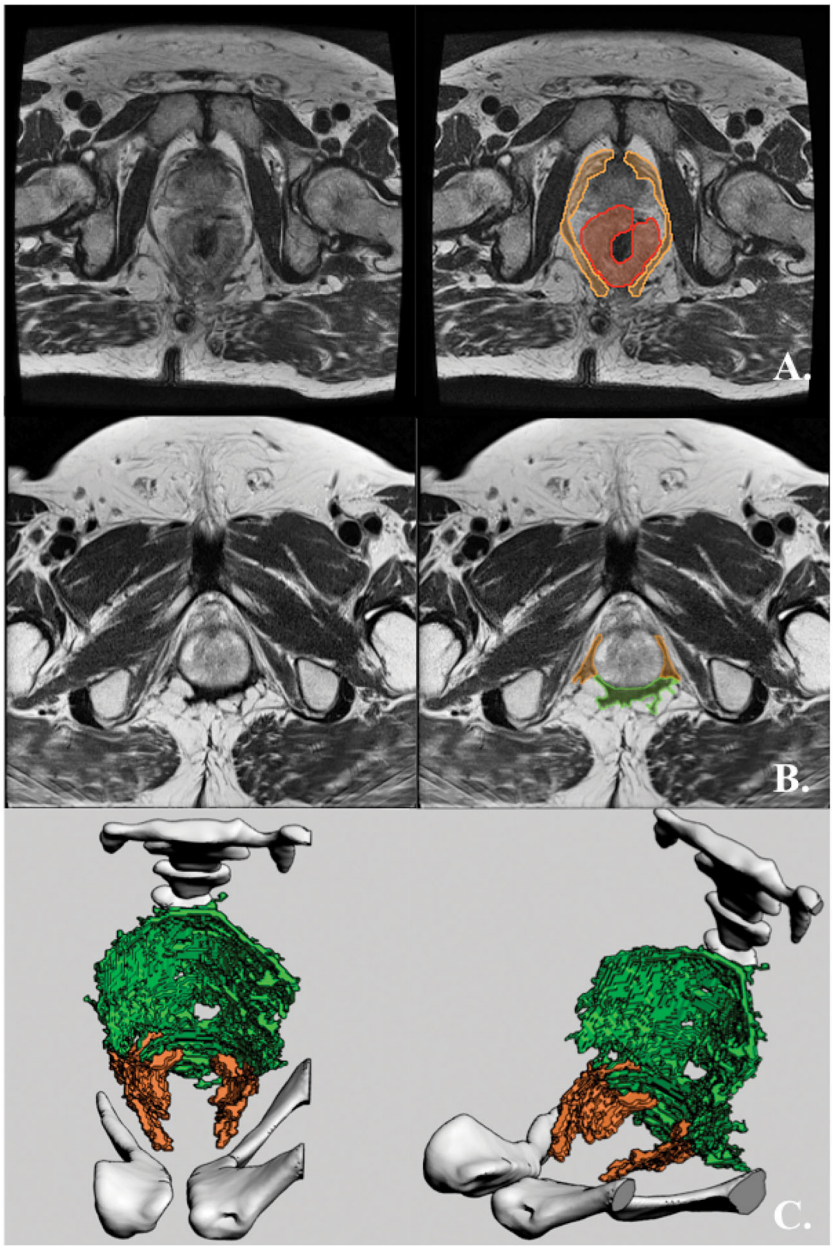

FIGURE 6 | ELAPE without RPD in the posterior quadrants. **(A)** Preoperative axial T2-weighted MRI of a rectal cancer patient with an mrT3 tumor with circumferential growth (from 1 o'clock to 1 o'clock) and invasive growth from 3 o'clock to 8 o'clock. RPD is hatched in orange, while the tumor is hatched in red. **(B)** Postoperative axial T2-weighted MRI of the same patient. RPD hatched in orange while supporting mesh hatched in green. **(C)** The pelvic diaphragm of the same patient, 3D-rendered and shown in superior and antero-lateral superior views. The rendering is made from the above postoperative MRI. The bony pelvis is rendered in white, RPD is rendered in orange, and supporting mesh is rendered in bright green.

risk in anteriorly oriented tumors was the same in the subgroup of patients treated with ELAPE ($n = 125$, $p = 0.038$). Advanced pathological tumor stage ($p < 0.001$), venous invasion ($p < 0.001$), regional lymph node involvement ($p < 0.001$), and tumor height above 6 cm by rigid proctoscopy (p= 0.034) were also found to be univariate risk factors for an involved CRM (**Table 3**).

Correlation Between Histopathological Assessment and Postoperative MRI

In 24 (32%) of the 75 specimens, no pathological data were recorded on defects in the levator ani in the specimen. Of those remaining 51 specimens (45 ELAPE, 6 c-APE), the pathologist's re-evaluation based on standardized photographic documentation showed the presence of defects in the levator

TABLE 3 | Full cohort by CRM ($n = 147$).

	CRM+ ($n = 23$)	CRM– ($n = 124$)	*p* value
Sex ratio (M:F)	11:12	80:44	
Age (years)*	68	67	
Distance of primary tumor to anal verge by rigid proctoscopy (cm)			0.034
→ 0–1.9	1 (10)	9 (90)	
→ 2–3.9	9 (17)	45 (83)	
→ 4–5.9	4 (9)	38 (91)	
→ ≥6	5 (42)	7 (58)	
→ Missing	4 (14)	25 (86)	
Neoadjuvant therapy			0.655
→ None	7 (13)	47 (87)	
→ CRT	16 (17)	77 (83)	
T-category on MRI€			0.656
→ T2	4 (11)	32 (89)	
→ T3	11 (14)	67 (86)	
→ T4	8 (25)	24 (75)	
→ Tx	0 (0)	1 (100)	
Tumor orientation on MRI			0.038
→ Anterior	16 (22)	57 (78)	
→ Other	7 (9)	67 (91)	
Surgery$			>0.999
→ ELAPE	20 (16)	105 (84)	
→ c-APE	3 (14)	19 (86)	
Pathological T-category§,€			<0.001
→ pT0	0 (0)	10 (100)	
→ pT1	1 (20)	4 (80)	
→ pT2	0 (0)	48 (100)	
→ pT3	15 (21)	56 (79)	
→ pT4	7 (54)	6 (46)	
Venous invasion			<0.001
→ V0	7 (7)	99 (93)	
→ V1-V2	16 (39)	25 (61)	
Lymph node involvement			<0.001
→ N0	10 (9)	103 (91)	
→ N1-N2	13 (39)	20 (61)	
→ Missing	0 (0)	1 (100)	
Mesorectal plane of surgery			0.280
→ Mesorectal	3 (8)	36 (92)	
→ Intramesorectal	8 (19)	35 (81)	
→ Musc. Propria	12 (19)	52 (81)	
→ Not reported	0 (0)	1 (100)	
Perineal plane of surgery			0.128
→ Extralevator plane	1 (5)	18 (95)	
→ Sphincteric plane	8 (14)	51 (86)	
→ Intramuscular/submucosal plane	14 (23)	46 (77)	
→ Not reported	0 (0)	9 (100)	
Local recurrence			0.002
→ Yes	6 (55)	5 (45)	
→ No	17 (13)	119 (87)	

Values in parentheses are percentages unless indicated otherwise.

** Values are median (range).*

§ Based on pathological evaluation of excised specimen (the pathological tumor category for the 94 patients who had preoperative adjuvant therapy (ypT) was: T0, 10; T1, 4; T2, 24; T3, 43; T4, 11).

$: Fischer's exact test.

€: Freeman–Halton test.

CRM, circumferential resection margin; MRI, magnetic resonance imaging.

ani in 90% (46 of 51) and 89% (40 of 45) of those treated with ELAPE. In the subgroup of patients treated with ELAPE, findings of any RPD in posterior quadrants on postoperative MRI were in agreement with findings of any defects in the levator ani by pathological evaluation in 76% of cases (34 of 45).

Local Recurrence

Local recurrence was detected in 11 (7%) of 147 patients within the follow-up period. Involved CRM was an independent risk factor for local recurrence ($p = 0.002$). Five (11%) of 46 patients with RPD after ELAPE developed local recurrence compared with 1 (7%) out of 15 of those who had no RPD.

DISCUSSION

During the study period, a standardized ELAPE was the procedure of choice, performed with the intent to remove all muscular pelvic diaphragms in the two posterior quadrants to reduce the risk of an involved margin. Inadvertent RPD was found in 46 (75%) of 61 postoperative MRIs of patients treated with ELAPE. Since RPD was detected in all patients who had a c-APE performed, we conclude that postoperative MRI of the pelvis reliably estimates the prevalence and localization of RPD.

An involved CRM was determined in 23 (16%) of 147 patients and associated with anteriorly located tumors.

A recent national Danish study has evaluated the rate of CRM positivity and surgical outcome after standard APE vs. ELAPE and found no difference in the outcomes following standard APE or ELAPE, but more patients suffered from wound complications and perineal pain after ELAPE (18, 21, 22). However, this was solely registry based and exact definitions of the surgical planes were lacking.

Anteriorly located tumors presented a univariate risk factor for CRM involvement (22%). Among those treated with ELAPE, the comparatively low rate of involvement of the CRM in non-anteriorly oriented tumors (9%) in the present study suggests that patients with these tumors benefited from the wide posterior excision that is the hallmark of the ELAPE. The available literature emphasizes the importance of anterior dissection,

as the CRM will be narrower in this area, particularly with anterior tumors (33). Preoperative evaluation and identification of patients at risk of positive CRM with MRI is crucial for appropriate tailoring of both neoadjuvant therapy and operative approach. This corresponds well with the notion that ELAPE would not reduce the risk of CRM involvement in anterior tumors compared with c-APE as the volume resected in the anterior compartment is essentially the same. Thus, choosing an ELAPE over a c-APE for an anteriorly oriented tumor provides no oncological benefit for the patient, although it retains its associated higher morbidity. Whether or not a tumor invades the anterior compartment should be carefully considered when deciding surgical approach. In these situations, a negative margin is feasible by extending the surgical plane into the anterior viscera for partial or en-bloc removal—individualizing the optimal surgical plane (34–36).

In mesorectal excision surgery, the mesorectal fascia presents an anatomical border, which may be readily assessed for completeness of surgery—by MRI and pathological analysis alike. The attachment sites of the muscular pelvic diaphragm present no such solid anatomical border, and histopathology by definition only evaluates that which is removed. This leaves room for the pathologist over- or underestimating the amount of pelvic diaphragm left behind. Thus, in the case of ELAPE and c-APE, histopathological evaluation may be insufficient for the assessment of the completeness of surgery.

Low rectal cancer is a multifaceted malignancy that runs a highly variable course with a high risk of severe post-treatment outcomes. Algorithms for selecting a proper treatment course and measures for quality assurance should be multifaceted as well. Individualized surgery has been implemented in many leading surgical centers around the globe. Thus, unilateral ELAPEs and extended c-APEs (c-APE with a slightly wider resection of the pelvic diaphragm without reaching sites of attachment to the pelvis) are often performed today. This has become possible due to a better understanding of the individual case, which may be preoperatively visualized by MRI and discussed at a preoperative MDT conference. As technical advancements continually improve outcomes for patients with low rectal cancer, postoperative MRI may be used for quality control of intended surgery. The authors recommend individualized surgery implemented in a standardized program that includes quality control by MRI after surgery, thus eliminating the use of and reliance on self-reported classifications.

This study enjoys a large degree of data completeness at the individual patient level. Data were collected prospectively for all included patients. As the initial cohort contained all patients with low rectal cancers treated with either ELAPE or c-APE at our treatment center, the patients constitute a consecutive, unselected cohort. The same MRI protocol was adhered to for all patients. None of the previous studies on the subject of ELAPE contained an in-depth analysis of circumferential tumor orientation, although Battersby et al. and Salerno et al. previously described anterior tumor location on MRI as a risk factor for the involvement of CRM in low rectal cancer (37, 38). No previous studies on ELAPE have used postoperative MRI for the assessment of surgical planes. Unfortunately, the data were not stratified by the individual surgeon, which would have enabled us to account for possible operator-dependent differences in outcomes.

In conclusion, RPD after any APE can be depicted by postoperative MRI and was found in the posterior quadrants of the pelvis in 46 (75%) of 61 patients treated with ELAPE. Anterior tumor orientation was a risk factor for CRM involvement regardless of chosen surgical technique.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

In 2007, an audit on quality of rectal cancer treatment and surgery was implemented at Aarhus University Hospital, Denmark. The audit was part of a large regional audit with focus on postgraduate training of colorectal MDTs in North and Central Denmark Regions. This study was approved as a quality assurance project with no need for oral or written consent required by Danish law.

AUTHOR CONTRIBUTIONS

KMO: main author and researcher. PB: project co-supervisor. SL: senior advisor. RH-M: pathological evaluations and expertise. HC: contribution of surgical expertise. HL: contribution of expertise in 3D rendering of MRIs. BGP: main project supervisor.

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REVIEW
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One-Stage Total Laparoscopic Treatment for Colorectal Cancer With Synchronous Metastasis. Is It Safe and Feasible?

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Sena G, Picciariello A, Marino F, Goglia M, Rocca A, Meniconi RL and Gallo G (2021) One-Stage Total Laparoscopic Treatment for Colorectal Cancer With Synchronous Metastasis. Is It Safe and Feasible? Front. Surg. 8:752135. doi: 10.3389/fsurg.2021.752135

Liver is the main target organ for colorectal cancer (CRC) metastases. It is estimated that ∼25% of CRC patients have synchronous metastases at diagnosis, and about 60% of CRC patients will develop metastases during the follow up. Although several teams have performed simultaneous laparoscopic resections (SLR) of liver and colorectal lesions, the feasibility and safety of this approach is still widely debated and few studies on this topic are present in the literature. The purpose of this literature review is to understand the state of the art of SLR and to clarify the potential benefits and limitations of this approach. Several studies have shown that SLR can be performed safely and with short-term outcomes similarly to the separated procedures. Simultaneous laparoscopic colorectal and hepatic resections combine the advantages of one stage surgery with those of laparoscopic surgery. Several reports compared the short-term outcomes of one stage laparoscopic resection with open resections and showed a similar or inferior amount of blood loss, a similar or lower complication rate, and a significant reduction of hospital stay for laparoscopic surgery respect to open surgery but much longer operating times for the laparoscopic technique. Few retrospective studies compared long term outcomes of laparoscopic one stage surgery with the outcomes of open one stage surgery and did not identify any differences about disease free survival and the overall survival. In conclusion, hepatic and colorectal SLR are a safe and effective approach characterized by less intraoperative blood loss, faster recovery of intestinal function, and shorter length of postoperative hospital stay. Moreover, laparoscopic approach is associated to lower rates of surgical complications without significant differences in the long-term outcomes compared to the open surgery.

Keywords: colorectal cancer, liver synchronous metastasis, simultaneous laparoscopic resection, outcomes, timing, one stage treatment

INTRODUCTION

Colorectal cancer (CRC) represents the third most common neoplastic disease in the world with an incidence of about 1.4 million of new cases every year causing 694.000 deaths (1). The main target organ for CRC metastases is the liver (2). It is estimated that ∼20–25% of CRC patients have synchronous metastases at diagnosis, and about 60% of CRC patients will develop metastases in the course of the follow up (3–6). Surgery in association with other treatments, such as neo- or adjuvant chemoradiotherapy or the recently introduced molecular targeted-therapy, represents the only potentially curative option, and allows a significant increase in the overall survival (7, 8). The timing of hepatic and colorectal surgery has been strongly debated in last years with different approaches proposed by several authors. In particular, simultaneous resections have several advantages and, as demonstrated by various reports, do not show an increased morbidity and mortality compared to delayed hepatectomies with significant economic and biological advantages. Therefore, the only contraindications to simultaneous laparoscopic resections (SLR) are complicated CRC, high ASA score and the inability to obtain a radical resection (9–13) even though, some authors recommend performing major hepatectomies only accompanied by resection of the right-sided colon and minor hepatectomies associated with rectal resections (14).

STATE-OF-THE-ART

The management of metastatic liver CRC is multimodal and multidisciplinary and several strategies have been described so far (15, 16). In particular, Ratti et al. (15) recently investigated, in four tertiary high volume referral centers, the role of team strategy optimization in SLR demonstrating that there were no statistically significant differences between patients operated on by the same team for both colorectal and liver resections and patients operated on by the two different teams with particular colorectal or liver skill (15).

Besides the SLR there are three other possibilities: the primary tumor-first approach, the liver-first approach, and the up-front hepatectomy (**Figure 1**).

The "traditional approach" involves the resection of the primary CRC with subsequent adjuvant therapy and then possible treatment of liver metastases after 3–6 months. While this approach reduces the risk of primary tumor progression, it exposes the patient to the possibility of unresectable liver metastases (17). Furthermore, due to complications related to colorectal resection (i.e., anastomotic leak) few patients effectively benefit from this treatment (17, 18).

The liver-first approach, the so called "chemotherapy first," was initially described by Mentha et al. (17) and it is indicated in patients with primary asymptomatic tumors and liver metastases. It includes a preoperative chemotherapy with liver resection and a subsequent colorectal resection. In spite of the traditional approach, it is based on an immediate systemic treatment that aims to reduce the risk of progression of liver metastases as well as the possibility of downstaging the metastases which consequently might become resectable (19). In addition, it avoids unnecessary surgical treatment in chemotherapy non-responder unresectable tumors.

Lastly, the up-front hepatectomy, reported for the first time in 2008 for asymptomatic CRC and resectable liver metastases (20), includes both resections and adjuvant chemotherapy starting with the surgical treatment of liver metastases.

The introduction of minimally invasive procedures has completely transformed the surgical approach of oncological patients. Laparoscopic liver resections were introduced in the 1990s with the first publication in 1991 and 1992 (21–23), although the true spread, with major liver resections, occurred a few years later (24–26). Subsequently, the laparoscopic approach did not found great support by most surgeons due to concerns about the complexity of laparoscopically reproducing open surgery maneuvers, the difficulty of performing a satisfactory bleeding control, the risk of gas embolism and the oncological inadequacy or tumor spread risk (27, 28). Nevertheless, the technological improvements and the introduction of standardized good practices allowed the diffusion of the laparoscopic approach worldwide (29). Nowadays hepatic metastases represent one of the main indications for laparoscopy and, according to the recent Southampton Consensus Guidelines for laparoscopic liver surgery, laparoscopic liver resection has been confirmed as a valid alternative to open surgery, especially if performed by surgeons experienced in both advanced laparoscopic techniques and liver surgery (30). Recently Rocca et al. (31), in a national consensus involving 26 centers, analyzed the boundaries of minimally invasive simultaneous resections for synchronous liver metastasis and primary CRC. Although the authors produced 33 recommendations the level of evidence remains very low.

Indeed, although several teams have performed SLR of both liver and colorectal lesions, the feasibility and safety of this approach is widely debated and few studies on the subject are present in the Literature. The purpose of this review is to analyze the state of the art of SLR for synchronous liver metastases and primary CRC, identifying the potential benefits and limitations of this approach.

SURGICAL TECHNIQUE

The placement of the trocars depends on the type of resection that will be performed (**Figures 2**, **3**) (31, 32) and the surgical steps are performed as described by other authors (33, 34) (**Figure 4**).

ADVANTAGES AND DISADVANTAGES OF ONE STAGE LAPAROSCOPIC APPROACH

SLR have several advantages and disadvantages (**Figure 5**) (35). The formers are represented by the execution of a single surgical procedure, the possibility of performing a complete neoadjuvant therapy, the removal of the whole macroscopic neoplastic region and the interruption of the "metastatic cascade," and the absence of immunosuppression following the first surgery which increases metastatic cell proliferation and progression of the tumor. However, the combination of a "clean" and a "contaminated" procedure can increase the risk of septic

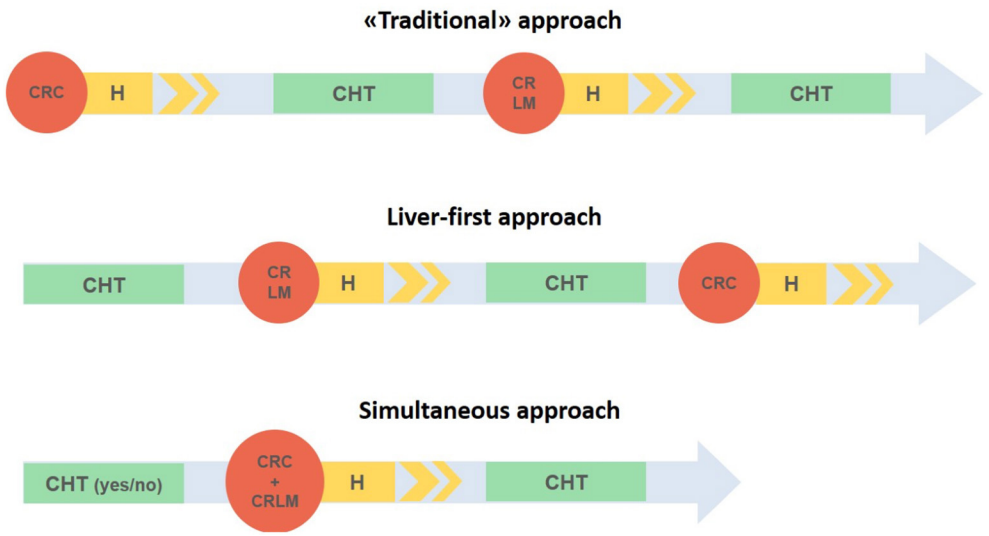

FIGURE 1 | Three different strategies in case of synchronous liver metastases and colorectal cancer. CRC, Colorectal cancer; CRLM, colorectal liver metastases; H, hospital stay; CHT, chemotherapy.

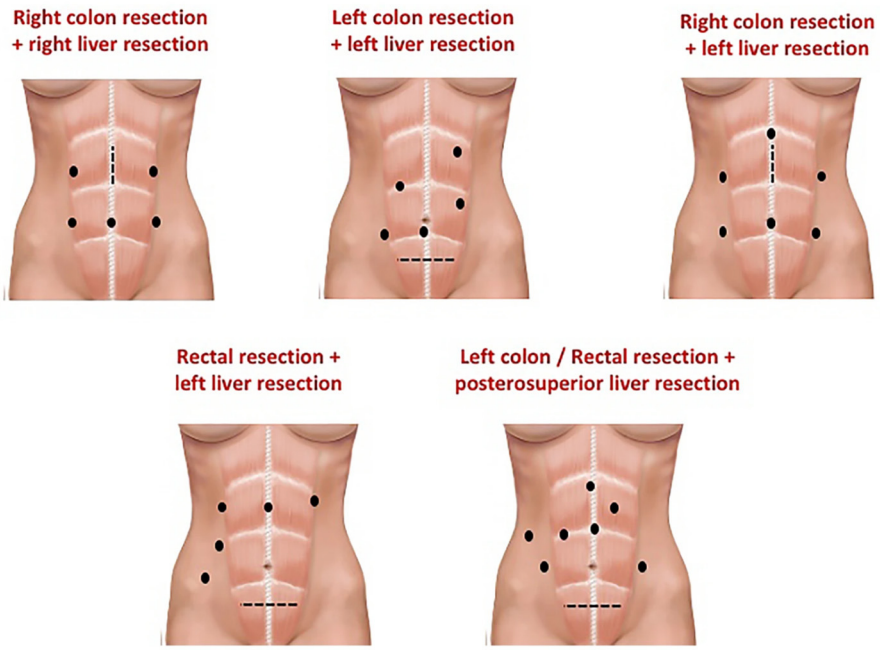

FIGURE 2 | Example of trocar placement to perform a combined resection. From Rocca et al. (31).

complications (36, 37). In particular, the most frequent event is an intraoperative bacterial contamination of the liver surface.

Moreover, a technical aspect that could worsen the outcome of combined resections is the risk of anastomotic leak due to splanchnic congestion following the liver pedicle clamping (38). For this reason, Pringle maneuver should not be used routinely (28).

Usually, low rectal anastomoses present a greater risk of anastomotic leakage compared to other intestinal anastomoses (39–41).

Several studies have shown that SLR can be performed safely and with short-term outcomes similarly to the two-stage procedures (9–11, 13). Moreover, in the last few years the indications have been progressively enlarged regarding the extension of hepatic resections. Indeed, in a 19-year case series, Capussotti et al. showed that 31 patients who underwent major hepatic resections concurrent with colorectal surgery had similar mortality and morbidity rates compared to 48 patients with delayed liver surgery (3 vs. 0% and 33 vs. 33%, respectively) (12). These results were consistent with those reported by other

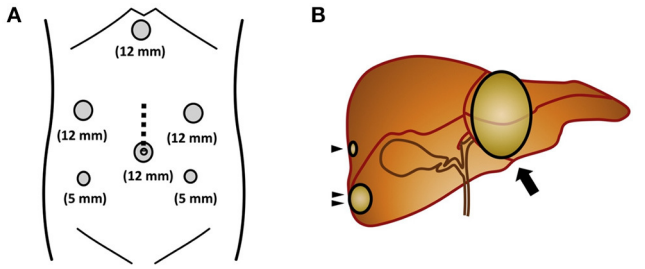

FIGURE 3 | (A) The surgical trocar sites. The dotted line indicates the incision line used for the hand-assisted laparoscopic procedure, which was 7-cm long. **(B)** Liver scheme. Arrowhead, a tumor measuring 5 mm was found in the right hepatic lobe (segment 7); Double arrowhead, another tumor was detected in the right hepatic lobe (segment 6); Arrow, a third metastatic tumor was observed in the left hepatic lobe (segments 2/3). From Ito et al. (32).

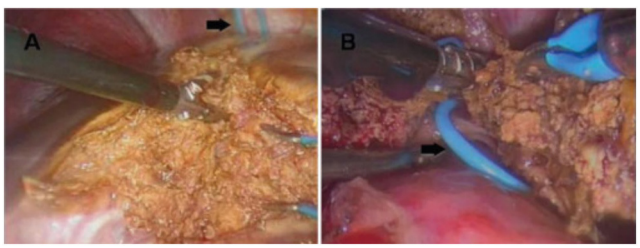

FIGURE 4 | (A) Parenchymal transection during a left hepatectomy, performed with a thermofusion device. **(B)** The hepatic vein previously controlled with a vessel loop (black arrow) is sectioned at the end of liver division. From Tranchart et al. (34).

authors (9, 13). Therefore, major hepatic resections should not be considered as absolute contraindications to SLR, but a careful patient selection is recommended. Interestingly, Ito et al. (32) demonstrated the feasibility of simultaneous resection in two elderly patients aged 78 and 83 years with ascending colon cancer and synchronous liver metastases. This study is consistent with the fact that an SLR should be considered in patients with limited liver metastases extension. Usually, in a patient with rectal cancer and a concomitant involvement of the liver that requires a major hepatectomy, it is preferred to avoid this kind of strategy (14, 42).

SLR combine the advantages of one stage surgery with the classic ones of laparoscopic surgery. An important technical advantage of laparoscopy is the magnified view which allows a better identification of the structures to be preserved (43, 44). Nevertheless, the laparoscopic approach eliminates the need for long incision laparotomy allowing less postoperative pain, faster gastrointestinal recovery and reduced bowel adhesions. Lastly, lesions located in the left anterior and lateral segments remain the best candidates for laparoscopy, even in the case of SLR. However, among the examined papers, postero-superior resections are also documented (VII and VIII segment) (45, 46).

Currently, contraindications to simultaneous resections are as follows: urgent colorectal surgery for symptomatic cancers, low performance status or high ASA score, impossibility of obtaining a radical resection. Besides these, the classic contraindications of laparoscopy such as severe heart disease, coagulation diseases, severe respiratory diseases, should be considered.

An important limitation to the laparoscopic approach of the liver is given by the need to adapt to a caudal-to-cranial view, unlike the broader vision obtained in open surgery. For this reason, lesions located very high or laterally can be difficult to be visualized (47). Moreover, laparoscopic instruments do not allow the same degree and freedom of movement as the human hand, nor the "tactile feedback." Therefore, the mobilization of the liver is more difficult and severe bleeding cannot be controlled for a long time in laparoscopy. Despite the introduction of 3D cameras, flexible instruments, and increasingly effective and performing devices for dissection, laparoscopic liver surgery remains technically challenging and requires a long and complex learning curve. In a recent review of the Literature, evaluating 19 retrospective studies, it was shown that the learning curve was 15–64 cases for minor resections and at least 50 cases for major resections (48).

OUTCOMES

There are significant differences between the open and laparoscopic approach not only from a technical point of view but also from the outcomes (**Figure 6**) (49).

Several reports assessed the short-term outcome of hepatic and colorectal SLR showing a similar or inferior blood loss, a similar or lower complication rate, and an important reduction of hospital stay for laparoscopic surgery respect to open surgery. On the contrary, longer operating times of laparoscopic surgery are generally reported (34, 50–56) even though in some referral centers shorter operative times are also registered (57, 58). The long-term outcomes are also comparable with the previously described cases of abdominal metastases especially at port sites (59, 60). The latter have been largely overcome thanks to some technical measures like the "no touch" technique, the specimen bag, and the abdominal wall protection (61).

The morbidity ranges between 5 and 48% for minor liver resections and between 33 and 55% for major resections (19, 20, 62).

The first studies have been published at the end of the last decade and evaluated the safety and feasibility of a simultaneous approach (63, 64).

In this context, Akiyoshi et al. showed acceptable operative time (the median total operating time was 446 min, including 222 min for colorectal resection) and blood loss (the median total estimated blood loss was 175 ml, including 10 ml for colorectal resection) with reduced complications (65).

Polignano et al. showed a shorter operating time (370 vs. 467 min, $p = 0.005$), reduced blood loss (50 vs. 40 ml, $p = 0.02$) and reduced hospital stay (7 vs.14 days; $p = 0.1$) of one stage laparoscopic surgery compared to two-stage laparoscopic surgery (66). Most of the studies considered SLR with minor hepatectomies.

After Capussotti and colleagues (12), also Tranchart et al. reported two cases of one stage major liver resections associated with colic resections in patients with large unilobular metastases,

Controversial issue	Advantages	Disadvantages
Mini-invasive *vs* open colorectal surgery	Achieves better perioperative results; achieves similar oncological results	In case of rectal resection, may determine a higher risk of suboptimal oncological results at histopathology; in case of rectal resection, its overall impact on oncological outcomes is still uncertain
Mini-invasive *vs* open liver surgery	Achieves better perioperative results; achieves at least similar oncological results; rapid technological evolution; rapid growth of surgical experience and skill	Usually preferred for limited disease, in favourable locations and selected patients; may determine more complex and longer procedures; may determine more extended hepatectomies; less frequently used for major LR, including TSH and ALPPS, and for CRLM in postero-superior segments and in the caudate lobe; may determine higher costs
Mini-invasive *vs* open simultaneous colorectal and liver resection	Achieves better perioperative results; achieves similar oncological results	Usually preferred for limited liver disease, in favourable locations, and higly selected patients; may determine more complex and longer procedures; may determine higher costs
Mini-invasive *vs* open PSLR	Achieves better perioperative results; achieves similar oncological results; rapid technological evolution; rapid growth of surgical experience and skill	The principles of PSLR are time-consuming and rather difficult to apply during mini-invasive procedures; usually preferred for limited disease, in favourable locations and selected patients; may determine more complex and longer procedures; may determine higher costs
The impact of PSLR on mini-invasive simultaneous resection	May achieve better perioperative results; may achieve similar oncological results	May determine more complex and longer procedures; may have very limited indications

FIGURE 5 | Controversial issues involving mini-invasive (laparoscopic and robotic) surgical strategies for colorectal cancer with synchronous resectable liver metastases. LR, Liver resection; TSH, Two-stage hepatectomy; ALPPS, Associating liver partition and portal vein ligation for staged hepatectomy; CRLM, Colorectal liver metastases; PSLR, Parenchymal-sparing liver resection. From De Raffele et al. (35).

demonstrating their reliability without an increase in the complication rate (34).

Spampinato and colleagues reported a case series of 5 patients underwent major hepatectomies (67). Although with longer operating times, the results were consistent with those reported by Tranchart (34). None of the patients experienced anastomotic or bile leak and there were only 1 liver metastasis recurrences that were treated with a new laparoscopic operation.

Muangkaew et al. compared SLR, including major hepatectomies, with major liver resections alone, reporting no differences in hospital stay length (14.9 days vs. 13.3 days; $p = 0.345$), overall rate of postoperative complications (76.4 vs. 62.5 %; $p = 0.126$), colonic anastomotic leakage or sepsis, but a longer time in starting a soft diet for SLR (6.0 vs. 3.4 days; $p < 0.001$) (68).

In a recent systematic review, which examined 12 retrospective studies (4 comparative and 8 non-comparative), Moris et al. reported no differences in operating times (335.5 vs. 325.5 min) and incidence of complications between patients undergoing laparoscopic surgery and open surgery and lower blood losses for laparoscopic surgery (266.5 vs. 398 ml) (4). According to the same authors, also oncological outcomes were similar.

In a single-center and -surgeon experience considering 17 SLR, the authors reported a 94% rate of R0 resection margin on the liver and 100% distal and circumferential free-margin for the colorectal specimen (69).

Ferretti et al. (70) reported 142 laparoscopic liver resections in a SLR setting. Tumor recurrence occurred in 40 patients (28.2%) after a median follow-up of 29 (1–108) months with an overall survival of 98.8, 82.1, and 71.9% after 1-, 3, and 5-years, respectively.

From the meta-analysis by Ye et al. involving 10 cohort studies with 522 patients, it was found that minimally invasive surgery was associated with less intraoperative blood loss [weighted mean difference (WMD) $= -130.09$ min, $p = 0.002$] and blood transfusion ($p = 0.03$), faster recovery of intestinal function (WMD $= -0.88$ days, $p = 0.01$), shorter length of postoperative hospital stay (WMD $= -4.06$ days, $p < 0.0001$), and lower rates of surgical complications ($p = 0.04$). Interestingly, no differences were found about operating times and the rate and severity (Clavien–Dindo grade ≥ 3, $p = 0.33$) of overall complications (71). Furthermore, also the oncological outcomes OS $p = 0.74$; disease-free survival (DFS) $p = 1.0$] were also equivalent.

A more recent meta-analysis including twelve studies with 616 patients confirmed these results (72). Moreover, there has been a trend in favor of laparoscopy in terms of reduced rate of ileus, wound infection, and intra- abdominal infection. The authors concluded that SLR can be considered the first option in high-volume tertiary referral centers.

Many other retrospective studies that compared long term outcomes of laparoscopic one stage surgery with open one stage surgery did not identify differences in OS (30, 33) but only a slight difference in terms of DFS.

In the report by Shin et al., three-year OS rate of the laparoscopic group was similar to that of the open group (74.4 vs. 74.2%, $p = 0.606$). However, 3-year postoperative DFS rate of the laparoscopic group was significantly higher than that of the open group (57.8 vs. 47.4%, $p = 0.017$) (52). Consistently, Gorgun et al. reported an OS comparable between the two groups ($p = 0.10$) after a 24-month follow-up but a DFS longer in the laparoscopic group ($p = 0.028$). The two groups were comparable in terms of recurrence rates [41.3% ($n = 12$) vs. 14.2% ($n = 2$), $p = 0.08$] (54).

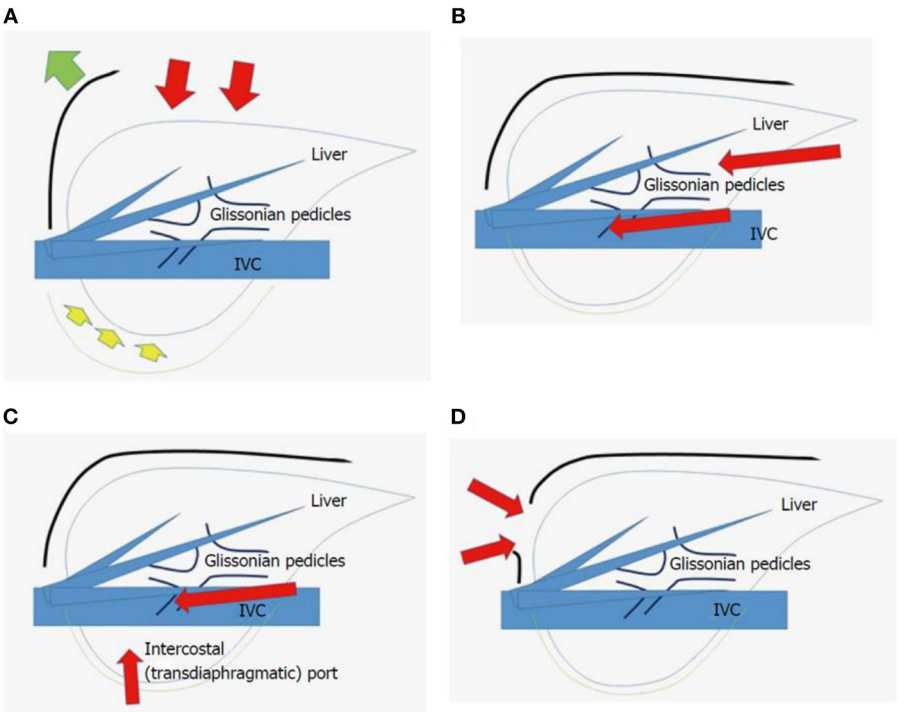

FIGURE 6 | Scheme of open liver resection **(A)**, laparoscopic liver resection [regular caudal approach, **(B)**], laparoscopic liver resection [lateral approach, **(C)**] and thoracoscopic liver resection **(D)**. Red arrows indicate the directions of view and manipulation in each approach. **(A)** In the open approach, the subcostal cage containing the liver is opened with a large subcostal incision and instruments are used to lift the costal arch, after which the liver is dissected and mobilized (lifted) from the retroperitoneum; **(B)** In the regular laparoscopic caudal approach, the laparoscope and forceps are placed into the subcostal cage from the caudal direction, and the surgery is performed with minimal alteration and destruction of the associated structures; **(C)** In the laparoscopic lateral approach, the intercostal (transdiaphragmatic) ports combined with total mobilization of the liver from the retroperitoneum can allow the direct lateral approach into the cage and to the posterosuperior tumors; **(D)** Thoracoscopic approach is employed for lesions in segment 8, with direct exposure of the tumor into the pleural cavity upon incision on the diaphragm adjacent to the tumor, with the endoscope placed in the pleural cavity. From Morise and Wakabayashi (49).

CONCLUSION

The choice of SLR must be based on several factors such as the location, the extent and the resectability of the lesion, the general status of the patient (age, comorbidity, previous treatments) and also the experience of the surgeon.

SLR is a safe and effective approach that should be offered to patients with primary limited extension of liver metastases, characterized by less intraoperative blood loss, faster recovery of intestinal function, shorter length of postoperative hospital stay, and lower rates of surgical complications than the laparotomic approach with no significant differences in long-term outcomes. Currently, there isn't sufficient level of evidence able to demonstrate the superiority of one strategy over the others. Therefore, future reports with larger series and randomized controlled trials will be needed.

AUTHOR CONTRIBUTIONS

GS and GG substantial contributions to the conception and design of the work, acquisition, analysis, interpretation of data for the work, drafting the work and revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy, and integrity of any part of the work are appropriately investigated and resolved. AP, FM, MG, AR, and RM substantial contributions to the conception and design of the work, acquisition, analysis, interpretation of data for the work, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy, and integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted final version.

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Scanner-Assisted CO_2 Laser Fissurectomy: A Pilot Study

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Introduction: Surgery for chronic anal fissure is challenging for every proctologist. Solving the pain by guaranteeing rapid and effective healing is the objective, but what is the price to pay today in functional terms? Though this result is nowadays partially achievable through interventions that include the execution of an internal sphincterotomy among the procedures, it is necessary to underline the high rate of patients who can present faecal incontinence. The aim of this study is to explore the effectiveness of scanner-assisted CO_2 laser fissurectomy.

Methods: From April 2021 to September 2021, all consecutive patients who affected by chronic anal fissure suitable for surgery, meeting the inclusion and exclusion criteria, were evaluated. All planned data were recorded before surgery, then at 24 h, 1 week, and 1 month follow-up. A scanner-assisted CO_2 laser was used in this study to achieve a smooth and dried wound with a minimal tissue thermal damage, to ensure good postsurgical pain control, rapid and functional, elastic and stable healing, and to prevent potential relapses. Paracetamol 1 g every 8 h was prescribed for the first 24 h and then continued according to each patient's need. Ketorolac 15 mg was prescribed as rescue.

Results: Mean pain intensity $\leq$3, considered as the principal endpoint, was recorded in 26 out of the 29 patients who enrolled in the study with a final success rate of 89.7% at 1-month follow-up. Pain and anal itching showed a statistically significant reduction while bleeding, burning, and maximum pain, and REALIS score showed a reduction too at the end of the follow-up period. Reepithelisation proved to be extremely fast and effective: 22 of 29 (75.9%) showed a complete healing and 5 showed a partial reepithelisation at 1-month follow-up.

Discussion: Outcomes of this study showed that it is undoubtedly necessary to change the surgical approach in case of anal fissure. The internal sphincterotomy procedure must be most of all questioned, where the availability of cutting-edge technological tools must be avoided and offered only in selected cases. Scanner-assisted CO_2 laser showed great results in terms of pain control and wound healing, secondary to an extremely precise ablation, vaporisation, and debridement procedures with minimal lateral thermal damage.

Keywords: scanner-assisted CO_2 laser, fissurectomy, chronic anal fissure, faecal incontinence, internal sphincterotomy, wound healing, functional healing, low pain intensity

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INTRODUCTION

Chronic anal fissure usually causes recurrent pain mostly at defecation and bleeding per annum which negatively affect patients' life quality (1).

Sometimes, it can worsen and evolve into a perianal abscess or fistula in anus and this helps to reinforce the indication to a surgical resolution.

Anal fissure has a widespread diffusion and its incidence is 10–15% among all proctologic consultations (2).

An epidemiologic study underlined that United States count approximately 3,42,000 new anal fissure cases per year where the main affected are middle-aged and younger people with an equal male to female ratio (3).

The exact aetiology is still debated but usually the trauma of the anoderm derived from hard stool passage is considered the main cause followed by chemical irritation due to diarrhoea, postsurgical rigid and retracted scars, and anal intercourse too (4, 5).

This painful wound causes a reactive internal sphincter hypertone and the increase in the resting anal pressure.

Several pharmacological agents have been studied first to directly reduce anal pressure and/or indirectly control anal fissure pain and second both to improve the blood supply to the anal fissure and to facilitate healing (6).

A chronic anal fissure is diagnosed when anal fissure and related symptoms persist not <6 weeks and are associated with the presence of visible transverse internal anal sphincter fibres, sentinel skin tag, anal papillae, anal polyp, and indurated margins (7, 8).

It is sustained by local recurrent traumas, inadequate or failure to adhere to therapies and comorbidities.

When medical treatments fail, surgery is the only solution.

Diathermy fissurectomy is the surgical procedure for removing this chronic longitudinal tear of the anus by eliminating the fibrotic tissue, the sentinel skin tags, and anal polyp. If on the one hand, it is able to remove the fibrotic tissue, on the other hand, the surgical wound results to be very painful. Fissurectomy can be performed alone though it is usually associated with lateral internal sphincterotomy.

Despite the high incidence of anal incontinence (faecal incontinence 1:200, permanent flatus incontinence 1:20) after internal sphincterotomy (9–11), it still remains the gold standard to reduce postoperative pain and allow wound healing.

To avoid the high rate of incontinence secondary to internal sphincterotomy and at the same time ensure good postsurgical pain control and a rapid surgical wound healing too, we explored the effectiveness of scanner-assisted CO_2 laser technology, already widely used in speciality such as colposcopy, with a similar approach.

CO_2 laser technology is well known in various surgery fields, from the late 70s. Its wavelength of 10.600 nm is entirely absorbed by water, thus making this laser undoubtedly the best surgical one, due to its excellent characteristics of tissue interaction.

Nevertheless, improvements in CO_2 laser technology have brought to sources excited with radiofrequency (so-called Ultrapulsed) and the introduction of tools such as surgical scanners, in association with focusing handpieces and high precision microspot micromanipulators coupled to surgical colposcopes or high-definition cameras, which allow to overcome the results of first CO_2 laser generation. Scanners allow to move a micrometric focused spot on the tissue in an extremely fast (up to 1/1,000,000 of a second of prevalence or "dwell time") and precise manner, reproducing predefined shapes of cutting and plane ablation. By this way, surgical procedures are extremely selective, and the surrounding healthy tissues are not thermally damaged. Furthermore, coagulation feature of the laser can be improved when needed by simply adapting scanning and emission mode settings.

In general, laser surgery is a minimally invasive procedure that reduces hospitalisation time, decreases the postoperative pain, oedema, and discomfort, and results in fewer complications, faster and more functional wound healing (12, 13).

The aim of this study is to overcome the limits of the current surgery for chronic anal fissure in terms of postoperative pain, pain and other symptom resolutions, healing time, incontinence rate, and patient's satisfaction with respect to safety and reproducibility.

METHODS

From April 2021 to September 2021, all consecutive patients who arrived at the clinics of SOSD Proctologia (USL Toscana Centro-Firenze) and affected by chronic anal fissure (7, 8) suitable for surgery were evaluated.

We planned a strict selection to obtain homogeneous group of patients: we considered only patients complaining anal pain secondary to a single chronic anal fissure unresponsive to medical therapies, ASA 1 and 2 only and Lee index <1 (14), who are able to understand all medical instructions and to adhere to our perioperative protocol.

We excluded those patients with concomitant perianal abscess or fistula in anus or any anal disease or previous proctologic surgeries, with history of radiotherapy, pregnancy, age below 18 years, Crohn's disease, constipation requiring manual manoeuvres during evacuation, anal neoplasms, human immunodeficiency virus infection, faecal incontinence, proctitis, severe systemic diseases, uncontrolled comorbidities as diabetes, kidney failure, and anticoagulant therapy.

All participants provided with verbal and written informed consent either to surgery or to participation in the study.

All patients underwent a complete medical history, clinical evaluation, proctologic physical examination, anoscopy and endoanal ultrasound. All data were collected at different time, preoperative (T0), at 24 h (T1), then at 1 week (T2), and finally at 1-month follow-up (T3), and recorded in a prospective maintained database.

All data collected are reported in **Table 1**.

Endpoints

The principal endpoint was mean anal pain intensity ≤3 (VAS 0–10).

Anal pain intensity and symptom intensity were measured by means of a 10-point visual analogue scale (VAS) (15).

TABLE 1 | Data collection.

	T0 Pre Operative	T1 24 h	T2 1 week	T3 1 month
Anal fissure position (12 o'clock position for anterior and 6 for posterior)	√	–	–	–
Sentinel skin tag	√	–	–	–
Sentinel anal polyp	√	–	–	–
Pain (yes-no)	√	√	√	√
Bleeding (yes-no)	√	√	√	√
Anal itching (yes-no)	√	√	√	√
Burning (yes-no)	√	√	√	√
Constipation (yes-no)	√	√	√	√
Diarrhoea (yes-no)	√	√	√	√
Anal intercourse (yes-no)	√	√	√	√
Duration of symptoms (months)	√	–	–	–
REALISE score	√	–	√	√
Mean pain (VAS 0–10) (Success VAS ≤3)	√	√	√	√
Maximum pain (VAS 0–10)	√	√	√	√
Maximum pain duration 1-Within 10 min 2-Between 10 and 30 min 3-Between 30 and 60 min 4-More then 60 min	√	√	√	√
Anal digital exploration 0-not painful 1-painful 2-impossible	√	–	√	√
Post operative data records - Number of painkiller days - Compliance with anal cream application (yes-no) - Complications (descriptive) - Re intervention (yes-no) - Faecal incontinence	–	√	√	√
- Patient satisfaction (VAS 0–10)	–	–	–	√
Surgeons satisfaction (VAS 0–10)		√	–	–
Degree of reepithelisation of the post surgical fissure 0-deep fissure still present 1-superficial fissure 2-partial reepithelisation 3-complete healing and reepithelisation	–	√	√	√

FIGURE 1 | Outpatient setting: SmartXide2 C80 laser system.

The following secondary endpoints considered were as follows: maximum pain intensity (VAS 0–10), maximum pain duration (1—within 10 min, 2—between 10 and 30 min, 3—between 30 and 60 min, and 4—more than 60 min), days of painkiller intake, specific symptoms, and REALISE score (16).

Then, we focused on other secondary endpoints: the proportion of patients healed at 1 week and then at 1-month follow-up and graded according to a previous published degree of reepithelisation scale (0—deep fissure still present, 1—superficial fissure, 2—partial reepithelisation, 3—complete healing and reepithelisation); by the end of fissurectomy, all patients were found to be at the lowest grade (17).

Finally, we also considered patient's satisfaction at 1 month and surgeons' satisfaction (about surgery), and these were recorded through a VAS 0–10 scale.

Short-term complications were recorded; reoperation and discharge within 2 h were evaluated too.

Withdrawal Criteria

Failure to follow the protocol, further surgery during the follow-up, patient request.

Perioperative Protocol

Patients were instructed to correct constipation already before surgery by taking stool softeners and sticking to a diet rich in fibres and fluids.

After surgery, all patients received written instruction thoroughly explained before discharge.

Surgical wound protection protocol required patients to apply a 3% sucralfate cream (18–20) (Emoflon™- Servier Italia S.p.A.) circumferentially up to 1–2 cm inside the anus with the tip of a finger every 12 h and to daily warm sitz bath for the entire period of the study (21, 22).

Paracetamol 1 g every 8 h was prescribed for the first 24 h and then continued according to each patient's need. Ketorolac 15 mg was prescribed as rescue.

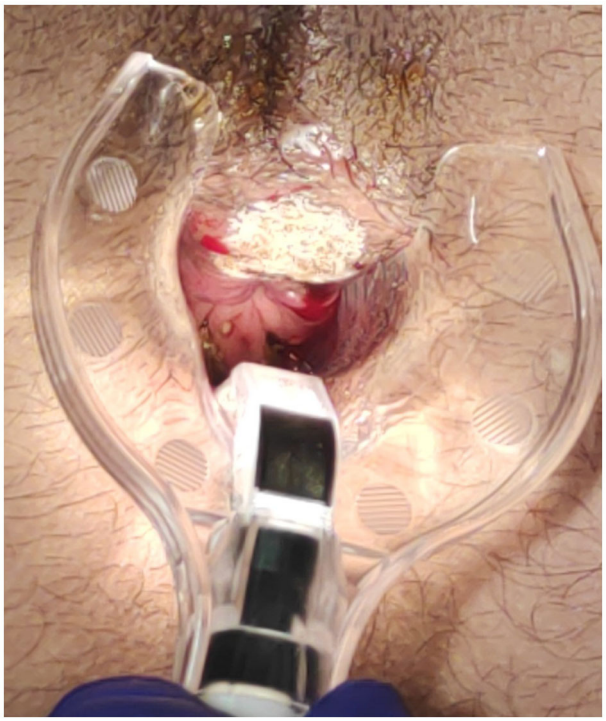

FIGURE 2 | Anterior fissure: sentinel sking tag CO_2 laser scanner vaporisation.

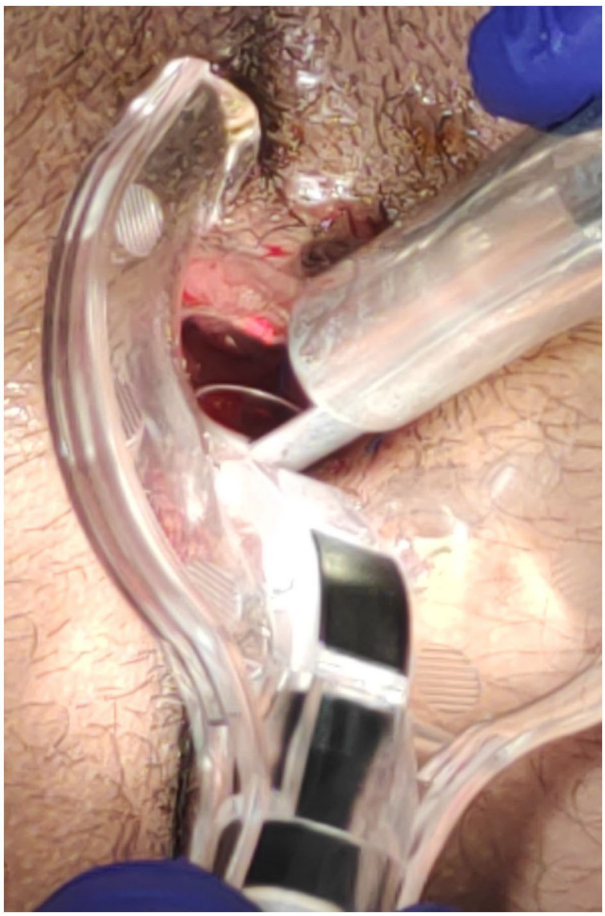

FIGURE 3 | Anterior fissure: fissure CO_2 laser scanner superficial vaporisation and debridement.

Treatment

All patients were treated under local anaesthesia (ropivacaine 10 mg/ml, ranging from 5 to 10 ml) performed directly on anal fissure with a 25-G needle, in an ambulatory setting with a planned discharge time of 2 h.

System used SmartXide2 C80 laser system by DEKA, Calenzano, Italy, a RF excited CO_2 laser, with 80 W of max power; this system is also equipped with a second 50 W 980 nm diode laser source fibre delivery, which results very useful in those procedures where higher coagulative power is necessary (**Figure 1**).

Accessories: scanning micromanipulator Easyspot + HiScan Surgical or ColpoScan (connected to a 300 mm lens colposcope (Z4—Centrel S.r.l.), EndoScan and microscan scanners connected to long focal 5" handpieces.

The scanner-assisted CO_2 laser provided with the appropriate accessories was used to treat various proctologic pathologies, such as abscesses, fistulas, condylomas, AIN, as the CO_2 laser scanning fast vaporisation and excision are extremely effective on soft tissue surgery. The article's aim is nevertheless to focus on the fissurectomy procedure.

The procedure involves two surgical stages: vaporisation and superficial vaporisation and debridement.

The CO_2 laser was used in fissurectomy to vaporise sentinel skin tag, sentinel polyp, and fissure margins.

Here, the parameters for vaporisation used according to the scanning shape and depending to the area to treat: Clover (interpolated double ellipsoid): UP Mode, 15–20 W, dwell time 0.2 ms, continuous or repeated scanning (T-Off 0.1 s); hexagon: CW Mode, 18–25 W, dwell time 0.1 msec, repeated scanning (T-Off 0.1 s).

Then, fissure superficial vaporisation and debridement, to obtain a more uniform plane eventually removing biofilm and stimulate the tissue to regenerate, was performed using these parameters: Clover (interpolated double ellipsoid): UP Mode, 4–8 W, dwell time 0.2 ms, continuous or repeated scanning (T-Off 0.1 sec); hexagon: CW Mode, 12–18 W, dwell time 0.1 ms, repeated scanning (T-Off 0.1 s).

In case coagulation was needed, the laser emission mode was switched to CW and the power reduced.

Haemostasis, when needed, was achieved by defocusing the CO_2 laser (Clover, low power CW mode continuous scanning), or using a monopolar electrosurgical energy or by suture.

The surgical goal is to achieve a smooth and dried wound with a minimal tissue thermal damage, to ensure good postsurgical pain control, rapid and functional, elastic and stable healing, and to prevent potential relapses (**Figures 2**–**5**).

All surgical data were recorded: from the number of vaporised sentinel polyp to the number of skin tag treated. Surgical time,

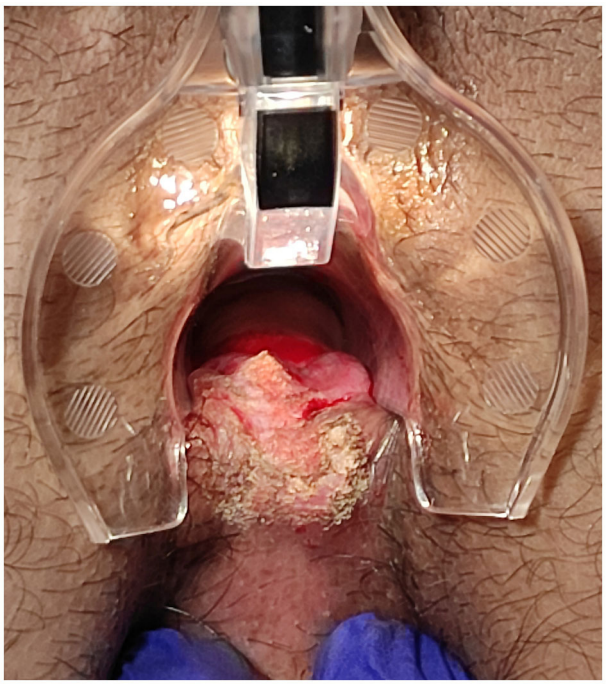

FIGURE 4 | Posterior fissure: sentinel skin tag CO_2 laser scanner vaporisation and fissure superficial vaporisation and debridement.

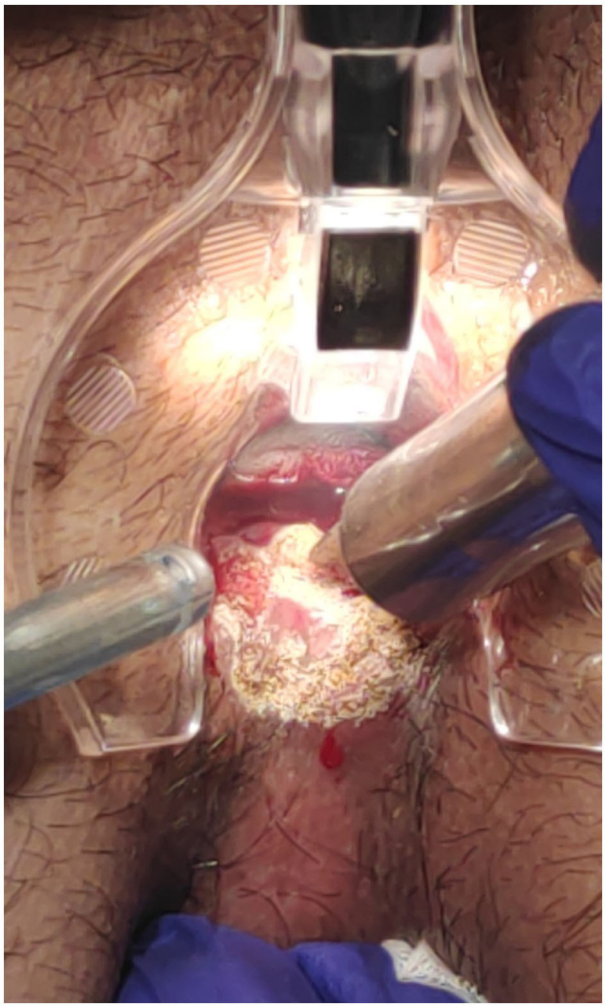

FIGURE 5 | Posterior fissure: ongoing CO_2 laser vaporisation.

intraoperative, 24 h, 1 week, and 1-month complications and surgeon's satisfaction (VAS 0–10) were recorded too.

Statistical Analysis

In this study, the statistical analyses focused on postoperative results related to specific scanner-assisted CO_2 laser treatment in a selected patient group: the clinical and follow-up data were stored in a prospective maintained database.

Association between median VAS after surgery, time of treatment after diagnosis and grade of reepithelialisation variables, patients' characteristics, and surgical procedure were examined by chi-square and Fisher's exact tests. *p-value* <0.05 was considered significant.

XLSTAT software (version 2021.3.1) (By Addinsoft PARIS, France, Europe) was used for statistical analysis: $p < 0.05$ was considered significant.

This was a retrospective single centre study and is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies (23).

RESULTS

During the study conduct period, we subjected 105 patients to proctology surgery using a scanner-assisted CO_2 laser, as reported in **Table 2**.

In total, 29 out of the 105 patients were those who met the inclusion and exclusion criteria of the study. The mean age of these patients was 49.7 years old (range 19–84). Totally, 6 of them were women, and 3 patients out of 29 was suffering from an anterior fissure whereas 26 out of 29 from a posterior fissure. The number of sentinel skin tag was 23 whereas the number of sentinel anal polyp was 9.

In summary, the number of fissurectomy procedures alone was found to be 5 whereas the number of associate surgical procedure, for example, fissurectomy with simultaneous polyp vaporisation and/or sentinel skin tag vaporisation, was 24.

Recorded fissure and fissurectomy-related symptoms are reported in **Table 3**.

Overall, 17 patients reported a preoperative history of constipation in particular with episodes of hard stool and 2 of diarrhoea. Only one patient reported anal sex.

During the period of examination, 1 month after surgery, 3 patients experienced episodes of constipation, none of diarrhoea, and 1 felt confident to restart anal intercourse.

The duration of symptoms mean time was 10.6 months (range 3–36).

TABLE 2 | Scanner CO_2 laser proctological procedures.

Surgery	Number of patients
Fissurectomy	29
Fissurectomy + other treatments	39
Fistulotomy	5
Treatment of fistula tract ad internal orifice	14
Hemorrhoidectomy	8
HPV Lesions vaporisation	6
Sinus Pilonidalis wound defect	3
Anal Polyp vaporisation	1
	105

TABLE 3 | Symptoms (number of patients) changes.

	T0 pre operative	T1 24 h	T2 1 week	T3 1 month	*p*
Pain	29	22	11	5	0.002
Bleeding	17	9	0	2	0.21
Anal itching	6	1	0	0	0.04
Burning	14	20	14	7	0.15

TABLE 4 | REALISE score.

	T0 pre operative	T2 1 week	T3 1 month	*p*
REALISE score	13.62 (range 7–22)	6.69 (range 4–18)	5.41 (range 4–14)	0.484

REALISE score was employed to evaluate and asses the severity on anal fissures. Data are reported in **Table 4**.

Pain severity was carefully evaluated and recorded (**Table 5**).

Mean pain intensity ≤ 3, considered as the principal endpoint, was recorded in 26 out of the 29 patients who enrolled in the study with a final success rate of 89.7% at 1-month follow-up. This percentage reached 85.7% in our cases only 1 week after procedure.

Compliance with anal cream application was evaluated questioning each individual patient on the correct and daily application: at 1 week, 22 out of 29 responded positively whereas only 20 out of 29 at 1-month follow-up.

Degree of reepithelisation of the postsurgical fissure was measured (**Table 6**).

No statistical correlations were found between grade of reepithelialisation after 1 month and age ($p < 0.855$), gender ($p < 0.568$), operative time ($p < 0.506$), and associate surgical procedure group ($p < 0.258$).

A most important relief, in our data, was the excellent clinical result in term of reepithelisation grade 3 in the subgroup of patient's compliant with the application of anal cream ($p < 0.017$).

An interesting correlation, even without statistical value ($p < 0.258$), was found in our data between the precocity of treatment, related to pain symptom duration before laser treatment, and reepithelisation grade. The mean duration of pain before treatment in our data was 10.6 months.

Those treated before the mean time of 10.6 months showed a very good result in term of success (grade 3 reepithelisation) (86.7%) vs. patients treated after 10.6 month (64.2%).

A correlation was also sought between the trend of mean pain intensity and reepithelisation but it was not found.

On average, the surgical procedure lasted 19.3 min (range 10–40).

Complications

We must also report that no changes in surgical strategy have been recorded, confirming the efficacy of the anaesthetic technique, selection of patients, accuracy of the care pathway and, last but not least, the safety and reproducibility of the scanner-assisted CO_2 laser surgery.

The recorded complications were 3 at 1 week of follow-up, all related to the painful oedema of the surgical wound margins, whereas only 1 case continued to have oedema 1 month after surgery.

No reoperation during the follow-up period was performed. Any patients complained about of faecal incontinence of all grades.

Satisfaction

The satisfaction of the treated patients was 8.83 (VAS 0–10) at 1 week and 9.17 at 1 month. The 3 cases of failure, according to our protocol (mean pain severity scored ≤ 3), recorded scores 5, 7, and 7 again, respectively. Surgeons' satisfaction that was measured at the end of the surgical procedure was 9.07 (range 7–10).

DISCUSSION

Anal surgery is taxed by a high rate of postoperative pain. Anal fissure stigmata symptom is high intensity and long duration pain, so long that it is disabling for patients.

Most patients with anal fissure report a good response to medical therapy in terms of both pain control and healing (87%) (24); however, both are achieved very slowly, so much so that patients need several days to regain some well-being. Pain control always coincides with adequate healing. The effectiveness of medical therapies is also further lower in case of chronic fissure (50%) (25–29).

When none of the medical therapies adopted are effective, excluding the possible presence of a neoplasm through the execution of a biopsy, mandatory in doubtful cases, it is necessary to proceed with surgery. Among the numerous surgical operations proposed, from anal stretch to standardise anal dilatation with pressurised balloons to anoplasty, internal sphincterotomy has been found to be the "gold standard".

In a Cochrane review by Nelson et al. (27), a prospective randomised controlled trial demonstrated that the internal sphincterotomy operation is more effective than medical treatments.

TABLE 5 | Pain.

	T0 pre operative	T1 24 h	T2 1 week	T3 1 month
Mean Pain (VAS 0–10)	5.24 0 pts without pain 3 pts with pain = 3	4.45 2 pts without pain 6 pts with pain ≤3	1.96 13 pts without pain 21 pts with pain ≤3	0.86 20 pts without pain 26 pts with pain ≤3
Maximum Pain (VAS 0–10)	9.03 all with pain ≥7	7,.10 1 pts without maximum pain	3.55 12 pts without maximum pain	1.59 20 pts without maximum pain
Maximum pain duration			12 without pain	22 without pain
1-With 10 m	6 pts	26 pts	12 pts	5 pts
2-Between 10 and 30 m	12 pts	3 pts	3 pts	1 pt
3-Between 30 and 60 m	4 pts	0 pts	1 pt	1 pt
4-More then 60 m	7 pts	0 pts	1 pts	None
Anal digital exploration				
0-not painful	6	–	17	21
1-painful	20	–	12	8
2-impossible	3	–	0	0
Painkiller days	–	1	4.48 11 pts still under painkiller	8.7 5 pts still under painkiller

TABLE 6 | Degree of reepithelisation.

Degree	T2 24 h	T3 1 week	T4 1 month
0-deep fissure still present	29	0	0
1-superficial fissure	0	13	2
2-partial reepithelisation	0	15	5
3-complete healing and reepithelisation	0	1	22

Though its extreme efficacy in controlling anal pain derived from the spasm of the internal anal sphincter and its capability to heal the fissure have widely been proved, it is necessary to critically analyse the result of the internal sphincterotomy which has a high rate in various degrees incontinence.

Therefore, the problem we had to face was to find a surgical solution for those patients who failed in medical therapies, a surgical solution that had to be able to heal the fissure without postoperative burden and faecal incontinence.

According to experience, the majority of patients (89.7%) reached the main goal of mean intensity pain ≤3 (VAS 0–10) 1 month after the operation. Moreover, this percentage had already reached optimal outcomes (85.7%) 1 week after procedure: clear evidence of high value in terms of both absolute effectiveness and speed. The maximum pain intensity disappeared in 68% of our cases after 1 month although 5 patients started from a value of VAS ≥ 7. The initial mean value was equal to 9.03 whereas it was equal to 1.59 after 1 month.

This result is comparable with reports in the literature of internal sphincterotomy surgery (26).

Moreover, it is interesting to notice the healing rate speed of this approach compared with traditional fissurectomy (30).

However, our aim was to analyse the symptom pain from different points of view, as suggested by other authors (16).

Maximum pain intensity at 1 month disappeared in 20 out of 29 patients, 5 of them had a VAS ≥7. The initial mean value was equal to 9.03 whereas it was equal to 1.59 after 1 month.

In particular, we measured the duration of the maximum perceived pain, an important consequent element of disability but often little considered in the literature: 1 month after treatment, 1 patient reported a duration of pain between 30 and 60 min, 1 patient a duration between 10 and 30 min whereas 5 patients <10 min.

Anal digital exploration by the surgeon was evaluated and was measured at both 1-week and 1-month follow-up, resulting in zero-not painful, respectively, in 17 and 21 out of the 29 patients who were examined. This report has the function of objectifying the patient's pain during the visit and associating it with what was reported during the collection of the medical history.

Digital exploration also has the function of monitoring the healing process and adopting any changes in the postsurgical medical strategy, from the indication to the use of other creams (29, 31, 32) to the use of anal dilators (33).

Stepping back to the symptom pain, we have also investigated the pain impact on the daily patients' life by measuring how long was the painkiller self-intake period: at 1 week, the average number of days reached a value of 4.48 and 11 out of 29 patients reported that they continue to intake painkillers because of the need; at 1 month, the mean reached a value of 8.7 days with only 5 patients continuing to take painkillers.

This result indirectly indicates how much the pain weakens each patient and represents an objective element of analysis that allows to homogenise the subjective variables of each treated case.

Since the painkiller days was taken, value of 8.7 shows that particular attention has to be paid to the first week; moreover, any strategies to be adopted in addition to those explored, which may allow a reduction in this value, should be evaluated.

Anyway, we never forget that the anal fissure can be characterised not only by the pain symptom but also by other symptoms that can be equally weakening and that we therefore wanted to analyse bleeding, anal itching, and burning (16).

Our experience demonstrates that the strategy adopted is able to determine a significant reduction primarily not only in pain but also in the other 3 symptoms too. In particular, the result on burning, however, deserves to be analysed: though surgery halves the symptoms, 7 patients still continue to suffer from it 1 month after and in any case present together with pain in the 3 patients with mean VAS $\geq$ 3.

The recent introduction in the literature of a score dedicated to the clinical evaluation of the anal fissure, or the REALISE score (14) allowed us to adopt it in our series: we were able to record a statistically significant reduction between the situation before surgery and the follow-ups at 1 week and at 1 month, since it confirms the great benefits and efficacy of the surgical strategy adopted.

Despite the low number of failure cases, we still wanted to evaluate what the variables affecting the outcome might be.

The statistically significant correlation between adherence to the anal cream application and healing demonstrated, in our experience, the importance of this local postoperative procedure: clearly emerged from the literature and also the need to continue with the suggested treatment for at least 6 weeks (29).

These data are essential to better educate patients in postsurgical wound care. Our mind to allow functional healing is to daily treat these wounds by applying a cream with a finger, as claimed by other authors (34).

About reepithelisation our experience shows an important correlation with adherence to the anal cream application and no correlation with other variables.

An important relief was the relationship with symptoms' duration: those patients with a shorter symptom duration actually demonstrated a better healing tendency than the others, suggesting the early use of fissurectomy.

In addition, the lack of correlation between pain resolution and level of healing opens up an interesting discussion and also confirming what the literature has already demonstrated. In fact, it had already emerged that the pain had a faster resolution than reepithelialisation, a dynamic that must be known by an expert and essential to proctologist to better follow the healing process (30).

Looking at the pure numbers, we would like to underline that 27 out of 29 patients demonstrated complete (22) or partial (5) reepithelisation.

This result is extremely superior to the reports in the literature regarding traditional diathermy fissurectomy, which averages a mean healing time of 10.3 weeks (30). Although our experience involves a small group of patients, the results obtained are so clear that they represent a solid basis for future studies.

CO_2 laser technology, widely used in several surgical fields (otorhinolaryngology, neurosurgery, wound healing, and gynaecology) for many years, has enjoyed a technological upgrade thanks to the introduction of scanning units that have allowed the execution of extremely delicate, precise, and effective procedures.

By analysing the literature about the use of laser technology in fissurectomy operations, we found that in 2015, an Iranian group had explored the use of CO2 laser for fissurectomy and fractional CO_2 laser for a multipoints myotomy of the internal anal sphincter (as an alternative to internal sphincterotomy), demonstrating an extremely rapid healing with no relapses at 1 year of follow-up (35).

Scanner-assisted CO_2 laser has also been used to promote secondary intention healing of several wounds: first of all, diabetic foot ulcers through bacterial load reduction and the promotion of healing (36, 37); also in sporadic cases of complex wounds such as a rectal vaginal fistula in a patient with Crohn's disease (38).

In our experience where this technology has been used for the very first time in proctology surgery, the scanner-assisted CO_2 laser demonstrated to be extremely safe and effective as no cases of change of strategy during surgery or complications related to its use have been reported. It has also proved to be an excellent ally in settings such as the outpatient one in the context of a less invasive care pathway also thanks to the use of local anaesthesia and careful selection of patients. Moreover, the same scanner can also be used in the fractional mode to stimulate the tissue regeneration.

The new technical solutions introduced with this new generation of CO_2 lasers are paving the way to new and fascinating scenarios of use that will be the subject of future studies and that are radically changing the surgical approach to proctologic pathologies.

Let us now analyse the impact of the intervention we proposed on faecal incontinence: no patient complained of any episode or degree of incontinence after 1 month of follow-up.

We therefore asked ourselves whether or not it is right to continue to argue that internal sphincterotomy is considered the gold standard in the treatment of anal fissure. It would probably be more correct to proceed with a less invasive method such as scanner-assisted CO_2 laser fissurectomy and restrict the sphincterotomy to those cases complaining of pain persistence during the follow-up: this tailored attitude could drastically reduce the number of cases of incontinence while increase the percentage of healed and satisfied patients.

However, few said about any relapses as our experience is limited to only 1 month of follow-up. The certainty is that relapse prevention is the result of a series of elements that must act synergistically with each other: first of all, a functional, elastic, and stable postfissurectomy healing, the correction of constipation or the use of enemas in case of hard stools, the application of an anal cream in case of diarrhoea, and a careful surgical follow-up that can identify any delays or defects in healing that require changes in the medical strategy (other creams, dilatant, etc.).

Limits of the Study

This study reports the very first application of a scanner-assisted CO_2 laser technology in proctologic surgery and, more specifically, in the treatment of chronic anal fissure through a fissurectomy procedure.

The limits this procedure presents are related to the small number of patients treated in addition to the fact that it was conducted in a single centre, without randomisation too.

The excellent outcomes obtained are however an excellent basis to develop future experiences.

It will also be essential to explore the possibility of carrying out this procedure in the context of enhanced recovery after surgery programmes and possibly in association with different anaesthetics or analgesics.

In future, it will be necessary to design multicentre randomised trials that can confirm the results obtained either in terms of fissure healing, low complications (as faecal incontinence), and postoperative pain, studies that can make use of new digital technologies such as telemedicine (39) or the use of digital custom-made applications to follow patients.

CONCLUSIONS

Scanner-assisted CO_2 laser turned out to be a useful aid in proctology surgery and in particular during fissurectomy, as it allows extremely precise ablation, vaporisation, and debridement procedures with minimal lateral thermal spread.

The wide versatility of pulse shape and energy delivery has proved to be both an added value by allowing an extreme modulation of the energy delivered but also a limitation due to the lack of consolidated experience with the use of this technology in this surgical field.

Randomized multicentre studies based on comparison with traditional techniques are the next step necessary to ensure the good results obtained with this experience.

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

IG: surgical procedures, data collection, and paper writer. TC: surgical procedures, data collection, and statistics. CL, FC, PD, GR, and CT: surgical procedures and data collection. GT: paper writer. FB, AA, SG, and AP: data collection. LG: laser supervisor and paper revisor. CE: study organizer, surgical procedure, and data collection. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.799607/full#supplementary-material

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Quality of Life in Patients With Rectal Resections and End-to-End Primary Anastomosis Using a Standardized Perioperative Pathway

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Objectives: Lower rectal resection is associated with a high rate of postoperative complications and, therefore, adversely impacts the postoperative health-related quality of life (QoL). Though sporadically practiced in different centers, there is no standard perioperative protocol for the management of patients with rectal growths. The aim of this analysis is to evaluate the patient-reported outcomes after low rectal resections followed by an end-to-end-reconstruction and temporary covering ileostomy using a multidisciplinary fail-safe-concept.

Methods: Between 2015 and 2020, we evaluated patient reported outcomes after open and laparoscopic rectal resections with end-to-end reconstruction with a primary straight anastomosis using a standardized perioperative pathway All patients with stoma were excluded from the study. The data for the QoL of patients was collected using the established Low Anterior Resection Syndrome (LARS)-score and the EORTC-C30 and CR-29 questionnaires at a single postoperative timepoint.

Results: We recruited 78 stoma-free patients for this analysis. Of 78 patients included in the study, 87.2% were operated laparoscopically and the mean global health status was 67.95 points, while a major LARS was detected in 48 (61.5%) patients. No anastomotic leakage (AL) occurred within the study cohort. There was no significant change in the LARS-score or the global health status depending on the follow-up-period.

Conclusion: This study shows that good QoL and functional outcomes with no AL are achievable following end-to-end straight anastomosis using a standardized perioperative surgical fail-safe protocol procedure.

Keywords: rectal resection, PROM (patient reported outcome measures), quality of life, colorectal surgery, anastomosis

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INTRODUCTION

Colorectal cancer is the third leading cancer worldwide and the second leading cause of cancer-related deaths with an estimated 1.8 million new cases per year and 881,000 deaths worldwide (1, 2). Surgical therapy remains the gold standard for rectal growths and the outcomes of surgical treatment for rectal pathologies primarily depend on the location

and stage of the tumor, the perioperative surgical protocol and the surgical technique (3). The most reported adverse mid-term-consequence of low anterior resection (LAR) is a deranged bowel function, often referred as "low anterior resection syndrome" (LARS) (4). The manifestations of LARS are far ranging; fecal incontinence, urgency, evacuatory and sexual dysfunctions, abnormal bowel frequency. As evident, LARS carry a direct impact on the quality of life (QoL) after rectal surgery (5). QoL, the individual's state of wellbeing, is deeply influenced by illness and treatment, especially in cancer patients (6).

In the recent years, the health-related quality of life (HRQOL) has been recognized as a mandatory requirement for the approval process of new anticancer drugs by the European Medicines Agency (7). Additionally, during the routine management of patients with a range of elements, the HRQOL has been embedded as a part of the patient-reported outcomes. LAR with primary anastomosis carries a high risk for adverse postoperative patient-reported outcomes due to a rise in postoperative complications such as anastomotic leakage (AL), sepsis and delayed bowel functions (8). Moreover, sphincter-preserving rectal surgery often leads to autonomic nerve damage with its associated functional disorders. Following LAR for the rectal cancer, defecation disorders have been reported in 41% (9), sexual dysfuction in 64% (10) and urinary dysfunctions in 50% patients (10). Such alarming rates of complications following LAR adversely affect the patient's psychosocial health status and the HRQOL.

Different tools for the assessment of patient-reported outcomes and HRQOL for rectal resections have been tested and validated. For a short-term evaluation, a popular instrument is the time-tested 5-item LARS score, which includes questions for incontinence for flatus or stool, the frequency of bowel movement, incomplete defecation, or urgency (11–13). This simple tool, available in different languages (13–15), focuses on the postoperative defecation disorders following rectal resections and correlates well with other QoL questionnaires (16).

In addition to the LARS questionnaire, the European Organization for Research and Treatment of Cancer (EORTC) has developed a well-evaluated 30-item core questionnaire (QLQ-C30), which investigates the general QoL with additional procedure-related instruments such as the questionnaire for the colorectal cancer (QLQ-C29) (17).

A range of remedial steps have been taken to prevent the dreadful long-term functional complications following rectal resections for cancerous growths. To reduce the rate of autonomic nerve complications, the intra-operative autonomic nerve preservation has been successfully established (18–21). This mandates the use of laparoscopic or robotic surgery in high-volume centers by experienced colorectal surgeons. The reservoir functions of the rectum is lost following the resection for the rectum along with its ampulla (22). In order to prevent a high stool frequency, the bowel reconstruction could be performed using a J-pouch (23), a coloplasty (24) or side-to-end-reconstruction (22, 25). This surgical step might reduce the frequency of defecation; however, the placement of sutures or stapling lines can possibly lead to an increased leakage rate. Following these beneficial observations in the literature, the German guidelines for colorectal cancer surgery recommend the use of a reservoir building reconstruction such as pouch or end-to-side-reconstruction, wherever possible (26).

Despite an escalating rise in the rates of complications and poor QoL after rectal surgery, unfortunately there is no standard peri-operative management protocol that can mitigate these risks. Though literature has shown the QoL related outcomes of patients following rectal surgery using cross-sectional study designs, there is a limited data about the reference population or pretreatment guidelines (27, 28).

The aim of this study is to evaluate the patient-reported outcomes after low rectal resections and end-to-end-reconstruction for benign and malignant rectal lesions using a multidisciplinary fail-safe-protocol. We used the EORTC-C30, C29 questionnaires and the LARS-score for the assessment of the QoL after rectal resections, which provide an insight into the efficacy and safety profile of the fail-safe peri-operative protocol.

MATERIALS AND METHODS

Study Design

In this study, we prospectively included all patients who underwent open or laparoscopic rectal resections with end-to-end anastomosis at Reinbek St. Adolf-Stift Hospital Germany to a colorectal surgical database. Between January 2015 and December 2020, patients with a tumor localized $\leq$8 cm from the anal verge were treated by rectal resections and end-to-end primary anastomosis. The hallmark of our management plan was the multi-modal fail-safe protocol, which included a standard

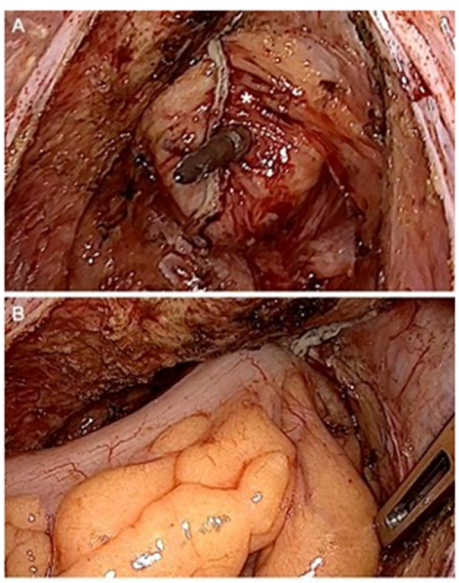

FIGURE 1 | Performing an end-to-end reconstruction after low rectal resection. **(A)** Rectal stump (*) still covered with fatty tissue to ensure perfusion with the spine of the stapler is piercing near the previous stapling line. **(B)** Compression after joining both ends to flatten fatty tissue before releasing the stapling device.

surgical technique for tension-free anastomosis was adapted in the fail-safe approach. All patients with rectal resections and primary end-to-end-anastomosis had an ileostomy, which were closed after the completion of adjuvant therapy soonest 6 weeks after the primary procedure. Patients who still had ileostomies at the time of conducting this study were excluded from the cohort. The patients' median follow-up period was 1 year.

After obtaining the ethical approval, the patients' medical records were extracted from the prospective clinical database according to the established inclusion criteria. Later, all recruited patients were invited to participate in this research. All patients gave their written informed consent to participate in this study. The EORTC-C30, C29 questionnaires and the LARS-scoring tool were posted to all patients by registered post at a single timepoint. The data presented in this study are reported in concordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) criteria (29). This trail was registered in the German Clinical Trial Register (DRKS00022492, date of registration: 10/20/2020).

Perioperative Fail-Safe Protocol

All patients suspected with rectal cancers were staged according to the German guidelines for colorectal cancer (26). Depending on the preoperative staging and according to the decision of the interdisciplinary tumor board, patients were treated by neoadjuvant radiotherapy, chemoradiotherapy or primary surgery. Patients with benign rectal lesions were not discussed during the interdisciplinary tumor board meetings. In case of severe diverticulitis, extended resections were performed.

All patients were treated according to the fail-safe-protocol with a preoperative mechanical bowel preparation using 2l of Endofalk®. No additional oral antibiotic decontamination was deemed necessary. In case of primary open procedures, epidural anesthesia was established. A single-shot-antibiotic was given intravenously perioperatively using 500 mg metronidazole and 1500 mg cefuroxime. After performing an end-to-end stapling anastomosis (**Figure 1**), a drainage was placed in the pelvis near the anastomosis and a diverting ileostomy was performed. In addition, an on-table-lavage via the efferent loop of the ileostomy was used to reduce the fecal load near the anastomosis (**Figure 2**). Three days after surgery, an endoscopic evaluation of the anastomosis was routinely performed. The diverting ileostomy was reversed after the completion of adjuvant therapy, if needed, at least 6 weeks after surgery and after performing colonoscopy for the evidence of intact anastomosis.

Postoperative complications were graded in accordance to the established Dindo-Clavien grading system, where all

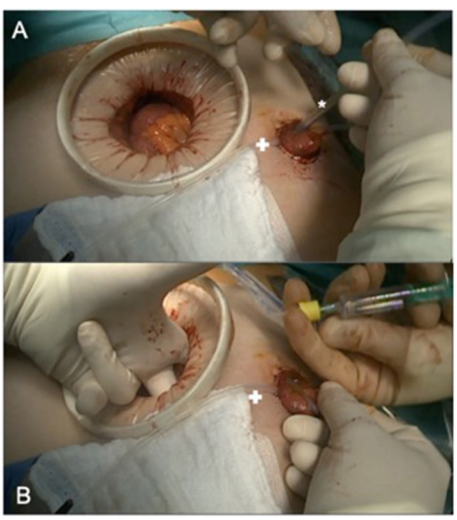

FIGURE 2 | Intraoperative colonic irrigation via ileostomy. **(A)** Placing the catheter (*) in the efferent loop (+ marking a loop, fixing the diverting stoma until fixation is completed. **(B)** Blocking the catheter under manual controll before starting the antegrade colonic irrigation.

TABLE 1 | Patient characteristics according to LARS/Major LARS.

	Total ($n = 78$)	No/minor LARS ($n = 30$)	Major LARS ($n = 48$)	*P*
Age [years] (mean ± SD)	65.64 ± 12.24	65.60 ± 12.71	65.67 ± 12.08	NS[c]
BMI (mean ± SD)	27.51 ± 8.89	25.94 ± 3.83	28.49 ± 10.86	NS[c]
Sex, n (%)				
Male	45 (57.7)	17 (56.7)	28 (58.3)	NS[b]
Female	33 (42.3)	13 (43.3)	20 (41.7)	NS[b]
ASA, n (%)				
I	4 (5.1)	3 (10.0)	1 (2.1)	NS[b]
II	54 (69.2)	20 (66.7)	34 (70.8)	NS[b]
III	20 (25.6)	7 (23.3)	13 (27.1)	NS[b]
Procedure, n (%)				
Laparoscopic, n (%)	68 (87.2)	25 (83.3)	43 (89.6)	NS[b]
Open	8 (10.3)	4 (13.3)	4 (8.3)	NS[b]
Conversion	2 (2.6)	1 (3.3)	1 (2.1)	NS[b]
Length of surgery [min] (mean ± SD)	263.36 ± 79.45	228.50 ± 71.37	285.15 ± 77.05	0.001
Time to follow-up [months] (mean ± SD)	19.50 ± 16.86	22.07 ± 17.77	17.90 ± 16.24	NS[c]
Global Health status (mean ± SD)	67.95 ± 20.37	75.83 ± 18.49	63.02 ± 20.11	0.003[c]
Major complication (DC > 3b), n (%)	4 (5.1)	4 (5.1)	0 (0)	0.019[b]
Dignity, n (%)				
Benign	16 (20.5)	8 (26.7)	8 (16.7)	NS[b]
Malign	62 (79.5)	22 (73.3)	40 (83.3)	NS[b]
	$n = 62$	$n = 22$	$n = 40$	
N+ (%)[a]	24 (38.70)[a]	9 (40.9)	15 (37.5)	NS[b]
T3/4 (%)[a]	29 (46.8)[a]	10 (45.5)	19 (47.5)	NS[b]
R0, n (%)[a]	61 (98.4)[a]	22 (100.0)	39 (97.5)	NS[b]

DC, Dindo-Clavien classification.
[a]*Including only cases with malignancy (n = 62).*
[b]*Fisher exact test.*
[c]*Man-Whitney-U-test.*

complications graded 3b and above are considered as major complications (30).

Patient Reported Outcomes

The EORTC-C30, C29 questionnaires and the LARS-scoring tool were used to measure the patient-reported outcomes and postoperative functional results in colorectal surgery.

LARS Score

The LARS score is a well-established simple scoring tool for the evaluation of bowel function after rectal resections. This tool assesses postoperative incontinence for flatus and liquid stool, frequency of bowel movement, incomplete defecation and urgency (13, 31). The final score in the LARS score ranges from 0 to 42; a score below 20 points indicates an absence of LARS, 21–29 is interpreted as a minor LARS and 29 up to 42 as a major LARS.

EORTC-C30 and C29

The EORTC-C30 measures the QoL regarding a global health status and contains five functional and nine symptoms scales. Depending on the responses by patients, according to the EORTC

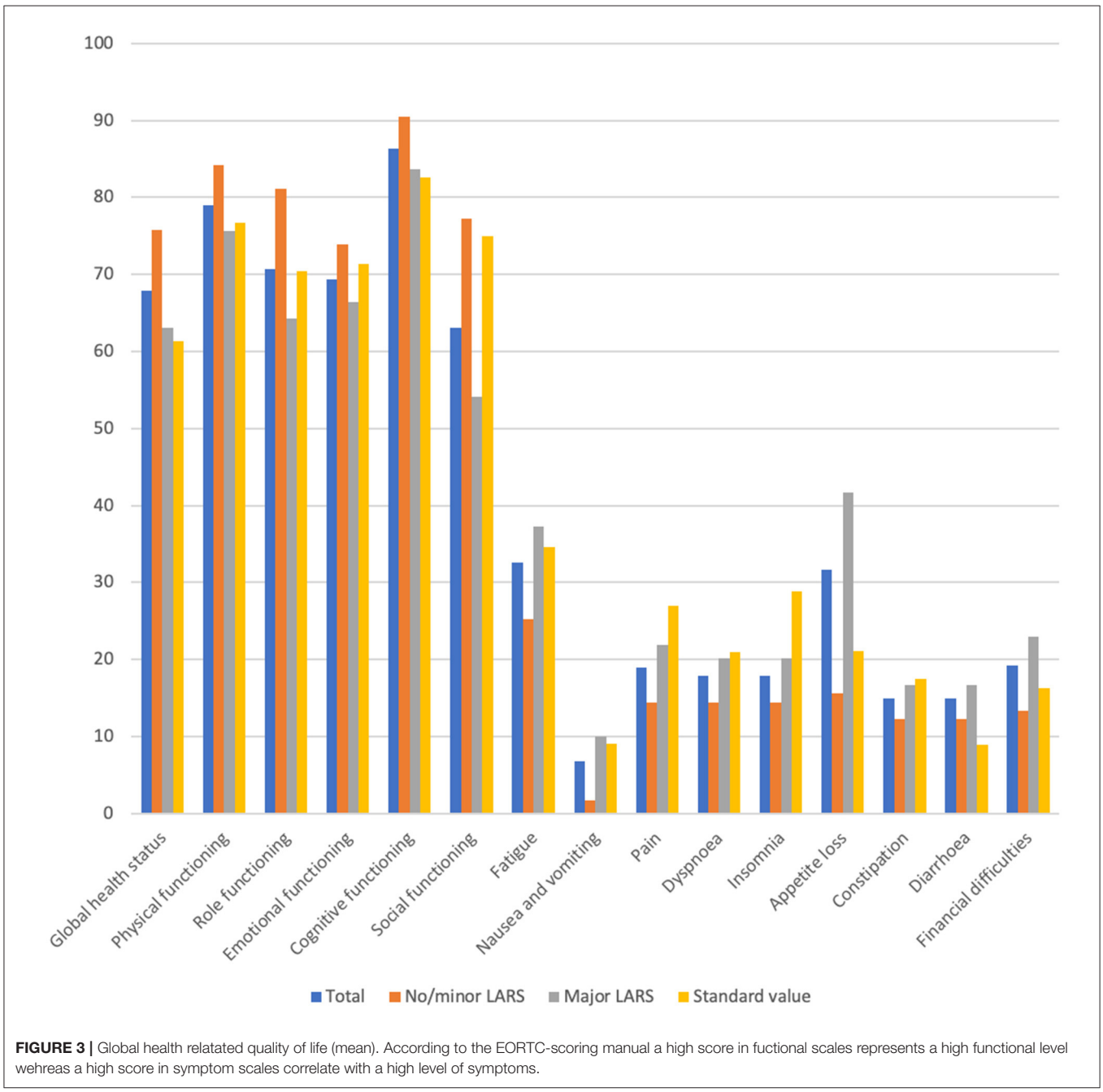

FIGURE 3 | Global health relatated quality of life (mean). According to the EORTC-scoring manual a high score in fuctional scales represents a high functional level wehreas a high score in symptom scales correlate with a high level of symptoms.

manual, a score ranging from 0 to 100 is calculated (17). Pursuant to the EORTC scoring system, a high score for the function or global health status indicates a better HRQOL; whereas a higher symptom scale means a greater burden by the scored symptom (17).

This tool was specified by an organ related module for colorectal malignancy with further 38 specific questions (QLQ-CR29) (32). The EORTC-C29 questionnaire was also scored following the published EORTC scoring manual (32). Some questions are focused on stoma-related issues which are excluded for non-stoma-patients. All data are compared to evaluate reference values (33). Also this combined EORTC-questionnaire with 68 items in total is very long, it provides a conclusive impression about the individual quality of life including organ-specific complications.

Statistical Analysis

All data was analyzed using SPSS 25.0 (IBM Corp, Ammonk, NY). The Chi-Square-test was used to compare categorical variables, and in case of <25 cases, the Fisher's exact test was used. In case of more than two groups, Kruskal-Wallis-test was performed. Continuous variables are presented as means and standard deviation as exemplified by the EORTC (17). For inter-group-evaluation, according to the EORTC and previous studies differences, were rated 5–10 as small difference, 10–20 moderate and more than 20 as a large difference (5). The Mann-Whitney U-test was used for inter-group comparison. A p-value of <0.05 was defined statistically significant.

TABLE 2 | Patient characteristics according to the global health status.

	Global health status > 65 (n = 51)	Global health status < 65 (n = 27)	p-value
Age [years] (mean ± SD)	65.06 ± 11.10	66.74 ± 14.32	NS[c]
BMI (mean± SD)	28.21 ± 10.23	26.18 ± 5.50	NS[c]
Sex, n (%)			
Male	30 (58.8)	15 (55.6)	NS[b]
Female	21 (41.2)	12 (44.4)	NS[b]
ASA, n (%)			
I	3 (5.9)	1 (3.7)	NS[b]
II	35 (68.6)	19 (70.4)	NS[b]
III	13 (25.5)	7 (25.9)	NS[b]
Technique, n (%)			
Laparoscopic	44 (86.3)	24 (88.9)	NS[b]
Open	5 (9.8)	3 (11.1)	NS[b]
Conversion	2 (3.9)	0 (0.0)	NS[b]
Length of surgery [min] (mean ± SD)	254.04 ± 74.65	280.96 ± 86.51	NS[c]
Time to follow-up [month] (mean ± SD)	19.02 ± 17.18	20.41 ± 16.52	NS[c]
Major LARS, n (%)	28 (54.9)	20 (74.1)	NS[b]
Major complication (DC > 3b), n (%)	2 (3.9)	2 (7.4)	NS[b]
Dignity, n (%)			
Benign	12 (23.5)	4 (14.8)	NS[b]
Malignant	39 (76.5)	23 (85.2)	NS[b]
	n = 39	n = 23	
N+ (%)[a]	18 (46.2)	6 (26.1)	NS[b]
T3/4 (%)[a]	19 (48.7)	10 (43.5)	NS[b]
R0 (%)[a]	38 (97.4)	23 (100.0)	NS[b]

[a] *Including only cases with malignancy (n = 62).*
[b] *Fisher exact test.*
[c] *Man-Whitney-U-test.*

During the study timeframe, 1.987 colorectal surgical procedures were performed in our center. This included 153 patients with rectal resections and with primary anastomosis. Twelve patients (7.8%) died during the follow-up-period and 12 patients (7.8%) were lost to follow-up. The questionnaire including the written consent form was sent to all remaining 129 patients. Seventy-eight returned the completed questionnaire (60.5%). Overall, there were 45 male (57.7%) and 33 females (42.3%) with a mean age of 65.64 ± 12.24 years. As many as 20.5% of the surgical procedures were performed for benign rectal lesions such as extended diverticulitis or large polyp of the rectum and 79.5% procedures were performed for malignant rectal growths. In this study cohort, no AL was reported. At the same time, 67 patients (85.9%) had an uneventfull recovery. Major complications requiring intervention under general anesthesia (Dindo-Clavien > 3b) were found in four patients (5.1%). These included one stoma revision, one subcutaneous hematoma, one uretheral obstruction without injury of the urethera, and a case of splenic bleeding which was treated by splenectomy.

In our series, the majority (87.2% were operated laparoscopically with no postoperative AL. The mean time to follow-up were 19.5 months. Major LARS was detected in 48 (61.5%) patients. There was no significant correlation between the time to follow-up- and the rate of major LARS following the end-to-end rectal reconstruction. Patients' characteristics did not differ significantly according to no/minor LARS or major LARS are shown in **Table 1**. The duration of surgery was significantly longer in patients with major LARS (285.15 min ± 77.05 min) than in patients without major LARS (228.50 min ± 71.37 min, p-value 0.001).

Using the EORTC-C30 questionnaire, the mean global health status score in our study cohort was 67.95 points. This score differed significantly between the major LARS and no/minor LARS groups (63.02 vs. 75.83, p = 0.003). A significant difference was observed between these groups in terms of physical functioning (p = 0.031), role functioning (p=0.012), social functioning (p = 0.002), and nausea and vomiting (p = 0.017) (**Figure 3**). There were no significant differences in patients' characteristics for a low or high global health status (**Table 2**).

Focusing on the EORTC-C29 questionnaire, we observed significant differences between no/minor LARS and major LARS groups for urinary frequency (p = 0.003), urinary incontinence (p = 0.007), buttock pain (p < 0.001), bloating

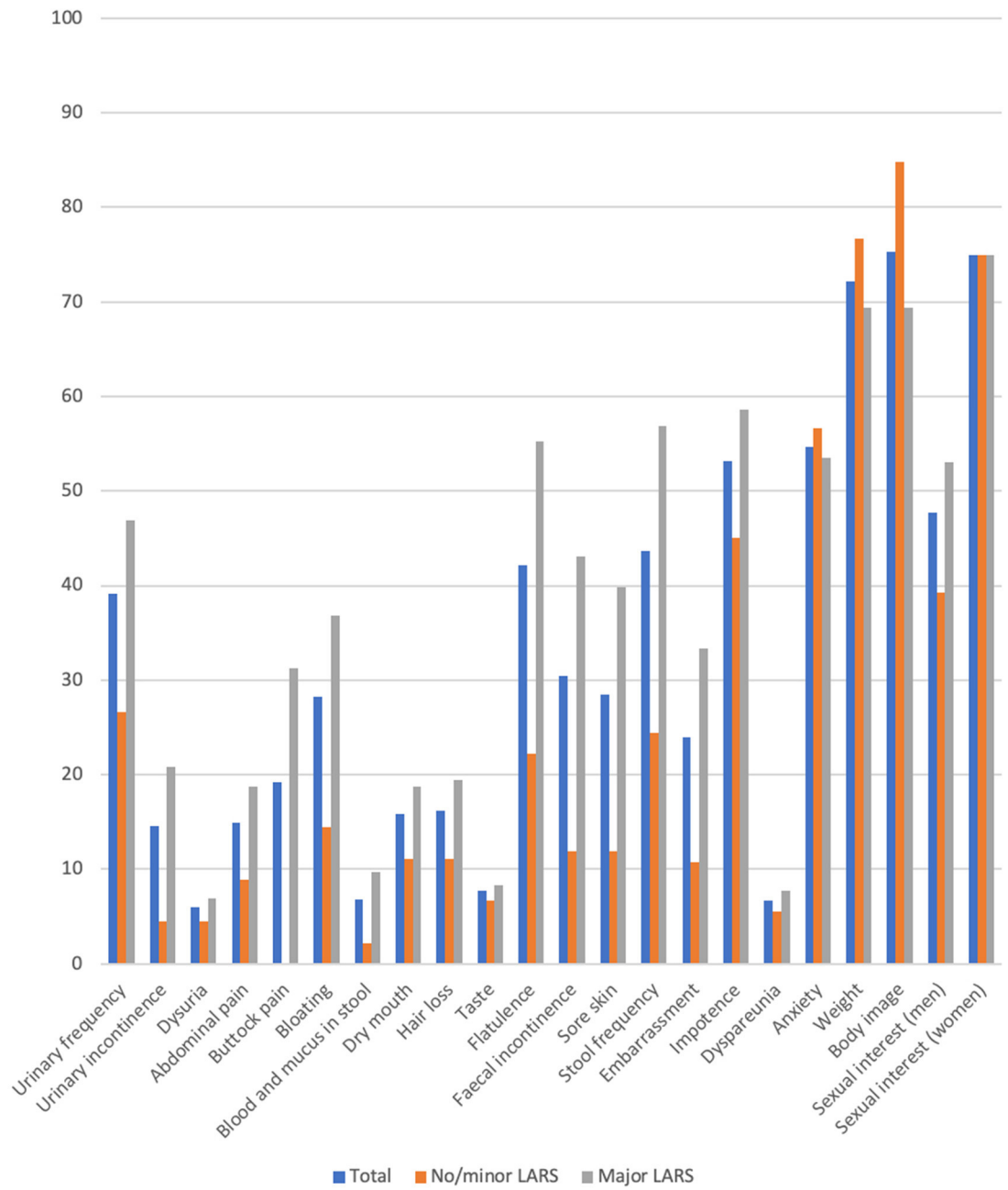

FIGURE 4 | Results of the QLQ-CR 29 questionnaire comparing no/minor with major LARS (mean). Scoring according to the EORTC-scoring manual a high score in fuctional scales represents a high functional level wehreas a high score in symptom scales correlate with a high level of symptoms.

($p = 0.006$), blood and mucus in stool ($p = 0.011$). In addition, significant differences were found for flatulence ($p < 0.001$), faecal incontinence ($p < 0.001$), stool frequency ($p < 0.001$) and sore skin ($p = 0.003$). Apart from the embarrassment ($p = 0.008$) and body image ($p = 0.021$), no further significant difference was reported for the sexual functioning (**Figure 4**).

The choice of the surgical approach (68 laparoscopic vs. 10 open) did not influence the mean LARS-score or the global health status. Furthermore, malignant nature of the rectal lesions had no significant impact on the postoperative mean global health status or the occurrence of a postoperative LARS (**Table 3**). The reported comorbidities such as cardiac or pulmonary diseases did not affect the postoperative LARS-score or the mean global

health status. Regarding the Man-Whitney-U-test, the need of a life-long medication for any medical condition did not have a significant impact on the LARS ($p = 0.906$) or global health score ($p = 0.812$).

Using the Kruskal-Wallis-test, we did not find a significant change in the LARS-score according to the time to follow up ($p = 0.676$). Additionally, no significant change was noticed in the follow-up-period in the global health status with a mean of 68 points ($p = 0.465$) (**Table 4**).

DISCUSSION

In our study, following a multimodal fail-safe perioperative protocol for rectal resections with end-to-end anastomosis and a temporary covering ileostomy, the patient-reported outcomes showed a high HRQOL with a global health status of 67.95 ± 20.37 points with no AL. The results signal the advantages of using a perioperative multimodal management protocol by adhering to surgical details in a structured fail-safe-protocol, thus reducing the postoperative AL rate with good functional outcomes after rectal resections and primary reconstruction.

Rectal resection causes the loss of specialized organ functions such as its reservoir function and the particularly the impairment of coordination between colonic movement, autonomic nerves and sphincter muscles. This complex interaction causes an increasing compartmentation following extended resection and deep anastomosis (34). This causes a rise in the LARS score following rectal dissection, resection and anastomosis, the surgical steps which explain the pathophysiology of LARS.

TABLE 3 | Global health status and LARS-Score according to potential influencing factors.

	Laparoscopic	Open/Conversion	*p*-value
Global Health status (mean ± SD)	67.89 ± 19.96	68.33 ± 24.15	0.712
LARS-score (mean ± SD)	29.22 ± 11.20	24.30 ± 14.06	0.216
	Benign	**Malignant**	***p*-value**
Global Health status (mean ± SD)	63.02 ± 23.95	69.22 ± 19.36	0.600
LARS-score (mean ± SD)	26.81 ± 11.82	29.05 ± 11.62	0.339

Higher score in Global health status means better global health status.
Man-Whitney-U-test.

This has led to the development of different techniques for rectal reconstruction to construct a new reservoir using a pouch or a coloplasty. The advantages of the rectal reconstruction using a J-pouch have been shown by different international multicenter trials (35). Until today, clinical trials have not provided a concrete advantage of the J-pouch compared to other non-straight reconstruction modes (36, 37). On the same note, the study by Kupsch et al. did not report any notable difference between different non-straight-reconstruction modes for functional outcomes (38). Consequently, the recommendation by the German Guidelines for colorectal cancer is only a non-straight anastomosis, wherever achievable (26). A great majority of studies have shown better clinical outcomes within the first months after the rectal resection for non-straight anastomosis, but a reduced advantage in long-term follow-up (36, 39). Rybakov et al. compared straight vs. side-to-end anastomosis describing less bowel movements as the only benefit after 6 months (22). On the other hand, Lazorthes et al. showed functional improvements after rectal resections for 24 months (23). The long-term outcomes of a non-straight reconstruction after rectal resection remain unclear. According to our analysis, we could not find a major change of global health status or LARS-score over the follow-up-period (**Table 4**).

A relatively new surgical technique for rectal resection is the transanal total mesorectal excision (TaTME), which has shown comparable postoperative outcomes in the initial phase (40). Further studies showed more inconsistent results regarding this technique. De Simone et al. have described acceptable functional outcomes during the short-term-follow-up (41), while other studies have reported high rates of complications especially AL rates. These findings have provided an impetus to abandon the TaTME approach (42). Additionally, Bianco et al. have recently published a new technique for the rectal resection with an adopted pull-through anastomosis (43). This technique has demonstrated a comparable mean LARS-score after 12 and 36 months and a comparatively low leakage rate.

As a part of the multimodal fail-safe-concept used in our institution, a reconstruction using pouch or coloplasty or even side-to-end-anastomosis was not used to reduce the rate of AL. The studies evaluating the functional improvements by a pouch, side-to-end-reconstruction or coloplasty showed a relative high rate of AL. The meta-analysis presented by Hüttner et al. showed no significant differences in AL rate according to different reconstruction techniques with an AL rate ranging from 3.6% in J-pouch to 9.9% in another J-pouch-group (36). The AL rate for straight reconstruction was as high as 7.7%. In

TABLE 4 | LARS and global health status according to time to follow-up (months).

	0–12 *N* = 39	13–24 *N* = 18	25–36 *N* = 7	37–48 *N* = 6	49–60 *N* = 7	>60 *N* = 1	Total *N* = 78	*p*-value
LARS (mean ± SD)	29.97 ± 9.94	30.61 ± 10.02	22.29 ± 16.93	24.67 ± 12.52	24.14 ± 16.87	37.00	28.59 ± 11.62	0.676[a]
Global Health status (mean ± SD)	69,87 ± 17.59	59.72 ± 21.82	76.19 ± 20.65	69.44 ± 19.48	69.05 ± 31.07	66.67	67.95 ± 20.37	0.465[a]

[a] *Kruskal-Wallis-Test.*

our cohort, 0% AL was recorded. Further refinements such as laparoscopic (18) or robotic surgery (44), pelvic intraoperative neuromonitoring (45), transanal total mesorectal excision (31) or fluorescence-guided imaging (46) may reduce the rates of AL and enhance the functional outcomes with or without a new reservoir made by pouch, side-to-end anastomosis or coloplasty.

HRQOL

In our study, a major LARS occurred in 61.5% patients. This rate is in line with the internationally published data ranging from 41% (16) up to 52%, as reported by Juul et al. (13).

In 2019, Kupsch et al. compared the correlation between LARS and the QoL using the EORTC-questionnaires (5). In their study, the investigators found a reduced global quality of life, according to the EORTC-C30 questionnaire, in the group of patients with major LARS. This is also seen in our study whereas the measured global health status in patients with major LARS was higher [63 ± 20 vs. 56 ± 19 Kupsch et al. (5)].

Limitations

As this is a retrospective analysis on the basis of a prospective database, no longitudinal comparison is achievable. Our data presents a median follow up of 1 year. A more longitudinal study design could establish the efficacy of the multi-modal fail-safe-protocol with substantial impact. Due to the small number of the answered questionnaires, the size of our study is small. Additionally, there are no internal or external control-groups with non-straight anastomosis, so an inter-group or pairwise comparison was not possible.

This study includes postoperative patients after surgery for benign and malignant rectal lesions. Even if there was no significant difference in the global QoL between both groups, this is a major study limitation, as the QoL and LARS could be influenced by neoadjuvant or adjuvant treatment, even if the surgery is performed following oncological criteria.

CONCLUSION

Our study eludes that the functional outcomes following rectal resections with straight anastomosis are not worse than reported by reconstruction with J-pouch-, side-to-end anastomosis or coloplasty, even within the first 12 month of surgery. Despite our small study group, we emphasis that we did not record even a single AL following rectal resections and primary end-to-end anastomosis with temporary covering ileostomy. In conclusion, the straight anastomosis after rectal resection is an achievable procedure with a good functional outcome and a reduced leakage rate following the multimodal fail-safe-protocol.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article are available on request from the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee Medical Association Schleswig-Holstein Bismarckallee 8-12 23795 Bad Segeberg Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JH and VB collected and analyzed the data and drafted the manuscript. SK and HH drafted and reviewed the manuscript and made an impact on discussion. TS reviewed the manuscript and supervised the study. SG performed a scientific enrichment, linguistics manuscript drafting, and statistical analysis. All authors read and approved the final manuscript.

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Proctologic Surgery Prioritization After the Lockdown: Development of a Scoring System

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Introduction: The coronavirus disease 2019 (COVID-19) pandemic has shown a very critical impact on surgical procedures all over the world. Italy faced the deepest impact from the beginning of March 2020. Elective operations, screening, and follow-up visits had been suspended giving priority to urgent and oncologic surgery.

Patients: An observational study was carried out in the Surgical Coloproctology Unit of the Val Vibrata Hospital on 152 patients awaiting a proctological surgical treatment during the national lockdown.

Methods: In order to monitor the health status of patients and reschedule postlockdown surgical activities, patients were interviewed by telephone submitting a questionnaire based upon the judgment of an expert senior clinician. Following the interview, we calculated a severity index for all the proctologic diseases (hemorrhoidal disease, anal fissure, anal sepsis, slow transit or obstructed defecation, incontinence), classifying the patients according to the score. Mean age of patients was 53 (±16) years, and there were 84 males (55.3%) and 68 females (44.7%). In total, 31% of our patients suffered from anal fissure, 28% suffered from hemorrhoidal disease, 14% suffered from anal sepsis, and the remaining patients suffered from benign anorectal diseases to a lesser extent.

Results: A total of 137 patients were available and divided into three classes: priority surgery (PS) with 49 patients (36.2%), deferrable surgery (DS) with 25 patients (18.1%), and long-term surgery (L-TS) with 63 patients (45.6%). There was a significant correlation between the perceived health status reported during the interview and the priority class index (Spearman's rho = 0.97, $p < 0.001$).
Differences related to age and sex were not significant (F-test = 0.43, $p = 0.653$; chi-squared test = 0.693, $p = 0.707$). 49 patients in class PS needed a prompt surgical treatment, while 24 patients allocated in class DS and 65 patients allocated in class L-TS could wait for a new ride plan for surgery.

Conclusion: New tools, such as this simple score obtained during the telephone interview, can be useful for prioritization of patients on the waiting list for surgical coloproctology after the lockdown without further clinical examination and hospital access.

Keywords: COVID-19, surgical priority, surgical scheduling, proctologic surgery, scoring system

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INTRODUCTION

With the advent of the new coronavirus disease 2019 (COVID-19) pandemic, the strain on health systems all over the world forced to stop the majority of diagnostic procedures, elective consultations, and surgical operations (1) starting from the first week of March in Italy. Apart from emergency and oncologic procedures, nearly 90% of the elective surgical procedures canceled due to the lockdown were for benign or functional disorder (2, 3). In Italy, the waiting list for elective surgical procedures has been divided as follows into four classes based on the risk of complications or worsening of the conditions: class A to be operated within 30 days, class B to be operated within 60 days, class C to be operated within 180 days, and class D to be operated within a year. Most of elective surgical procedures for benign disease belong to classes B and C. This implies that, at the date of the lockdown, patients ready for surgery have been waiting already for 2 to 6 months.

Elective operations for coloproctological diseases suffered noticeably since they had been completely canceled at the time of the lockdown (4–6). Delayed surgery even for benign or functional disease may result in complications, unplanned emergency surgery, deterioration of individual health, disability, and social costs (7, 8).

In fact, although the prognosis is relatively good, proctological diseases such as hemorrhoidal diseases (HDs), anal fissure (AF), perianal fistula (PF), and pilonidal disease (PD) are among the most common conditions a patient may deal with.

In our surgical unit at the beginning of the lockdown, there were 152 patients on the waiting list belonging to classes B and C, affected by common colorectal and anal diseases and who had their operation canceled, waiting for the end of the emergency as well as for a reschedule of the procedure.

This study aimed to monitor the health of the patient as well as to detect possible worsening of clinical conditions needing urgent treatment through a questionnaire that all the patients filled out by telephone and which allowed us to classify the urgency of each patient. Furthermore, we aimed for the reorganization of admission of patients on a new waiting list, forecasting the end of the lockdown, and the restart of surgical activity.

PATIENTS AND METHODS

A staff doctor retrieved patients' charts from the waiting list of those 152 patients selected for surgical treatment due to common coloproctological diseases. An expert surgeon of the staff contacted the patients by telephone explaining the reason for calling and the interview started after obtaining informed verbal consent from the patient.

The first item of the questionnaire used for the telephone interview ("Would you say that in general, your health is excellent, very good, good, fair, bad, or very bad? in the last 30 days)" aimed to investigate the health status perceived by the patients (9) (**Table 1**). The second part of the interview was addressed to clinical information and symptoms of the coloproctological disease affecting the patient (**Table 2**). This part of the questionnaire was developed based on the clinical judgment expressed by the expert senior coloproctologist of the staff.

TABLE 1 | Item of the telephone interview: general health.

Identification number		
Initial		
Phone contact (home, mobile)		
Diagnosis		
Planned surgery:		
Items		
1.	Would you say that in general your health is excellent, very good, good, fair, bad or very bad? (in the last 30 days)	Please indicate
2.	Would you say that in general your bowel is?	Normal/ diarrhea/constip
3.	If constipated, please specify daily difficult evacuation	Yes/no
	Chronic constipation abdominal distention	Yes/no
	Worsening of the above symptoms	Yes/no
4.	Did you see blood at defecation?	Yes / no
	If yes how often?	Rarely/daily
5.	Did your last laboratory exams report anemia?	Yes/no
6.	Would you say that in general your perceived pain, on the numerical scale 0 to 11, with 0 being "no pain" and 11 being "the worst pain imaginable" is__?	Please indicate
7.	Do you feel something out of the anus (Prolapse)?	Yes/no
	If yes is it is…?	Intermittent/stable
8.	Do you have anal fistula?	Yes/no
9.	Do you have a seton in place?	Yes/no
10.	Do you have discharge from the fistula?	Yes/No
	If yes, its amount is …	Little/large
11	Do you have abscess around the fistula? (Pain, swelling, fever)	Yes/no
	If yes does this occur…	rarely/frequently
12.	Are you taking any medication? Please specify	

The answers given in the second part of the questionnaire were compared with data recorded on the chart of the patient, obtaining information concerning the evolution or stability of the disease.

Thus, as for HD, scored symptoms were prolapse, bleeding or association of both. Frequency was scored as well as occasional or frequent bleeding, intermittent, or stable prolapse.

AF was graduated with respect to pain intensity using the Numeric Rating Scale-11 (NRS-11), i.e., an 11-point scale for

TABLE 2 | Construction of a severity score based on symptoms severity and frequency.

Disease	Symptoms	Scoring	Priority class
2 A. Hemorrhoids	Presence of prolapse	1	
	Intermittent	1	
	Stable	2	
	Total score range	**2–3**	**Low L-TS**
	Bleeding	2	
	Occasional	1	
	Daily	3	
	Total score range	**3–5**	**Deferrable DS**
	Prolapse and bleeding	3	
	Intermittent prolapse	1	
	Stable prolapse	2	
	Occasional bleeding	1	
	Daily bleeding	2	
	Total score range	**5–7**	**High PS**
2 B. Fissure	NSR of Pain 0–3	2	
	Occasional bleeding	1	
	Daily bleeding	2	
	Total score range	**3–4**	**Low L-TS**
	NSR of Pain 4–7	4	
	Occasional bleeding	1	
	Daily bleeding	2	
	Total score range	**5–6**	**Deferrable DS**
	NSR of Pain ≥8	6	
	Occasional bleeding	1	
	Daily bleeding	2	
	Total score range	**7–8**	**High PS**
2C. Anal sepsis	Seton	0	
	Total score range	**0**	**Low L-TS**
	Stable fistula	1	
	Low output	1	
	High output	2	
	Total score range	**1–3**	**Deferrable DS**
	Instable fistula	2	
	Occasional abscess	1	
	Frequent abscess	2	
	Low output	1	
	High output	2	
	Total score range	**4–6**	**High PS**

patient self-reporting of pain (10). The presence of bleeding, occasional, or frequent was added.

PFs were graded according to the occurrence of relapsing acute abscess and the amount and frequency of discharge.

Obstructed defecation was classified according to the Cleveland Clinic Constipation Score (CCCS) scale (11), giving priority to patients reporting higher scores at clinical evaluation (18-30) and the presence of rectal internal prolapse at anoscopy and defecography. Other conditions such as condylomata or anal stricture were considered of intermediate priority and treated accordingly at short or midterm. Pilonidal sinuses and fistulas drained with seton were deferred, unless complicated by acute sepsis or severe discharge.

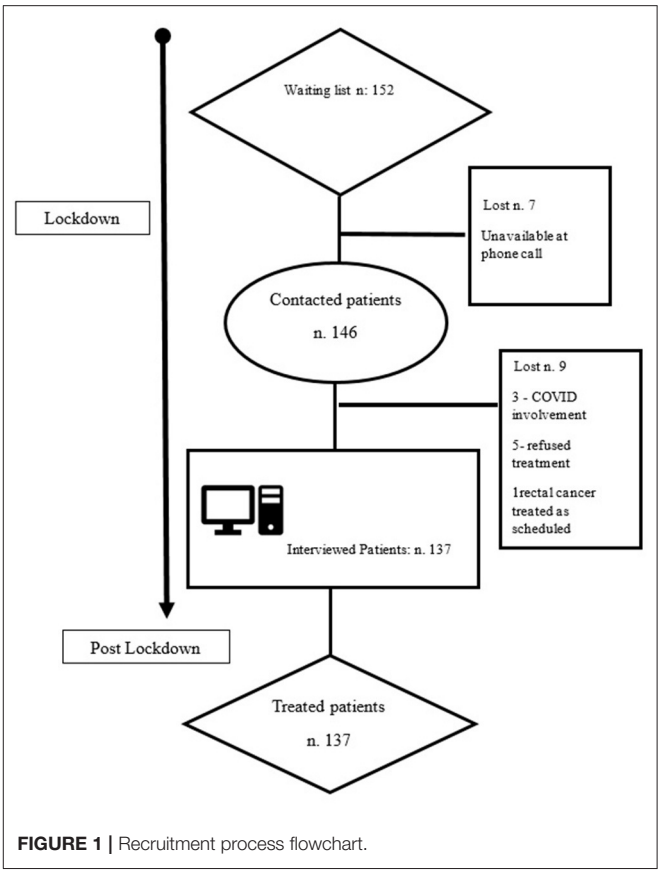

FIGURE 1 | Recruitment process flowchart.

The sum of the scores (priority class index) gave origin to a stratification in three classes of priority as follows: priority surgery (PS), deferrable surgery (DS), and long-term surgery (L-TS). Details of the scores for each disease are given in **Table 2**.

Descriptive statistics were calculated for all the variables in this study. Mean and SD were reported for continuous variables, while frequencies and percentages were reported for categorical variables. To compare sex among the three classes of priority, the chi-squared test was used, whereas the F-test for the one-way ANOVA model analysis was used to compare age. The Spearman's rho coefficient was performed to analyze the correlation between self-perceived health investigated with the first item of the telephone interview and the priority class index (PS, DS, and L-TS).

All the statistical analyses were performed using StataCorp. 2015, Stata Statistical Software: Release 14 College Station, TX, USA: StataCorp LP., setting alpha to 0.05.

RESULTS

Out of 152 patients awaiting treatment in the Surgical Coloproctology Unit in the Hospital Val Vibrata, 137 patients were finally available, answered the questionnaire, and were evaluated (**Figure 1**).

TABLE 3 | Data from 152 clinical records pre-lockdown (84 M, 68 F).

Diagnosis	*n*	%
III, IV degree hemorrhoidal disease	41	26.9
Anal fissure	45	29.6
Anal sepsis	23	15.1
Rectal prolapse internal/complete	5	3.2
Slow transit constipation, acquired megacolon	4	2.6
Pilonidal sinus	13	8.5
Condiloma	7	4.6
Fecal incontinence	7	4.6
Anal and rectal stricture	6	3.9
Rectal carcinoma	1	0.6
Total	152	

TABLE 4 | Clinical features of patients available at interview ($n = 137$).

	n (%)
Sex	
Male	74 (54.1%)
Female	63 (45.9%)
Mean age (range)	51 (21–78)
Diagnosis	
Hemorrhoidal disease	39 (28.4%)
Anal fissure	42 (30.6%)
Anal sepsis	20 (14.5%)
Rectal prolapse, obstructed defecation	5 (3.6%)
Slow transit constipation	3 (2.1%)
Sinus	12 (8.7%)
Condiloma	5 (3.6%)
Fecal incontinence	6 (4.3%)
Anal/rectal stricture	5 (3.6%)
Total	137
Self-perceived health	
Very good/good	68 (49.6%)
Fair	15 (10.9%)
Bad/very bad	54 (39.4%)

The mean age of patients was 53 years ± 16 (SD) and there were 84 males (55.3%) and 68 females (44.7%).

Before the lockdown, the main types of diseases observed were as follows: 41 (26.9%) patients were diagnosed with III-IV degrees HDs, 45 (29.6%) with AFs resistant to medical treatment, and 23 (15.1%) with anal sepsis including one anovulvar fistula (**Table 3**).

These data were consistent with the reported incidence of proctological and colorectal diseases at the end of the lockdown (June 2020) (**Table 4**). As far as self-perceived health status, most of the patients declared a very good/good health status (49.2%—fair in 11.5%). However, as many as 54 patients reported their health as bad or very bad (39.1%) (**Table 4**).

As given in **Table 5**, 49 patients were classified as PS (35.7%), 25 patients were classified as DS (18.1%), while 63 patients were classified as L-TS (45.6%).

TABLE 5 | Re-scheduling surgery according to the Priority Class in 137 patients.

Diagnosis	Priority surgery (PS)	Deferrable surgery (DS)	Long-term surgery (L-TS)
Hemorrhoidal disease	14 (28.5%)	7 (30.4%)	18 (27%)
Anal fissure	11 (22.4%)	13 (56.5%)	18 (27%)
Anal fistula/abscess	11 (22.4%)	3 (28.6%)	7 (10.7%)
Rectal prolapse/Obstructed defecation	2 (4%)	1 (4.3%)	2 (3%)
Severe constipation/adult megacolon	3 (6.1%)	0 (0%)	1 (2%)
Pilonidal Sinus	0 (0%)	0 (0%)	12 (18.4%)
Condilomata	5 (10.2%)	0 (0%)	0 (0%)
Incontinence and Ectropion	2 (4%)	0 (0%)	4 (6.1%)
Anal stricture	1 (2%)	0 (0%)	4 (6.1%)
Total 137	49 (35.7%)	23 (16.7%)	65 (47.4%)

The mean age of patients classified in PS category was 53 (±15) years and they were older than patients classified as DS and L-TS, respectively (52 ± 11) and (50 ± 17); the differences were not significant (F-test = 0.43; $p = 0.653$).

The distribution between males and females was not different by classes (Pearson's chi-squared test = 0.6926; $p = 0.707$) and there was a high positive correlation between the self-perceived health and the estimated priority index (Spearman's rho = 0.97, $p < 0.001$).

Patients affected by HD in class PS complained mainly of daily and severe bleeding, leading to anemia in four patients, whereas those affected by AF reported high scores (8–11) at pain evaluation with daily, frequent analgesic intake (2.8 daily doses + −0.5; range 0–4).

As for obstructed defecation, the CCCS score of 25 gave priority for surgical treatment in one patient with internal rectal prolapse [stapled transanal rectal resection (STARR)]. Another female patient affected by complete rectal prolapse had a Delorme procedure. In severe chronic constipation with dolichomegacolon, three out of four patients complained of recurrent episodes of acute intestinal subocclusion. In these patients, the diameter of the ascending colon was larger than 10 cm on plain, abdominal X-rays and, thus, surgical treatment was planned in class PS (subtotal colectomy and ileorectal anastomosis) after a short course of medical treatment for two patients.

The patients within class PS were treated consecutively at reopening of elective surgery starting from the first week of June. 11 cases out of 50 cases showed a progression of the disease compared to the prelockdown evaluation and this made a change in surgical treatment as follows: three patients waiting for dearterialization moved to excisional hemorrhoidectomy, four fistula patients planned for ligation of intersphincteric fistula tract necessitated drainage of recurrent acute sepsis and seton placement instead, and three patients with AF were given

anoplasty in place of lateral sphincterotomy due to deepening of the fissure and enlargement of skin tag and sentinel polyp.

In those cases belonging to the DS category and operated between August and September, we noticed an evolution of the disease although to a lesser extent; three patients affected by AF showed local sepsis and were treated by means of drainage, posterior sphincterotomy, and anoplasty. Interestingly, none of those three patients complained of a substantial change of symptoms and, thus, of the score.

Anoplasty was performed in three patients affected by anal stricture (one in the PS group and two in the DS group) or in the case of mucosal ectropion (2 patients in the DS group). In two of them, incontinence was associated and treated by sphincteroplasty or sphinkeeper placement.

Finally, five patients affected by large anoperineal condylomata were treated by means of diathermic excision. The patient affected by low rectal cancer was treated at the end of neoadjuvant treatment as planned since oncologic surgery was not affected by the lockdown and underwent an abdominoperineal amputation.

In the L-TS category, all the operations were performed as planned previously when patients were selected for operation. In this respect, medical treatment or conservative procedures helped notably as a bridge to surgery.

DISCUSSION

The occurrence of the COVID-19 pandemic implied partial or complete cancelation of diagnostic procedures, outpatient visits, and elective surgical operations starting from the beginning of March 2020. Elective surgery for benign conditions faced a cancelation of procedures to an estimate of 71.2–87.4% (2). The practice of surgical coloproctology was heavily affected by this lockdown, since most operations performed in this area were for benign, functional disorders (4–6).

At the beginning of the lockdown, patients placed on the waiting list in our institution belonged to classes B or C according to our "national plan for management of waiting lists" (12). We aimed to establish criteria for reclassifying the priority of patients in view of the end of the lockdown. In addition, we had the opportunity to monitor the clinical conditions of patients, acting promptly for urgent treatment in case of complications or progression of the disease.

At the end of the lockdown, June in our area, patients who had their operation canceled deserved a prompt evaluation to reassess their conditions in view of the time passed. To make more than a hundred visits to re-evaluate and reschedule patients in a new order of priority, also in consideration of the restrictions imposed by the COVID-19 pandemic still going on, it would have been challenging or even impossible.

Our scoring system helped in reassessing the conditions of the patient by means of a simple telephone call, also comparing the answers with patient's chart handled by us and containing relevant clinical data. We observed concordance between the severity of disease and a bad health status declared by the patient.

Self-perception of health status in a patient judged as bad, fair, or good is a trustable predictor of reduced functional capacity, depression, increased search for hospital care, and even mortality (9).

Perceived health is an overall indicator of the general health status of a population. Our results are in line with what is reported in the literature. In fact, several studies have highlighted the association of the perception of the state of health, with mortality, morbidity, functional decline, and higher request of health services resources (13–15).

In total, 39% of patients felt their health status was bad. This result is difficult to understand since the mean age of patients was not very old. However, in this respect, stress played a role due to the lockdown itself and to the COVID-19 pandemic.

Giani et al. divided patients into deferrable and not deferrable based on both the symptoms and COVID-19 infection risk. Interestingly, 198 out of 548 (36.1%) visits were canceled, and there was a 55% increase of office-based procedures (29 visits in 2019 and 45 visits in 2020).

None of the patients or surgeons resulted COVID-19 positive (16).

With the adoption of the scoring system, we obtained a new stratification in three different classes of patients in each disease requiring different priorities. Indeed, benign proctological diseases such as HD, AF, PF, and PD covered 73% of patients. Our simple score helped in identifying those patients in each group necessitating operation as soon as activity was resumed.

The results of our interview showed that, in the sample of 138 patients contacted after the lockdown, there were 50 patients in class PS ready for operations, while 63 patients were in class L-TS could wait for a new ride plan to access the hospital care.

With the restart of elective surgery, the operations were performed accordingly to the new priority order in June and July whereas, in August and September, patients in DS underwent surgical treatment.

As expected, we observed in class PS a certain degree of progression and worsening of clinical conditions of patients, affecting 13% of the total of patients with HD, AF, and PF and leading to a change in surgical strategy. In class DS, we found a progression of the disease and worse clinical conditions only in a minority of cases as compared to the prelockdown selection.

Indications for surgery in case of benign surgical disorders are usually posed after a failed course of conservative measures; in this respect, the availability of alternative, nonoperative treatments or tools is to be considered, since they may represent a tamponade treatment waiting for surgery (17).

With the restrictions imposed in hospital access by the COVID-19 pandemic and the subsequent lockdown, our telephone interview helped in monitoring the health of patients and it was extremely useful in prioritizing again patients after initial evaluation. The questions of the interview are quite basic; therefore, it can be conducted by trained, nonspecialist personnel. In this respect, straightforward monitoring of the conditions of the patient, especially for those in a long-standing surgical waiting list, can be adopted independently from the present situation. This may be helpful to prevent worsening of the

diseases that, if occurring, shift the treatment to emergency with a rise in complications and costs.

Our results were consistent with the current growth trend manifested toward telemedicine, which has helped to overcome the burden of the COVID-19 pandemic (18–20).

This study has some limitations; the main one is represented by the need for a strong statistical validation of the simple score proposed. However, at the end of the lockdown, there was a strong need for reprogramming surgical activity, and our score showed to be a useful and simple method for this goal. In addition, the small size of subjects selected in a subspecialty unit may be a limit, although they represent a rather homogeneous group of patients. The easy and friendly use of our interview showed to be effective in prioritization a good amount of elective surgical operations minimizing the negative effect of the lockdown. Adoption of measures such as priority scores may enable to maintain a certain volume of elective surgery, despite restrictions due to the COVID-19 pandemic.

In conclusion, recovery plans for elective surgery after the lockdown are to be fundamentally prepared in all the areas of routine surgery for benign diseases. This is of the utmost importance also considering possible subsequent relapses of COVID-19 disease leading to repeated lockdown and cancelation of planned surgery. In replanning elective surgery during the COVID-19 pandemic, resources limitations and risk of COVID-19 transmission must be considered as additional adverse factors in limiting hospital access and surgical treatment.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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CASE REPORT
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Case Report: Low Rectal Cancer With Incidental Pelvic Solitary Kidney

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Purpose: Concurrence of pelvic solitary kidney and rectal cancer is a rare phenomenon. The presence of the kidney in a narrow pelvic cavity represents a great challenge for total mesenteric excision (TME) under laparoscopy.

Methods: We reported a male patient with low rectal cancer and incidental pelvic solitary kidney and reviewed relevant literature.

Results: The patient was successfully treated with laparoscopic surgery and was discharged on day 6 postoperatively without severe complications.

Conclusion: This case suggests the feasibility of laparoscopic TME with pelvic solitary kidney in a certain male patient with rectal cancer and emphasizes the importance of comprehensive preoperative radiological evaluation, a multidiscipline team, and careful intraoperative dissection.

Keywords: rectal cancer, pelvic kidney, laparoscopy, case report, 3D reconstitution

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INTRODUCTION

Pelvic kidney results from failure of the kidneys ascending to their usual position during the embryonic period. Most patients are asymptomatic and diagnosed accidentally. Pelvic solitary kidney occurs in 1:2,100–1:3,000 autopsies (1). The concurrence of pelvic kidney and rectal cancer is a rare phenomenon. In male patients, the presence of pelvic kidney makes the inherently narrow space of the pelvic cavity even more limited, posing a great challenge for total mesenteric excision (TME) under laparoscopy. Herein, we reported a male patient with simultaneous low rectal cancer and pelvic solitary kidney who was successfully treated with laparoscopic surgery.

CASE PRESENTATION

A 49-year old male patient visited our hospital with 1 month of irregular defecation and hematochezia. He was then diagnosed with low rectal adenocarcinoma based on colonoscopy and pathological biopsy. A mass could be touched on the abdomen wall above the pubic symphysis by physical examination. Digital rectal examination showed a hard and fixed mass 1 cm above the anal verge; the upper verge of the mass could not be palpated. Contrast CT revealed no distal metastasis, and a previously unknown pelvic solitary kidney was identified. No seminal vesicle was observed. Three-dimensional CT reconstruction and pelvic MRI demonstrated that the pelvic kidney was 7.7 × 8.4 × 10 cm in size, and that 2/3 of the kidney was located in the pelvic cavity with the hilum facing toward the right common iliac artery (**Figures 1A,B**). Three separate renal arteries originated from the right common iliac artery and two separate renal veins drained into the left common iliac vein (**Figure 1C**). The ureter was short and tortuous (**Figure 1D**). The rectum and sigmoid colon were pushed to the right pelvic cavity. The patient had no awareness of the

pelvic solitary kidney before, and the kidney function was normal after admission. Contrast pelvic MRI showed that the tumor had invaded the muscular layer; hence, preoperative tumor staging was cT2N0M0. The patient used to be healthy with no past medical history. After discussion with the multidisciplinary team (including a radiologist, oncologist, urologist, and pathologist), laparoscopic extralevator abdominoperineal excision (LELAPE) without neoadjuvant therapy was proposed. The patient agreed to our proposal and signed a consent form.

In the operating room, two senior surgical urologists were standing by during the whole surgery in case of additional injury of the urinary system. Under general anesthesia, the patient was first placed in the Trendelenburg position (30°) with a right lateral tilt (15–20°). The operator stood on the right side of the patient, the first assistant on the left, and the camera holder on the cranial side. The pneumoperitoneal pressure was set at 12 mmHg. A 10-mm trocar was inserted above the umbilicus as the observation site, a 12-mm or 10-mm main operating port was made about 5 cm below the umbilical level on the right midclavicular line, and a 5-mm assistant trocar was made at the umbilical level on the same line. At the planned site for sigmoid colon stoma, a 5-mm trocar was placed for the assistant which was later lengthened for colostomy. Another 5-mm trocar was made 2 cm above the pubic symphysis for assistance.

At first, complete laparoscopic exploration was performed: the kidney was located in the pelvic cavity with the rectum and rectosigmoid pushed to the right (**Figure 2A**); adhesions were observed between the mesosigmoid and the peritoneum above the kidney as well as the mesoileum (**Figure 2B**); no tumor implants or occult liver lesions were identified. After adhesion lysis, a clear avascular plane between the mesosigmoid and the prehypogastric nerve fascia was identified and dissection proceeded medially along this plane to the left lateral peritoneal gutter. The inferior mesenteric artery (IMA) was ligated at about 1 cm from its origin after clearance of No.253 lymph nodes (**Figure 2C**). Pelvic dissection with TME began from the posterior and right sides and proceeded caudally. Despite the narrow pelvic space, the anatomy in these two sides was normal, and no difficulties in dissection were encountered. For the left side, the kidney and mesorectum were dissected under counter-traction using the superior rectal artery (SRA) as a landmark (**Figure 2D**). We were reminded of an increase in blood pressure by the anesthetist, so kidney retraction force was reduced to maintain the stability of blood pressure. The anterior dissection is the most challenging part. Usually, we cut the pelvic peritoneum approximately 1 cm above the peritoneal reflection. However, in this patient, without seminal vesicle being used as a landmark, we chose the peritoneal reflection as the cutting point, although we were still not able to recognize the Denonvilliers'fascia and accidentally entered an incorrect plane between the posterior wall of the bladder and the anterior layer of the Denonvilliers'fascia (**Figure 3A**). We had not realized this mistake until the ureter and left trigone of the bladder were exposed and identified (**Figure 3B**). Then, we transected the Denonvilliers'fascia and entered the correct surgical plane between the posterior layer of the Denonvilliers' fascia and the mesorectum (**Figure 3C**). The anterior dissection ceased after proceeding caudally for another 2 cm. The sigmoid mesocolon was trimmed to the edge of the sigmoid colon and then divided with a laparoscopic linear stapler intracorporeally. The end of the proximal colon was pulled out to create a colostomy.

The patient was then turned around into the prone jackknife position, and a purse-string suture was performed to close the anus. The perineal skin was incised from the coccyx to the perineum. Dissection followed the outer surface of the external sphincter muscle and the levator ani muscle, and the coccyx was removed. Posteriorly, the sacrococcygeal junction was divided to obtain access to the inner dissection plane. Afterward, the levator ani was divided laterally close to its origin. Then, the distal end of the sigmoid colon was pulled out of the pelvic cavity, and the anterior connection of the rectum and posterior wall of the prostate was exposed. Finally, the dissection was completed anteriorly with meticulous preservation of neurovascular bundles and the prostate. After the cylindrical specimen was removed, the ischiorectal fat and skin were closed. A presacral drainage tube was placed through the abdominal port incision, and a subcutaneous tube was placed in the perineal incision. The total operation time was 5 h and 10 min. Only one colostomy and several minor trocar incisions were presented in the abdominal wall without extra incisions (**Figure 4**). Postoperative pathology showed moderately differentiated adenocarcinoma with muscular layer invasion, no lymph node metastasis (pT2N0M0), and negative circumferential and longitudinal margins (R0). The patient was discharged on day 6 without any postoperative complications. No sign of recurrence was indicated by CT scan or blood test 6 months after the surgery.

DISCUSSION

Concurrence of pelvic kidney and colorectal cancer is a rare phenomenon. Nine case reports were found in the literature search (2–10), and only six full texts were available (2–7) (**Table 1**). Of the six reports, five patients were male and one patient was female. Pelvic solitary kidney was confirmed in one patient (5). Three patients were described with one kidney located in the pelvic cavity and and the other kidney located *in situ* (3, 4, 7). Two of the reports did not mention the situation of the other kidney (2, 6). Only one male patient with rectosigmoid colon cancer was successfully treated with laparoscopic surgery (4). For the rest, open surgery was initially chosen or intraoperative open surgery conversion was performed because of unexpected pelvic kidney or severe intraoperative complications. To our knowledge, the present case is the first report of a patient with simultaneous low rectal cancer and pelvic solitary kidney who was successfully treated with laparoscopic surgery.

The kidneys are retroperitoneal organs. Despite their ectopic location during ascent, the natural avascular space between the mesosigmoid and the prehypogastric nerve fascia still exists, which lays the anatomical foundation for surgical dissection in this special scenario. The only crossing point of the mesosigmoid and retroperitoneum is the root of the IMA. In the present patient, the procedure of the IMA exposure and resection was

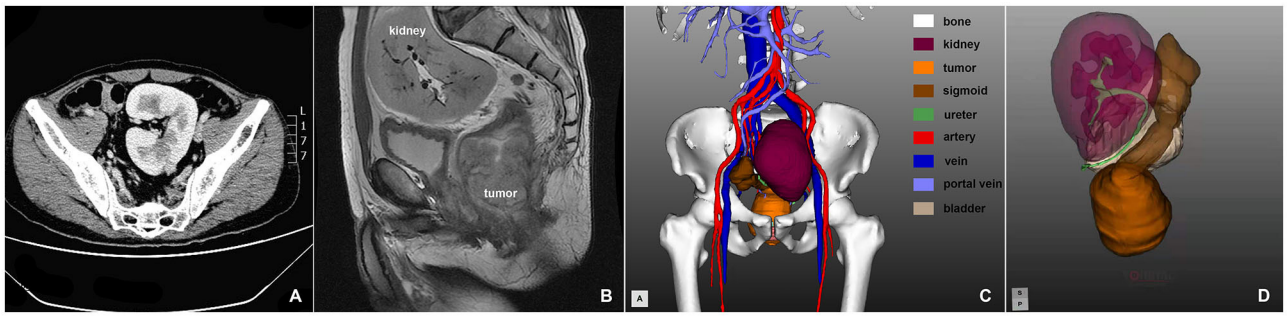

FIGURE 1 | (A) Axial CT scan of the pelvic solitary kidney; **(B)** sagittal MRI scan of the pelvic solitary kidney and the rectum; **(C,D)** three-dimensional reconstruction of the pelvic organs.

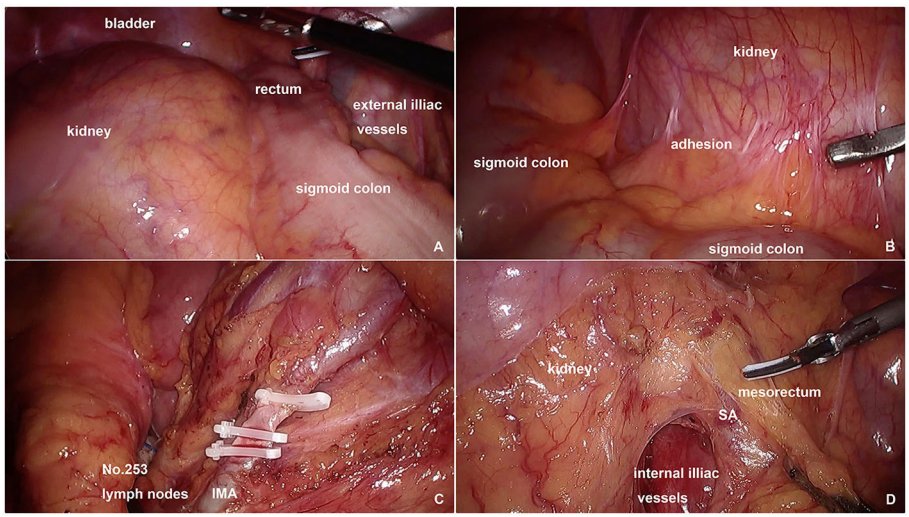

FIGURE 2 | (A–D) Intraoperative images of abdominal dissection under laparoscopy.

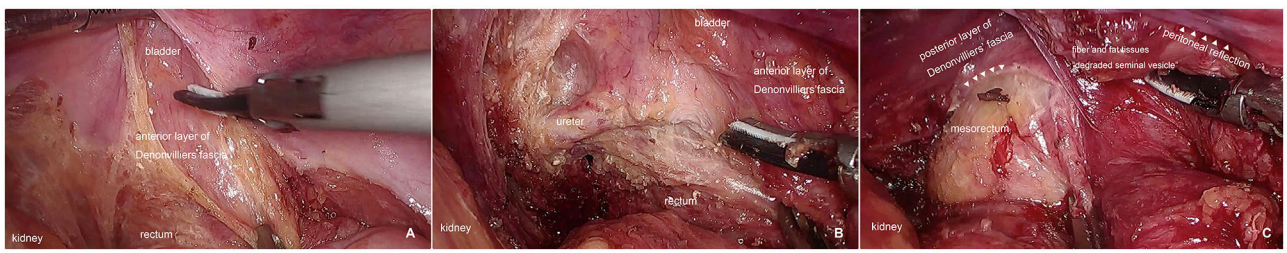

FIGURE 3 | (A–C) Intraoperative images of pelvic dissection under laparoscopy.

relatively easy, as the renal arteries, which originated from the right common iliac artery, were away from the IMA. In one Japanese female diagnosed with rectal cancer coupled with solitary pelvic kidney, the right renal artery branched off from the aortic bifurcation and thought as the IMA. The renal artery was ligated by mistake during laparoscopic surgery, leading to open surgery conversion and vascular anastomosis (6). Therefore, a detailed and precise preoperative CT evaluation of aberrant vessels is of great importance.

The pelvic kidney is sometimes complicated with congenital abnormalities of the genitourinary system. In this patient, the seminal vesicle was replaced by some fiber and fat tissues (**Figure 3C**). Because of this variation, pelvic anterior dissection was difficult. The seminal vesicle is an important landmark for pelvic anterior dissection. Normally, in males, after cutting the pelvic peritoneum 1 cm above the peritoneal reflection, the seminal vesicle is visible, and dissection should be performed between the seminal vesicle and the posterior layer of the

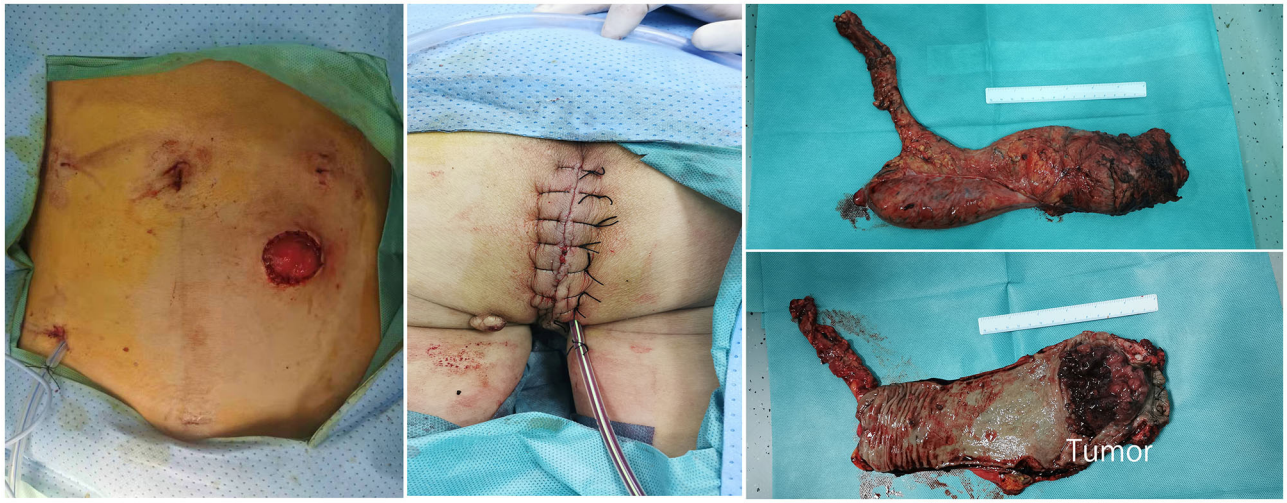

FIGURE 4 | Postoperative images of abdominal and perineal incision and specimen.

TABLE 1 | Case report of colorectal cancer with pelvic kidney.

Year	Author	Journal	Nation	Gender	Age	Diagnosis	Left kidney	Right kidney	Operation	Complication
1996	Malak B. Bokhari et al. (2).	J Surg Oncol	United States	Male	63	Rectal cancer	Not reported	In pelvis	Open surgery	Null
2005	Sakamoto K. et al. (5).	J Minim Access Surg	Japan	Male	55	Sigmoid colon cancer	In pelvis	Absent	Laparoscopic surgery and open surgery	Null
2018	Koki Takeda et al. (6).	Asian J Endosc Surg	Japan	Female	54	Rectal cancer	Not reported	In pelvis	Laparoscopic surgery with open surgery conversion	Intraoperative right renal artery ligation
2019	Hassan Moaiery et al. (3).	J Med Case Rep	Iran	Male	40	Rectal cancer	In situ	In pelvis	Open surgery	Postoperative anastomotic leak
2020	Katherine J. Zhu et al. (7).	ANZ J Surg	Australia	Male	65	Rectosigmoid colon cancer	In pelvis	In situ	Laparoscopic surgery and open surgery	Null
2021	Byung Kwan Park et al. (4).	Ann Coloproctol	Korea	Male	76	Rectosigmoid colon cancer	In pelvis	In situ	Laparoscopic surgery	Null

Denonvilliers'fascia until the lower edge of the seminal vesicle is reached, where the posterior layer of the Denonvilliers'fascia should be transected and a deeper surgical plane between the posterior layer of the Denonvilliers'fascia and mesorectum should be entered for subsequent caudal dissection. In the present case, the appearance of tissues in the location where the seminal vesicle should be was similar to that of the rectal wall therefore, a wrong surgical plane was entered. Fortunately, when the ureter and bladder were exposed and identified, we made timely corrections without severe intraoperative complications.

The low rectal tumor in this patient was relatively large and squeezed the mesorectum, leading to suspicion of positive marginal resection fascia (MRF). Additionally, a couple of lymph nodes within the mesorectum were also enlarged and visible. According to National Comprehensive Cancer Network Surveillance Guideline, positive MRF and lymph nodes in low rectal cancer require neoadjuvant radiotherapy. However, for this patient, pelvic irradiation would have an inevitable side effect on the solitary pelvic kidney despite mechanical shielding, resulting in slowly progressive radiation nephropathy or even uremia. Thanks to the radiologists in our multidisciplinary team (MDT), the preoperative tumor staging was precisely decided, and the patient underwent surgery without neoadjuvant therapy. Therefore, the significance of MDT discussion should be valued, particularly for complicated cases.

The present case suggests the feasibility of laparoscopic TME dissection of pelvic solitary kidney in male patients. Comprehensive radiological evaluation, MDT discussion, and careful intraoperative dissection are of great importance.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The authors that contributed to the conception and design of the study were XZ, YD, and YW. Data acquisition and interpretation were performed by XZ, CC, and KW. The first draft of the manuscript was written by XZ. All the authors commented on previous versions of the manuscript and revised it critically for important intellectual content and read and approved the final version of the manuscript to be submitted.

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Efficacy and Safety of Sphincter-Preserving Surgery in the Treatment of Complex Anal Fistula: A Network Meta-Analysis

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Background: There are many surgical methods of sphincter preservation in treating complex anal fistula, but the therapeutic effects of each operation are different. Therefore, this study aimed to compare the impact of other treatment methods through a network meta-analysis to evaluate the best sphincter preservation method for treating complex anal fistula.

Methods: We searched PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, Chinese Biomedical Literature Database, VIP Journal Database, and the Wanfang Database to collate randomized controlled trials on sphincter-preserving surgery for complex anal fistula.

Results: A total of 29 articles were included in this meta-analysis. The cure rates showed no statistically significant differences between any two interventions ($P > 0.05$). The recurrence rate results showed that the rate of patients after Fistulectomy was higher than others ($P < 0.05$). The incidence rate of complications showed that the incidence rate after fistulectomy treatment was higher than that of others ($P < 0.05$). The surface under the cumulative ranking (SUCRA) was used to arrange their advantages and disadvantages, and a larger SUCRA value indicates that the intervention may be more effective. The results showed that TROPIS may have the highest cure rate (SUCRA = 78.6%), stem cell transplantation (SCT) may have the lowest recurrence rate (SUCRA = 85.5%), and imLIFT may have the least complications (SUCRA = 88.2%).

Conclusion: According to the existing literature data, for patients with complex anal fistula, TROPIS may be the surgical method with the highest cure rate, SCT may be the treatment method with the lowest recurrence rate, and imLIFT may be the surgical method with the lowest incidence of postoperative complications.

Systematic Review Registration: PROSPERO, identifier: CRD42020221907.

Keywords: sphincter, treatment, complex anal fistula, meta, cure rate

INTRODUCTION

A complex anal fistula is a refractory disease in colorectal anal surgery. According to statistics, the incidence of anal fistula is approximately 3.6%. Anal fistula mainly affects young adults with a male predominance (1, 2). An anal fistula is usually caused by an infection of the anal glands in the sphincter space. The passage of bacteria generally causes this infection into the anal recess. Clinical manifestations include anal pus and skin itching, amongst others. The condition seriously affects the quality of life of patients.

Surgery is the primary treatment method for complex anal fistula, with the main aim being to preserve anal sphincter function and eliminate the fistula. Traditional surgery requires an incision of healthy tissue and has certain shortcomings, including large drainage wounds, severe pain, slow healing, and varying degrees of damage to the anal sphincter (3, 4). Severe anal sphincter injury can lead to fecal incontinence (5).

It is crucial to preserve sphincter function in patients with complex anal fistula, and because traditional surgical methods easily injure the sphincter, a variety of surgical treatment modalities have been developed to preserve anal sphincter function, such as sphincter-preserving thread drawing (SPTD) (6), ligation of the intersphincteric fistula tract (LIFT) (7–9), valve displacement repair (VDR) (10, 11), fibrin glue (FG) (12), and biological patch (13, 14) treatments. Sphincter-preserving surgery for a complex anal fistula can maximize the maintenance of sphincter function and reduce postoperative complications. However, there are many types of sphincter-preserving treatment for high complex anal fistula, and the efficacy of each surgical treatment differs. At present, no treatment comparisons have been made. Therefore, this study evaluated various randomized controlled trials on treating complex anal fistula. A network meta-analysis compared differences in recurrence, cure rate, and complications of each sphincter-preserving therapy for patients with highly complex anal fistula to evaluate treatment safety and efficacy.

METHOD

Search Strategy

This network meta-analysis was registered in PROSPERO (Registration number: CRD42020221907), an international register website of systematic reviews (https://www.crd.york.ac.uk/prospero/) and was reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (15) and AM- STAR (Assessing the methodological quality of systematic reviews) Guidelines (16).

We searched PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, Chinese Biomedical Literature Database, VIP Journal Database, and the Wanfang Database to collate randomized controlled trials on sphincter-preserving surgery for complex anal fistula from database establishment to July 31st, 2021. The languages were limited to Chinese and English. Search terms included "Stem Cell Transplantation", "Sphincter preserving thread drawing", "Biological patch", "video-assisted anal fistula", "Ligation of anal fistula", "endoscopic needle-knife incision", "anal fistula plug", "Pushing mucosa", "advancement flap", "Transanal opening of intersphincteric space", "Rectal Fistula", "Anal Fistula" and "Complex". Medical Subject Headings, free-text terms, and variants were used, including aliases for each surgery. Boolean Operators (AND, OR, and NOT) were used to connect the search terms to form search expressions.

Eligibility and Exclusion Criteria

The inclusion criteria were as follows: (1) inclusion of patients with a definite diagnosis of complex anal fistula; (2) studies including interventions with various types of sphincter-preserving surgery; (3) study outcome indicators of cure rate, recurrence rate, and complication rate; (4) randomized controlled trials; (5) studies with complete data.

The exclusion criteria were as follows: (1) incomplete statistical analysis of results or insufficient data; (2) repeated published literature; (3) case report; (4) studies not examining sphincter-preserving treatment of complex anal fistula; (5) conferences, meta-analyses, and review articles.

Quality Assessment and Data Extraction

Two investigators initially screened the retrieved studies independently according to the inclusion and exclusion criteria and then cross-checked. Controversial studies were evaluated by a third party and unified by discussion. Two investigators extracted relevant information from the included studies, including first author, publication year, publication country, sample size, age, sex, cure rate, recurrence rate, and complication rate.

Healing was defined as the absence of suppuration of the external orifice, and complete re-epithelialization was achieved after the end of follow-up. Recurrence occurred through the original tract and remained trans-sphincteric and was proven by clinical examination and ultrasound scanning. Complications refer to the occurrence of another disease or symptom during the treatment, and the latter is the complication of the former, which is not clearly defined in each literature.

Because the included studies were randomized controlled or cohort studies, the literature quality of randomized controlled trials was evaluated using the Jadad scale. The scores (0∼3) were classified as low-quality literature and (4∼7) as high-quality literature. The quality assessment of the included articles was performed using the Newcastle-Ottawa (NOS) scale, a quality evaluation tool specifically for case-control studies and cohort studies. The evaluation included three aspects: selection (four items), comparability (one item), and outcome (three items). Among them, the maximum score of each item of choice and outcome was 1, the total score of comparable items was 2, and the total score of scale evaluation results was 9. Scores (0–4) were classified as low-quality articles and (5∼9) as high-quality.

Statistical Analysis

Stata 16.0 software was used to analyze the data. Count data (binary data in this paper) are expressed by relative risk (RR), and the interval estimation used the 95% confidence interval

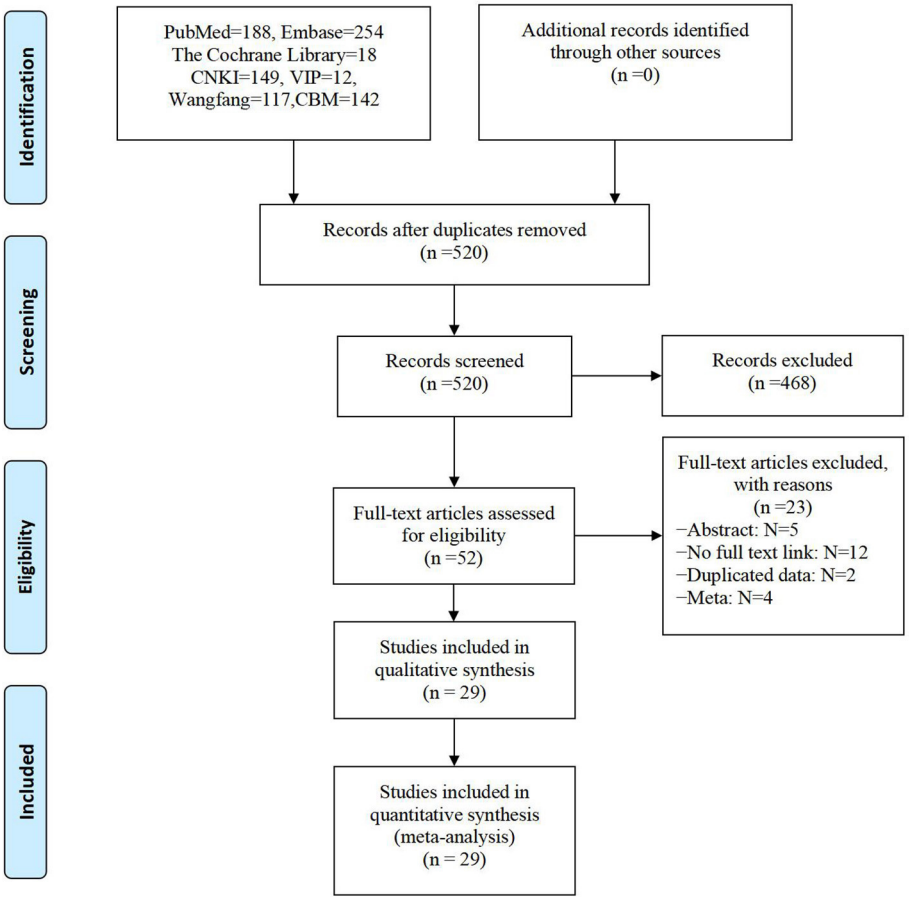

FIGURE 1 | Literature screening flow chart.

(CI) as an indicator of affect quantity. Heterogeneity in the results was assessed using the Cochrane Q test ($\alpha = 0.1$) combined with I^2. If heterogeneity was acceptable, the fixed-effects model was used. Otherwise, the random-effects model was used. When the 95% CI did not contain "1," the results were deemed statistically significant. If the 95% CI included "1," this indicated no statistical significance. An overall inconsistency test was conducted when data were entered into Stata 16.0. If $P > 0.05$, overall consistency was good, and there was no statistically significant difference. Then, the consistent model was used to perform a network meta-analysis on the efficacy and safety of various sphincter-preserving surgeries. If there was a statistically significant difference ($P < 0.05$), non-consistency was used for model analysis. Using the node-splitting model, direct and indirect comparisons were compared. If $P > 0.05$, there was no apparent local inconsistency. Otherwise, there was local inconsistency between direct and indirect comparisons. After comparing various surgical methods, the advantages and disadvantages of each were arranged using the surface under the cumulative ranking (SUCRA), and the possibility of each type of anal sphincter preservation surgery as the best treatment was evaluated.

RESULTS

Eligible Studies

A total of 880 relevant original articles were found in this reticular meta-analysis, including 460 English articles and 420 Chinese articles, involving 15 interventions. By carefully reading the titles and abstracts and screening the articles by inclusion and exclusion criteria, 52 articles were obtained and re-excluded by reading the complete text, and finally, 29 (17–45) articles were included in this study (**Figure 1**).

Basic Characteristics and Quality Evaluation of Included Literature

The 29 included articles, with 3,608 patients, included 23 randomized controlled trial studies and six cohort studies. Only two pieces of literature in the randomized controlled trial study had low quality, and the rest had a Jadad score $\geq$ of 4 points. None of the cohort studies had a NOS score $\geq$5. Therefore, the overall quality of the included studies was good. The basic characteristics of the included studies are shown in **Table 1**.

TABLE 1 | Basic characteristics and quality evaluation of the included studies.

Study	Year	Country	Type of study	Age(s)	Gender (M/F)	Sample sizes	Interventions	Outcomes	Jadad/NOS scores
Garcia-Arranz et al. (17)	2020	Spain	RCT	50.10 ± 10.7	16/7	23	SCTFG	①②	6
				50.86 ± 9.64	14/7	21	FG		
Garcia-Olmo et al. (18)	2009	Spain	RCT	42.64 ± 10.93	10/14	24	SCTFG	①③	5
				43.99 ± 8.97	14/11	25	FG		
García-Olmo et al. (19)	2015	Spain	RCT	42.64 ± 10.93	10/14	24	SCT	②	7
				43.99 ± 8.97	14/11	25	FG		
Panés et al. (20)	2016	Spain	RCT	39·0 ± 13.1	60/47	107	SCT	①③	6
				37·6 ± 13.1	56/49	105	SOC		
Tsang et al. (21)	2020	China	RCT	47.2 ± 11.1	38/10	48	LIFT	①③	6
				47.2 ± 11.1	9/1	10	BioLIFT		
Liu H et al. (22)	2020	China	RCT	NA	54/10	64	LIFT	①②③	6
				NA	52/12	64	SPTD		
Kun Gao et al. (23)	2018	China	RCT	44.19 ± 5.13	32/9	41	AF	①②③	4
				43.21 ± 5.08	44/13	57	LIFT		
Junyi Jia et al. (24)	2017	China	RCT	46.51 ± 6.39	24/20	44	LIFT	①③	5
				46.82 ± 6.70	21/23	44	SPTD		
Tong Jia et al. (25)	2019	China	RCT	36.59 ± 9.28	32/9	41	AFS	①②	5
				37.98 ± 11.38	35/14	49	SPTD		
Linyuan Lu et al. (26)	2019	China	RCT	42.33 ± 2.76	34/8	42	VAAFT	①③	5
				42.29 ± 2.69	30/8	38	SPTD		
Jian Peng et al. (27)	2014	China	RCT	35.4 ± 8.7	25/15	40	LIFT	①②③	6
				34.2 ± 8.5	23/17	40	SPTD		
Jinglin Wang et al. (28)	2018	China	RCT	38.94 ± 15.71	23/17	40	VAAFT	①③	3
				40.12 ± 16.33	21/19	40	SPTD		
Hongming Xu et al. (29)	2020	China	RCT	38.41 ± 9.58	35/12	47	imLIFT	①③	4
				38.07 ± 9.53	32/15	47	LIFT		
Changmou Yang et al. (30)	2007	China	RCT	38.7 ± 12.7	28/14	42	SPTD	①②③	6
				41.9 ± 14.5	25/17	42	Fistulectomy		
Ming Ye et al. (31)	2014	China	RCT	NA	NA	37	SPTD	①②③	3
				NA	NA	37	Fistulectomy		
Hexue Yuan et al. (32)	2019	China	RCT	44.3 ± 6.6	31/19	50	LIFT	①②③	6
				46.4 ± 7.2	28/22	50	AF		
Le Zhao et al. (33)	2017	China	RCT	39 (22–52)	33/10	43	SPTD	①②	4
				42 (24–60)	35/12	47	IDBSS		
Li Zheng et al. (34)	2018	China	RCT	37.4 ± 13.5	33/9	42	VAAFT	②	4
				42.1 ± 15.6	32/13	45	SPTD		
Junfeng Zhuang et al. (35)	2020	China	RCT	40.7 ± 5.2	25/32	57	ISDPS	①	5
				40.2 ± 5.3	26/31	57	LIFT		
Yee Chen Lau et al. (36)	2019	Australia	RCT	38 (19–75)	68/37	105	LIFT	①	6
				41 (26–69)	7/4	11	BioLIFT		
Chrispen Mushaya et al. (37)	2012	Australia	RCT	48.2 (20.6–72.9)	10/4	14	AF	①②③	6
				47.5 (25.0–70.1)	17/8	25	LIFT		
M. D. Herreros et al. (38)	2012	Spain	RCT	49.78 ± 11.39	47/17	64	SCT	①②	6
				47.27 ± 12.27	36/24	60	SCTFG		
				50.85 ± 12.51	44/15	59	FG		
Wiley Chung et al. (39)	2009	Canada	Cohort study	46 (23~68)	18/9	27	FP	①②③	5
				49 (22–68)	22/1	23	FG		
				46 (21–82)	70/16	86	SD		
				46 (28–75)	71/25	96	FA		

(Continued)

TABLE 1 | Continued

Study	Year	Country	Type of study	Age(s)	Gender (M/F)	Sample sizes	Interventions	Outcomes	Jadad/NOS scores
Oliver Maximilian Fisher et al. (40)	2015	Switzerland	Cohort study	41 (34–51)	17/14	31	AFS	②③	6
				44 (34–58)	29/11	40	AF		
A. Mujukian et al. (41)	2020	USA	Cohort study	35 (12–63)	16/22	38	LIFT	①②③	6
				43 (22–68)	10/12	22	AFS		
M. La Torre et al. (42)	2020	Italy	Cohort study	NA	NA	26	LIFT	①②	5
				NA	NA	28	VAFFT		
Ian Lindsey et al. (43)	2002	Australia	RCT	NA	NA	13	FG	①②③	4
				NA	NA	16	LIFT		
Pankaj Garg et al. (44)	2017	India	Cohort study	37.5 ± 10.7	510/101	611	Fistulectomy	①③	7
				40.5 ± 11.1	372/36	408	TROPIS		
				49.0 ± 10.9	52/4	56	AFS		
Zhiyun Zhang et al. (45)	2020	China	Cohort study	41.88 ± 13.38	18/7	25	Fistulectomy	①②③	5
				41.12 ± 16.61	17/8	25	TROPIS		

RCT, Randomized controlled trial; M, Male; F, Female; NA, Not available; SCTFG, Stem cell transplantation combined with fibrin glue; FG, Fibrin glue; SCT, Stem cell transplantation; SOC, Standard of care; LIFT, Ligation of intersphincteric fistula; BioLIFT, Biological patch combined with ligation of intersphincteric fistula; SPTD, Sphincter preserving thread drawing; AFS, Anal fistula suppository; VAAFT, Video-assisted anal fistula; VDR, Valve displacement repair; imLIFT, Improved ligation of intersphincteric fistula; IDBSS, Incision and drainage between sphincter and sphincter; ISDPS, Internal sphincterotomy and drainage with preservation of sphincter.
① Cure rate; ② Recurrence rate; ③ Complication rate.

Results of Network Meta-Analysis

Evidence Network

In the reticulated evidence diagram, each vertex represents different intervention methods, the size of the vertex represents the sample size included in each intervention method, the line between vertices represents the direct comparison existing between two intervention methods, and the thickness of the line is directly proportional to the number of related studies. There was direct or indirect evidence between the different intervention methods, with the basic conditions for reticular meta-analysis (**Figures 2A–C**).

Network Meta-Analysis of Cure Rate

Twenty-six studies reported the cure rate of anal fistula. There was a closed ring between the interventions. There were direct and indirect comparisons between the interventions, and the results of the consistency test showed $P > 0.05$. Therefore, statistical analysis could be performed directly under the consistency model. The results of the network meta-analysis of cure rates showed that there were no statistically significant comparisons between any two interventions ($P > 0.05$) (**Table 2**).

Network Meta-Analysis of Recurrence Rate

The recurrence rate was reported in 18 literature. There was a closed ring between the interventions. There were direct and indirect comparisons between the interventions. The consistency test results showed $P > 0.05$. Therefore, the statistical analysis could be performed directly under the consistency model. The results of network meta-analysis of the recurrence rate showed that the recurrence rate of patients after Fistulectomy treatment was higher than that of AF, AFS, LIFT, SCT, SCTFG, SPTD, and VAAFT, and the differences were statistically significant ($P < 0.05$); the recurrence rate of patients after FG treatment was higher than that of patients after SCTFG, and the differences were statistically significant ($P < 0.05$); the recurrence rate of patients after SOC treatment was higher than that of patients after SCT, and the differences were statistically significant ($P < 0.05$) (**Table 3**).

Network Meta-Analysis of Complication Rate

The incidence rate of complications was reported in 18 pieces of literature. There were closed rings between the interventions. There were direct and indirect comparisons between the interventions. The consistency test results showed $P > 0.05$. Therefore, the statistical analysis could be performed directly under the consistency model. The results of network meta-analysis of the incidence of complications showed that the incidence of complications in patients after fistulectomy treatment was higher than that of AF, AFS, imLIFT, LIFT, SPTD, and VAAFT, and the differences were statistically significant ($P < 0.05$); the incidence of complications in patients after SPTD treatment was higher than that of imLIFT and LIFT, and the differences were statistically significant ($P < 0.05$); the incidence of complications in patients after TROPIS treatment was higher than that of imLIFT, LIFT, and AFS and the differences were statistically significant ($P < 0.05$); the incidence of complications in patients after VAAFT treatment was lower than that of SPTD and TROPIS (**Table 4**).

Probability Ranking of Intervention Effects of Various Surgical Methods

A total of 15 interventions were included in this study. The probability of cure rate, recurrence rate, complication rate and other indicators under 15 interventions was ranked.

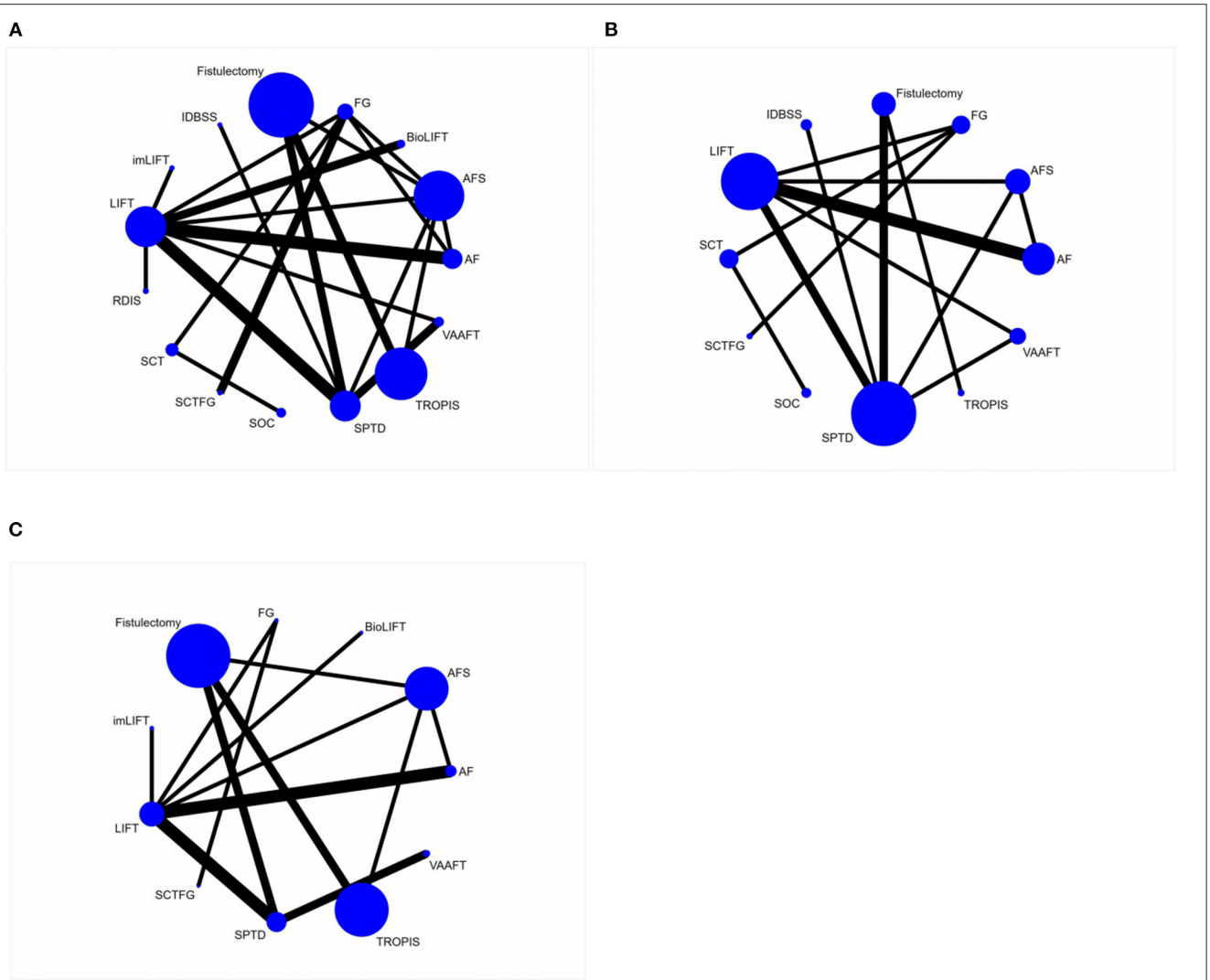

FIGURE 2 | Reticulated evidence diagram of different sphincter-preserving surgeries. **(A)** Network evidence for cure rate; **(B)** Network evidence for recurrence rate; **(C)** Network evidence for complication rate.

The probability indicated that the intervention was the best treatment. The results of probability ranking of cure rate showed: TROPIS (78.6%) > RDIS (68.3%) > imLIFT (66.9%) > SCTFG (66.3%) > VAAFT (64.8%) > Fistulectomy (58.4%) > LIFT (54.7%) > AF (51.1%) > IDBSS (47.8%) > SCT (44%) > SPTD (40.7%) > BioLIFT (34.5%) > FG (34.1%) > SOC (24.7%) > AFS (15.1%), suggesting that TROPIS may be the surgical method with the highest recovery rate in patients after treatment. The results of probability ranking of recurrence rate showed: SCT (85.5%) > SCTFG (83.7%) > SOC (66.2%) > VAAFT (65.5%) > LIFT (64.5%) > IDBSS (61.9%) > AFS (39.9%) > FG (38.1%) > AF (36.5%) > SPTD (31.7%) > TROPIS (24.2%) > Fistulectomy (2.4%), suggesting that SCT may be the surgical method with the lowest recurrence rate in patients after treatment. The results of probability ranking of complication rate showed: imLIFT (88.2%) > VAAFT (78.6%) > LIFT (69.1%) > AFS (68.8%) > BioLIFT (54%) > AF (49.7%) > SCTFG (47.9%) > SPTD (35.6%) > FG (34.2%) > TROPIS (16.3%) > Fistulectomy (7.6%), suggesting that imLIFT may be the surgical method with the lowest complication rate in patients after treatment (**Table 5**).

Node Analysis

The inconsistency test of cure rate, recurrence rate, and incidence rate of complications showed $P > 0.05$, indicating no significant inconsistency. The node analysis results showed no significant difference between direct comparison and indirect comparison ($P > 0.05$), indicating no inconsistency in the results between direct comparison and indirect comparison.

Small Sample Effect and Publication Bias

The funnel plot of outcome measures such as cure rate, recurrence rate, and complication rate was plotted. From the funnel plot of cure rate, recurrence rate, and complication rate, most studies' scatter points were located above the funnel plot.

TABLE 2 | Network meta-analysis results of cure rate (RR, 95% CI).

AF	AFS	BioLIFT	FG	Fistulectomy	IDBSS	imLIFT	LIFT	RDIS	SCT	SCTFG	SOC	SPTD	TROPIS	VAAFT
1.58 (0.90, 2.78)														
1.24 (0.58, 2.68)	0.79 (0.34, 1.79)													
1.24 (0.56, 2.72)	0.78 (0.34, 1.79)	0.99 (0.35, 2.81)												
0.91 (0.46, 1.81)	0.58 (0.31, 1.08)	0.73 (0.30, 1.79)	0.74 (0.29, 1.87)											
1.04 (0.42, 2.59)	0.66 (0.27, 1.61)	0.84 (0.29, 2.42)	0.84 (0.27, 2.60)	1.14 (0.47, 2.77)										
0.79 (0.34, 1.86)	0.50 (0.20, 1.24)	0.64 (0.24, 1.72)	0.64 (0.21, 1.93)	0.87 (0.33, 2.28)	0.76 (0.25, 2.35)									
0.97 (0.64, 1.45)	0.61 (0.36, 1.02)	0.78 (0.41, 1.48)	0.78 (0.35, 1.75)	1.06 (0.58, 1.94)	0.93 (0.40, 2.16)	1.22 (0.58, 2.60)								
0.77 (0.31, 1.90)	0.48 (0.19, 1.27)	0.62 (0.22, 1.74)	0.62 (0.20, 1.95)	0.84 (0.31, 2.32)	0.74 (0.23, 2.38)	0.97 (0.32, 2.94)	0.79 (0.35, 1.79)							
1.13 (0.36, 3.56)	0.71 (0.22, 2.31)	0.91 (0.24, 3.44)	0.92 (0.40, 2.10)	1.24 (0.36, 4.32)	1.09 (0.27, 4.42)	1.43 (0.36, 5.69)	1.17 (0.37, 3.72)	1.48 (0.36, 6.05)						
0.79 (0.26, 2.35)	0.50 (0.16, 1.54)	0.63 (0.17, 2.31)	0.64 (0.30, 1.34)	0.86 (0.26, 2.84)	0.76 (0.19, 2.95)	0.99 (0.26, 3.80)	0.81 (0.27, 2.47)	1.02 (0.26, 4.05)	0.69 (0.23, 2.11)					
1.64 (0.40, 6.62)	1.03 (0.25, 4.28)	1.32 (0.28, 6.22)	1.32 (0.42, 4.20)	1.79 (0.41, 7.91)	1.57 (0.31, 7.91)	2.07 (0.42, 10.21)	1.69 (0.41, 6.91)	2.13 (0.42, 10.81)	1.44 (0.65, 3.22)	2.08 (0.53, 8.21)				
1.10 (0.64, 1.87)	0.69 (0.42, 1.14)	0.88 (0.41, 1.89)	0.89 (0.38, 2.08)	1.20 (0.74, 1.96)	1.06 (0.50, 2.22)	1.39 (0.59, 3.25)	1.14 (0.76, 1.69)	1.43 (0.58, 3.53)	0.97 (0.30, 3.18)	1.40 (0.44, 4.38)	0.67 (0.16, 2.81)			
0.68 (0.28, 1.62)	0.43 (0.19, 0.97)	0.54 (0.19, 1.57)	0.55 (0.19, 1.57)	0.74 (0.41, 1.34)	0.65 (0.23, 1.87)	0.86 (0.28, 2.61)	0.70 (0.31, 1.59)	0.88 (0.28, 2.80)	0.60 (0.16, 2.29)	0.86 (0.24, 3.08)	0.41 (0.09, 1.98)	0.62 (0.29, 1.31)		
0.86 (0.45, 1.64)	0.54 (0.28, 1.04)	0.69 (0.30, 1.59)	0.70 (0.28, 1.77)	0.94 (0.48, 1.85)	0.83 (0.34, 2.00)	1.09 (0.44, 2.72)	0.89 (0.53, 1.50)	1.12 (0.43, 2.94)	0.76 (0.22, 2.65)	1.10 (0.33, 3.65)	0.53 (0.12, 2.32)	0.78 (0.49, 1.26)	1.27 (0.53, 3.06)	

TABLE 3 | Network meta-analysis results of recurrence rate (RR, 95% CI).

AF	AFS	FG	Fistulectomy	IDBSS	LIFT	SCT	SCTFG	SOC	SPTD	TROPIS	VAAFT
1.07 (0.63, 1.81)											
0.99 (0.17, 5.83)	0.93 (0.16, 5.51)										
0.08 (0.01, 0.85)	0.08 (0.01, 0.80)	0.08 (0.01, 1.33)									
2.74 (0.10, 79.07)	2.57 (0.09, 74.11)	2.77 (0.07, 109.24)	32.58 (0.75, 1412.71)								
1.98 (0.97, 4.03)	1.86 (0.89, 3.86)	2.00 (0.39, 10.16)	23.55 (2.56, 216.52)	0.72 (0.03, 19.53)							
8.89 (0.30, 263.52)	8.33 (0.28, 248.05)	8.98 (0.50, 161.47)	105.66 (1.96, 5698.76)	3.24 (0.03, 347.41)	4.49 (0.16, 123.32)						
7.59 (0.52, 110.77)	7.11 (0.48, 104.38)	7.67 (1.03, 57.22)	90.20 (2.99, 2719.25)	2.77 (0.04, 182.55)	3.83 (0.29, 50.77)	0.85 (0.03, 28.83)					
4.00 (0.13, 124.54)	3.75 (0.12, 117.22)	4.04 (0.21, 76.95)	47.54 (0.85, 2673.63)	1.46 (0.01, 162.00)	2.02 (0.07, 58.34)	0.45 (0.25, 0.80)	0.53 (0.01, 18.66)				
0.84 (0.28, 2.53)	0.79 (0.26, 2.37)	0.85 (0.13, 5.39)	9.96 (1.30, 76.02)	0.31 (0.01, 7.31)	0.42 (0.17, 1.03)	0.09 (0.00, 2.91)	0.11 (0.01, 1.70)	0.21 (0.01, 6.79)			
0.34 (0.01, 7.77)	0.32 (0.01, 7.28)	0.34 (0.01, 10.95)	4.00 (0.48, 33.33)	0.12 (0.00, 9.28)	0.17 (0.01, 3.65)	0.04 (0.00, 3.46)	0.04 (0.00, 2.45)	0.08 (0.00, 7.99)	0.40 (0.02, 7.58)		
2.07 (0.82, 5.21)	1.94 (0.76, 4.95)	2.09 (0.37, 11.81)	24.58 (2.65, 228.34)	0.75 (0.03, 20.52)	1.04 (0.57, 1.91)	0.23 (0.01, 6.75)	0.27 (0.02, 3.87)	0.52 (0.02, 15.76)	2.47 (0.99, 6.16)	6.14 (0.28, 133.17)	

TABLE 4 | Network meta-analysis results of patient complication rate (RR, 95% CI).

AF	AFS	BioLIFT	FG	Fistulectomy	imLIFT	LIFT	SCTFG	SPTD	TROPIS	VAAFT
1.71 (0.61, 4.75)	0.64 (0.08, 4.96)	0.41 (0.01, 16.87)	0.32 (0.01, 10.95)	25.62 (4.29, 153.00)	0.47 (0.14, 1.61)	0.41 (0.01, 13.26)	0.85 (0.02, 30.96)	0.35 (0.08, 1.50)	11.88 (1.89, 74.52)	
1.10 (0.14, 8.86)	0.26 (0.01, 8.11)	0.13 (0.01, 1.19)	8.27 (0.25, 272.27)	12.14 (3.29, 44.73)	0.19 (0.00, 7.74)	0.35 (0.14, 0.86)	0.30 (0.01, 13.76)	4.15 (1.36, 12.65)		
0.45 (0.01, 14.22)	0.08 (0.02, 0.39)	3.38 (0.39, 28.95)	3.92 (0.15, 103.46)	4.96 (0.12, 203.91)	0.16 (0.04, 0.75)	0.12 (0.02, 0.61)	3.52 (0.08, 152.09)			
0.14 (0.03, 0.75)	2.17 (0.44, 10.71)	1.60 (0.27, 9.37)	1.60 (0.49, 5.21)	4.21 (1.50, 11.86)	0.06 (0.01, 0.44)	1.44 (0.34, 6.06)				
3.70 (0.71, 19.36)	1.03 (0.37, 2.87)	0.65 (0.01, 32.40)	1.36 (0.05, 40.59)	1.47 (0.51, 4.23)	0.68 (0.10, 4.50)					
1.75 (0.57, 5.35)	0.42 (0.01, 15.81)	0.56 (0.08, 4.04)	0.47 (0.01, 18.28)	17.47 (3.82, 80.02)						
0.72 (0.02, 27.67)	0.36 (0.10, 1.29)	0.19 (0.02, 2.13)	5.64 (0.16, 201.31)							
0.61 (0.15, 2.40)	0.12 (0.02, 0.78)	2.30 (0.24, 22.47)								
0.21 (0.03, 1.49)	1.48 (0.27, 8.10)									
2.52 (0.43, 14.79)										

TABLE 5 | Ranking of probabilities for each intervention (SUCRA, %).

Interventions	Cure rate	Recurrence rate	Complication rate
AF	51.1	36.5	49.7
AFS	15.1	39.9	68.8
BioLIFT	34.5	-	54.0
FG	34.1	38.1	34.2
Fistulectomy	58.4	2.4	7.6
IDBSS	47.8	61.9	-
imLIFT	66.9	-	88.2
LIFT	54.7	64.5	69.1
RDIS	68.3	-	-
SCT	44.0	85.5	-
SCTFG	66.3	83.7	47.9
SOC	24.7	66.2	-
SPTD	40.7	31.7	35.6
TROPIS	78.6	24.2	16.3
VAAFT	64.8	65.5	78.6

The distribution of each issue was symmetrical, indicating that the included studies had less possibility of publication bias. At the bottom of each funnel plot, some scatter points are located at the bottom of the funnel plot, indicating that it is affected by some small sample effect (**Figures 3A–C**).

DISCUSSION

An anal fistula is a chronic abnormal sinus tract formed after ulceration of perianorectal abscess. The fistula of complex anal fistula has a complicated course, high recurrence rate, and partial loss of anal function, which is still one of the difficult problems in surgical treatment. Preservation of the patient's anal sphincter function is directly related to the quality of life later. For this reason, a variety of surgical treatments with anal sphincter preservation have been used in clinical practice.

Different treatment modalities vary in postoperative cure rate, recurrence rate, and complication rate. The drainage thread-drawing method allows the fistula to be in a continuous opening with adequate drainage to avoid recurrent episodes of the fistula and accelerate the epithelialization of the wall. However, some studies (46) have reported that the recurrence rate of anal fistula treated with thread-drawing therapy can be up to 40%. Women are more likely to experience treatment failure due to anal canal stenosis, rectovaginal fistulas, and complex fistulas. Fibrin glue is composed of fibrin and thrombin. After the mixture of the two is injected into the fistula, thrombin is activated to form a fibrous clot, which mechanically closes the fistula. Subsequently, the fibrous clot gradually dissolves to promote tissue healing and eliminate the fistula.

According to studies (47, 48), fibrin glue is well tolerated by patients in the treatment of anal fistula without the risk of anal incontinence. Still, its effect in treating complex anal fistula is not satisfactory, with a cure rate of <10%. For patients who did not respond to fibrin glue for the first time, there was

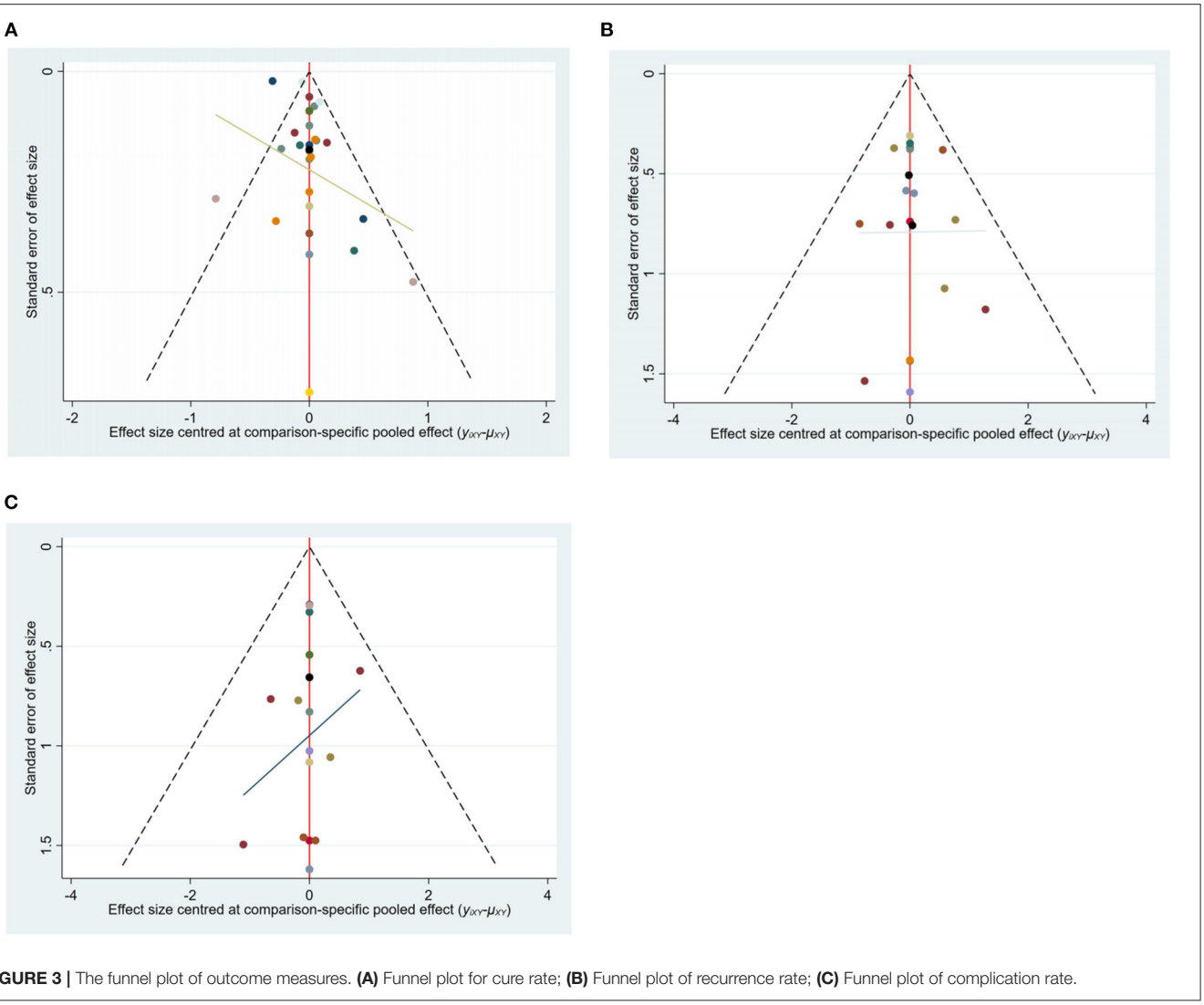

FIGURE 3 | The funnel plot of outcome measures. **(A)** Funnel plot for cure rate; **(B)** Funnel plot of recurrence rate; **(C)** Funnel plot of complication rate.

no response after retreatment with fibrin glue, indicating that fibrin glue is not suitable for local conditions in patients who failed fibrin glue for the first time (49). An anal fistula plug is a suppository made of biological collagen extracted from the submucosa of the lyophilized pig small intestine. Anal fistula plug provide a reticular scaffold structure for host tissue cell growth and promote local tissue repair. A prospective, multi-center, randomized controlled study included 106 patients with anal fistula caused by Crohn's disease. After treatment for 12 years, the efficacy of thread-drawing therapy was similar to that of anal fistula plug, without significant difference. However, it was found that the effectiveness of the anal fistula plug was due to thread-drawing in patients with complex Crohn's disease anal fistula (50). Recurrence after treatment of anal fistula plug may be due to displacement of anal fistula plug, incomplete closure of the internal orifice, or multiple fistulas. Although the effect of anal fistula plug treatment is general, it also has certain advantages, such as simple operation, minimally invasive, fewer complications, and not easy to cause anal incontinence.AF uses a mucosal flap to cover the high-pressure area of the internal orifice and form a firm anti-infective barrier to promote fistula healing. Theoretically, AF can protect the normal anatomy of the anal canal and anal continence function, but 9.4 to 23.5% of patients have incontinence symptoms, which may be due to intraoperative damage to the internal anal sphincter or postoperative mucosal eversion, abnormal stimulation of anal defecation receptors, resulting in incontinence symptoms (51, 52).VAAFT mainly includes anal fistula endoscopy, fistula ablation, and internal orifice closure technique so that the internal orifice is closed, which can cure the fistula without damaging the anal sphincter. There were some differences in the success rate of VAAFT in the treatment of patients with anal fistula. Minero et al. (53) found that the cure rate was up to 87.7%, but Seow-En et al. (54) concluded that the primary healing rate was 70.7%.LIFT is the mainstream treatment for transsphincteric anal fistula, which can effectively avoid sphincter injury and is often used to treat refractory or recurrent anal fistula. The incision of conventional LIFT is close to the medial side of the anal verge,

small and deep, which quickly leads to effusion or hematocele, which induces postoperative incision dehiscence, infection, and increases the risk of recurrence. In recent years, to achieve a better therapeutic effect, some new treatment methods continue to emerge, and researchers continue to report the efficacy of new treatment options.

Due to the differences and wide variety of measures for treating high complex anal fistula, there is no comparative analysis of the efficacy of different anal sphincter-preserving treatment measures. Therefore, this study is the first indirect comparison of different anal sphincter-preserving outcomes using network meta-analysis. In this meta-analysis, TROPIS was the treatment with the highest cure rate. As a newly used regimen in recent years, TROPIS has been confirmed to have an excellent therapeutic effect in several studies (44, 45). The surgical steps of TROPIS are mainly explored by using a probe at the external orifice. Then, based on the probe direction, a radioactive shuttle incision about 2.5 cm in length and perpendicular to the internal orifice is made to completely expose the internal and external sphincters, as well as the central space, a slight texture is used in the sphincter space to separate the internal and external sphincters; the probe is gradually elicited from the inner orifice, a rubber band is used to determine the tightness by the cumulative number of sphincters, and then the fibrotic wall tissue is trimmed (3). The infected anal glands and mucosa on both sides of the internal orifice are treated. After the internal orifice and infected anal glands are cleaned, the curette is used to curette the necrotic tissue in the fistula tract of the patient. Under appropriate circumstances, the lower part of the external sphincter and the superficial part can be removed to ensure patient drainage patency. Although TROPIS showed a higher cure rate, it did not perform very well in reducing the recurrence rate and complication rate. In terms of reducing the recurrence rate, stem cells have potent and immunomodulatory effects, differentiate into fibroblasts, and promote wound healing, an emerging method for treating complex anal fistulas. A multi-center phase I/IIa clinical trial initially reported 24 weeks of allogeneic adipose-derived stem cell transplantation for anal fistula in Crohn's disease, with an external orifice closure rate of 56% (55). Stem cell transplantation for patients with anal fistula has no serious adverse effects, and anal pain is one of the most common manifestations (20). The modified LIFT also ranked highest in reducing the complication rate. The surgical incision of modified LIFT is adjusted from the intersphincteric sulcus of the medial anal linea alba of the anal verge to the external orifice of the fistula. The external orifice is centered on keeping the incision away from the anal orifice to reduce the infection caused by feces entering the incision, reduce the risk of hematocele, effusion, and wound dehiscence. Perform tunnel resection of the fistula from the external orifice, stealth dissects the fistula to the intersphincteric sulcus and suture, seal the fistula and the internal orifice, and thoroughly dissect the fistula and suture the part of the internal orifice of the fistula to avoid residual necrotic tissue in the wall. For patients with long fistulas, a segmented incision can be made for tunnel sneak resection of the fistula. Suture the intersphincteric groove musculature and surgical incision, indwell multi-side hole negative pressure drainage tube for timely drainage of excess wound exudation, and compression bandaging at the incision skin during dressing change can promote adhesion and improve the wound healing rate.

Limitations of This Study

(1) There are few direct comparison studies among various interventions, and few closed rings are formed. The results mainly come from indirect comparison. Although the indirect comparison results have specific guidelines, the strength of evidence is weaker than direct comparison; (2) There are still few relevant studies reporting the postoperative pain level of patients with anal sphincter-preserving surgery for anal fistula. This Meta has not evaluated the tolerance of patients.

CONCLUSION

In the present study, it was found that TROPIS may be the treatment with the highest cure rate, SCT may be the treatment with the lowest recurrence rate, and imLIFT may be the surgical modality with the minor postoperative complications. Since the conclusion of this study is mainly derived from the results of the indirect comparison, it is hoped that the subsequent randomized controlled trial with rigorous protocol can be designed for further demonstration to provide better strong evidence support and guidance for the clinical treatment of patients with recurrent anal fistula.

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

HH: study design, data collections, and writing. YL and SX: data collections, data analysis, and writing. LJ: funding and study design. YG: study design and review. All authors contributed to the article and approved the submitted version.

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Perianal Diseases in Pregnancy and After Childbirth: Frequency, Risk Factors, Impact on Women's Quality of Life and Treatment Methods

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Hemorrhoids and anal fissures occur in about 40% of pregnant women and women during postpartum period. Usually they occur during the third trimester of pregnancy and 1–2 days after giving birth. Constipation during pregnancy, perianal diseases during previous pregnancy and childbirth, instrumental delivery, straining duration of more than 20 min, and weight of the newborn more than 3,800 g are associated with hemorrhoids. Perianal diseases reduce the quality of life of both pregnant and postpartum women. In the absence of acute conditions, surgical treatment of hemorrhoids is delayed after pregnancy, childbirth, and lactation. Thrombosed internal hemorrhoids and perianal thrombosis are to be treated conservatively in most instances by prescribing adequate pain relief, oral, and topical flavonoid preparations.

Keywords: hemorrhoids, pregnancy, delivery, perianal disease, obstetric

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INTRODUCTION

Pregnancy is a physiological condition; however, pregnant women experience severe anthropometric, physical, metabolic, and psychological changes as well as changes of internal and external organs. These changes can reactivate chronic diseases, present before pregnancy as well as cause new ones (1).

Normal components of the human anal canal are anal cushions (2). They consist of a thickened submucosa, blood vessels, smooth muscle fibers, and connective tissue above the dentate line (2–5). Hemorrhoids is a disease that manifests with symptoms of bleeding from the cushions, their prolapse or vascular space thrombosis (6–8).

Hemorrhoids are classified into external and internal (9–12). External hemorrhoids are vascular spaces below the dentate line, covered by anoderm (3–11). Enlargement and/or clinical symptoms occurring in anal cushions above dentate line are called internal hemorrhoids. They are covered by columnar epithelium and are weakly innervated (3, 4, 10, 11). Internal hemorrhoids are usually painless, even if they prolapse or bleed (9). Only strangulated and thrombosed internal hemorrhoids are very painful. External hemorrhoids are sensitive to palpation (11). Often both external and internal hemorrhoids occur together (10, 13).

It is necessary to distinguish grade IV hemorrhoids—elective, painless situation from the internal thrombosed hemorrhoids—urgent clinical condition accompanied by intense pain, when

nodules of internal hemorrhoids suddenly get stuck in the anal canal, thrombosis of the blood vessels occurs and hemorrhoids cannot be pushed back into the anal canal for several days.

ETIOLOGY, PATHOGENESIS, AND RISK FACTORS

The mechanism of development of hemorrhoids is not entirely clear, but several factors causing this disease have been identified.

During pregnancy, certain mechanical factors increase the development of hemorrhoids.

The growing of the uterus during pregnancy results in increased abdominal pressure in addition to mechanical pressure to the upper part of rectum, inferior vena cava, and portal vein which leads to development of venous stasis, especially in the second part of the pregnancy (4, 14–17). As a result, blood circulation to the internal anal sphincter decreases (4). In addition, during pregnancy, the circulating blood volume increases by 25–40% (3, 12, 15). These factors lead to vascular dilation and venous stasis in pelvis.

Hormonal factors also play an important role in the development of hemorrhoids. The increase in the progesterone can also contribute to the development of hemorrhoids, as it relaxes the walls of your veins, making them more prone to swelling (3–5).

The most common and already proven risk factors are constipation, diarrhea, pregnancy, and childbirth. Pregnancy, childbirth, and the period after childbirth definitely increase the risk of hemorrhoids (4, 5, 18). Natural childbirth is a risk factor for pelvic floor dysfunction (19). Constipation (due to low fluid intake and insufficient amount of fiber in the diet), difficult defecation, venous stasis due to increased abdominal pressure (with increasing uterus), increased volume of circulating blood, hormonal factors (progesterone), obesity, and sedentary lifestyle contribute to the development of hemorrhoids during pregnancy (3–5, 14, 15, 18, 20–23).

Symptoms of anal pathology most commonly occur in the second and third trimesters of pregnancy and after the childbirth (4, 8, 12, 24–27). Risk of developing hemorrhoids directly correlates with number of pregnancies and deliveries (21, 28); 70% of women diagnosed with hemorrhoids had at least one previous pregnancy (18). It was determined that after the first pregnancy, hemorrhoids occur in 37.9% percent of women, and after other pregnancies this number increases (after two pregnancies, 38.4%, after three or more pregnancies, 40%) (28). In addition, hemorrhoids occur in 85% of nonprimiparous women (29, 30). Childbirth increases the risk of hemorrhoids almost eight times (31). There is an ongoing discussion regarding the method of delivery and pelvic floor dysfunction. Some studies suggest that women who experience vaginal delivery have a higher risk of developing pelvic floor dysfunction than women who undergo cesarean section, while others failed to demonstrate any benefit with cesarean section (32).

The method of delivery can cause hemorrhoids- women who give birth naturally (normal delivery) and in whom instrumental delivery is used are more likely to develop hemorrhoids as compared to women that undergo cesarean section. A study in which a three-dimensional perineal ultrasound scanning of the anal sphincter complex was performed found out that the delivery method has a certain influence on the shape of the anal sphincter complex. The thickness of the internal and external anal sphincter of primiparous women in a certain direction is significantly smaller than that by caesarean section (33). However, patients with a cesarean section history should be encouraged to give vaginal birth. Although the second stage of labor is usually extended but the incidence of third- and fourth-degree perineal lacerations is not increased (34).

Other risk factors related to the previous deliveries are prolonged birth (more than 12 hrs), prolonged second stage of labor (35, 36) and straining duration (4, 37), high weight of the newborn (4,000 g and more), spontaneous childbirth (38), and prolonged pregnancy (more than 40 weeks of pregnancy) (4, 37, 39).

The risk between constipation and hemorrhoids is established. Constipation during pregnancy definitely increases the risk of development of perianal diseases during pregnancy and up to sixfold after childbirth (31, 36). Upto 40% of women experience constipation during pregnancy (40–42). The risk of constipation is associated with the number of births—it is more common in nonprimiparous women (14). Risk factors of constipation during pregnancy can be divided into four groups: (1) dietary changes (iron supplements' consumption, insufficient fluid levels in the body due to nausea, and vomiting during pregnancy); (2) behavioral changes (decreased physical activity, physical, and social stress); (3) humoral changes that affect slower bowel movements (increased levels of progesterone and estrogen, decreased motilin concentration); (4) other causes (growing uterus due to pregnancy, painful hemorrhoids) (3). Almost every woman's nutrition changes during pregnancy. It is very important to maintain the intake of fluids, which is often insufficient, due to nausea and vomiting especially during the first trimester of pregnancy. Pregnant women less commonly use fiber-containing foods (21). The risk of constipation may also increase due to medications: iron preparations are used to treat anemia, under hypertensive conditions—magnesium sulfate is also commonly used (21). Increased body mass index (BMI) was described as a risk factor for hemorrhoids and perianal diseases during pregnancy and postpartum period (42, 43). Hemorrhoids are more common in the older pregnant women and mothers (21, 28). Symptoms of hemorrhoids and other perianal diseases progress during pregnancy, therefore many women experience reduced quality of life, especially in the third trimester of pregnancy and after childbirth (22). Constipation and hemorrhoids have strong negative effect both on the physical and emotional well-being of women's health and deteriorate their quality of life after childbirth (44).

PERINEAL TRAUMA

Perineal trauma is a very common complication of vaginal delivery and plays an important role in pelvic floor dysfunction.

Traumatic delivery appears to be associated with thrombosed external hemorrhoids (37).

Lacerations can occur spontaneously or iatrogenically, as with an episiotomy, on the perineum. Severe lacerations are associated with a higher incidence of long-term pelvic floor dysfunction, pain, dyspareunia, and embarrassment (45–47). Perineal lacerations are classified into four basic categories (47). First and second degree describes lacerations which involve the vaginal mucosa and perineal skin or body. Though those lacerations are quite superficial, women having second-degree lacerations are not at increased risk for pelvic floor dysfunction other than increased pain, and slightly lower sexual function scores at 6 months postpartum (48). Third degree is a second-degree laceration with the involvement of the anal sphincter. Fourth degree perineal laceration is described as third-degree laceration involving the rectal mucosa. Severe perineal lacerations, which include third- and fourth-degree lacerations, are referred to as obstetric anal sphincter injuries (OASI) (47). The most often used methods to decrease risk of perineal trauma are episiotomy and hands-on approach and perineal support. There is an ongoing debate regarding the routine vs. restrictive use of episiotomy. Both the World Health Organization and the American College of Obstetrics and Gynecologists recommended restricted use of episiotomy (47). Meanwhile some studies suggest that episiotomy can significantly reduce the number of genital lacerations and selective use of episiotomy is clinically feasible and effective (49, 50). This policy seems to be associated with a lower delivery-related perineal trauma as showed by the sub-classification, which could be a useful tool to monitor obstetric care (50). Moreover, hand on the fetal head and perineal support both were protective factors for OASI (51). Rising rates of obstetric anal sphincter injury (OASI) led to a collaborative effort by the Royal College of Obstetricians and Gynaecologists (RCOG) and the Royal College of Midwives (RCM) to develop and evaluate the OASI Care Bundle (OASI-CB). The OASI-CB comprises four practices (antenatal discussion about OASI, manual perineal protection, mediolateral episiotomy at 60° from the midline, and systematic examination of the perineum, vagina and ano-rectum after vaginal birth) and was initially implemented as part of a quality improvement (QI) project—"OASI1"—in 16 maternity units across Great Britain. Evaluation of the OASI1 project found that the care bundle reduced OASI rates and identified several barriers and enablers to implementation (52). Those methods used to prevent perineal trauma can help avoid traumatic delivery and reduce the risk of hemorrhoids after childbirth.

FREQUENCY

Prevalence and risk factors of anal diseases during pregnancy and after delivery were previously studied (53, 54). The most common perianal diseases during pregnancy and after childbirth are hemorrhoids and peri-anal fissure with frequency of 43.9% and the most common time of occurrence being the third trimester of pregnancy (61%) and the first or the second day after delivery (34 %) (1). A study of 280 women found that 114 (92.7%) of them had hemorrhoids, 7 (5.7%) of women had hemorrhoids and anal fissure, and 2 (1.6%) of women had anal fissure. Of the 121 studied women diagnosed with hemorrhoids, hemorrhoidal thrombosis was diagnosed for 64 (52.9%) women.

SYMPTOMS

The most common clinical symptoms of perianal diseases were pain, discomfort, itching, nodules, burning, mucus in the anus, and bleeding from anus. Hemorrhoids in pregnant women, as mentioned, can occur under two acute conditions:

1. Thrombosed Internal Hemorrhoids-Urgent Clinical Condition Accompanied by Intense Pain, When Nodules of Internal Hemorrhoids Suddenly get Stuck in the Anal Canal, Thrombosis of the Blood Vessels Occurs and Hemorrhoids Cannot be Reduced Back Into the Anal Canal for Several Days.
2. Perianal Venous Thrombosis-Subcutaneous Venous Thrombosis can be Painful; However the Main Symptom Is a Nodule Composed of a Clot Occurring in the Subcutaneous Tissue, Sometimes the Clot Stretches the Skin and Causes Necrosis and Perforation, With Subsequent Evacuation of the Clot and Spontaneous Recovery. In Some Cases, the Clot Gradually Disappears, Often Leaving Excessive Skin in the Anal Area.

TREATMENT

In the absence of acute conditions, hemorrhoids like most other surgical diseases, are not treated before the end of the period of lactation.

Currently in Europe and the US, similar hemorrhoids' treatment guidelines are used (55). In all the cases of hemorrhoids, it is recommended to start with conservative treatment, with regulation of defecation. It is recommended to avoid constipation, long straining during defecation, and long sitting on the toilet. It is recommended to wash-up each time after defecation. Effective conservative treatment methods are flavonoids and topical preparations. In cases when a conservative treatment is ineffective, minimally invasive procedures can be tried: rubber band ligation, sclerotherapy, or infrared photocoagulation. Quite popular but more expensive dearterialization or stapled hemorrhoidopexy are not better than more traditional rubber band ligation and excisional hemorrhoidectomy interventions. In case of grade III-IV hemorrhoids with/or large external skin tags, surgical treatment is recommended (55). The search for new treatment methods of hemorrhoids is in continuation—laser hemorrhoidoplasty appears to be more effective than the suture hemorrhoidopexy but less effective than excision (56).

Most common acute perianal condition during pregnancy and after childbirth is perianal thrombosis and thrombosed internal hemorrhoids. Both diseases are characterized by a severe, sudden onset of pain forcing the seeking of medical help quickly. It is most commonly recommended to treat patients conservatively by prescribing adequate pain relief, oral, and topical flavonoid preparations. Warm sitz baths are recommended, which improve

blood circulation in the anal tissue and reduce pain by reducing the internal anal sphincter tonus. Although most pregnant women experience resolution of their symptoms with the conservative methods mentioned above, some women will need surgical treatment.

In cases of large symptomatic perianal thrombosis, thrombectomy may be performed, ideally under local anesthesia (57). Also, surgical interventions in the presence of internal hemorrhoid thrombosis are not recommended, because of increased anal sphincter damage, and the increased risk of anal stenosis.

CONCLUSIONS

Hemorrhoids and anal fissures occur in about 40% of pregnant women and women after delivery, usually in the third trimester of pregnancy and 1–2 days after giving birth. Constipation during pregnancy, perianal diseases during previous pregnancy and childbirth, instrumental delivery, straining duration of more than 20 min, and newborn weight of more than 3,800 g are associated with hemorrhoids. Perianal diseases reduce the quality of life of women. In the absence of acute conditions, surgical treatment of hemorrhoids is delayed after pregnancy, childbirth, and lactation. Thrombosed internal hemorrhoids and perianal thrombosis are to be treated conservatively in most instances by prescribing adequate pain relief, oral, and topical flavonoid preparations.

AUTHOR CONTRIBUTIONS

DB is the designated first author and TP is the designated senior author of the publication. All authors drafted parts of the article and reviewed the article and agree with the final version of the manuscript.

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Outcomes of Modified Tissue Selection Therapy Stapler in the Treatment of Prolapsing Hemorrhoids

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Objective: Tissue selection therapy staplers (TSTs) are widely used to treat prolapsing hemorrhoids; however, some disadvantages exist. We describe a modified technique for the treatment of prolapsing hemorrhoids, with the aim of minimizing the risk of anal stenosis and anal incontinence and reducing the impact of postoperative complications from the stapling technique. We applied a modified TST procedure, and the preliminary data were used to test the efficacy and safety of this new technique.

Methods: We conducted a retrospective study of patients who underwent modified TST for prolapsing hemorrhoids at our department between January 2018 and January 2020. All patients received a modified TST. Most prolapsing hemorrhoids were not segmentally resected and were instead selectively removed. The demographics, preoperative characteristics, postoperative complications, therapeutic effects, and patient satisfaction were collected and analyzed.

Results: A total of 106 patients were included in the study; 53 were men and 53 women (mean age, 49.24 years). The mean operative time was 55.01 min, and the mean hospital stay was 7.82 days. After surgery, three patients experienced bleeding (2.83%), 2 patients experienced anal discharge (1.89%), 2 patients experienced tenesmus (1.89%), and 5 patients experienced anal tags (4.72%). Anal incontinence, persistent post stapler pain, rectovaginal fistula and anal stenosis did not occur. Two patients developed recurrent symptomatic hemorrhoids (1.89%). The total effective rate of the surgery and the total satisfaction rate of the patients was 97.17%.

Conclusions: The modified tissue selection therapy stapler technique was a satisfactory and economical treatment for prolapsing hemorrhoids at a follow-up period of 1 year. The modified TST was associated with reduced anal stenosis and anal incontinence, less persistent post stapler pain and a minimal risk of rectovaginal fistula.

Keywords: tissue selection therapy stapler, prolapsing hemorrhoids, modified, complication rate, conformal

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INTRODUCTION

Prolapsed hemorrhoids are a common anorectal disease, and their incidence has been reported to be ∼50.1% among adults (1). Surgery is the most effective treatment, especially for severe prolapsing hemorrhoids (2, 3). Milligan-Morgan hemorrhoidectomy (MMH) is the gold standard for resecting hemorrhoids. Although it has been widely used in clinical practice, there might be disadvantages, such as slow healing of the wounds, a poor suspension effect after mucosal resection, residual hemorrhoids, and severe postoperative pain. A procedure for treating prolapse and hemorrhoids (PPH) was invented by Longo (4) to treat circumferential mixed hemorrhoid patients, and the aim of the Longo technique is to promote the reduction of the anal cushion by resecting the submucosal tissue of the lower rectum and anastomosing the broken end of the mucosa. However, negative effects of PPH have been reported, and the recurrence rate of prolapsed hemorrhoids is high (5, 6). Postoperative complications and adverse events have been reported, including acute urinary retention (7), chronic sustained pain (8), anastomotic stenosis (9), and anal incontinence (10).

The tissue selecting technique (TST) is a new minimally invasive technique for prolapsed hemorrhoids. It maintains a normal mucosa bridge while simultaneously reducing surgical trauma, and it has achieved desirable efficacy after PPH. However, its side effects have been reported in recent years, such as pendant expansion and anastomotic bleeding (11). On the other hand, single-window anoscopy, double-window anoscopy and triple-window anoscopy were found to be inaccurate for the resection of hemorrhoids with variable shapes and sizes, and the cost of the TST device is very high (470–627 dollars).

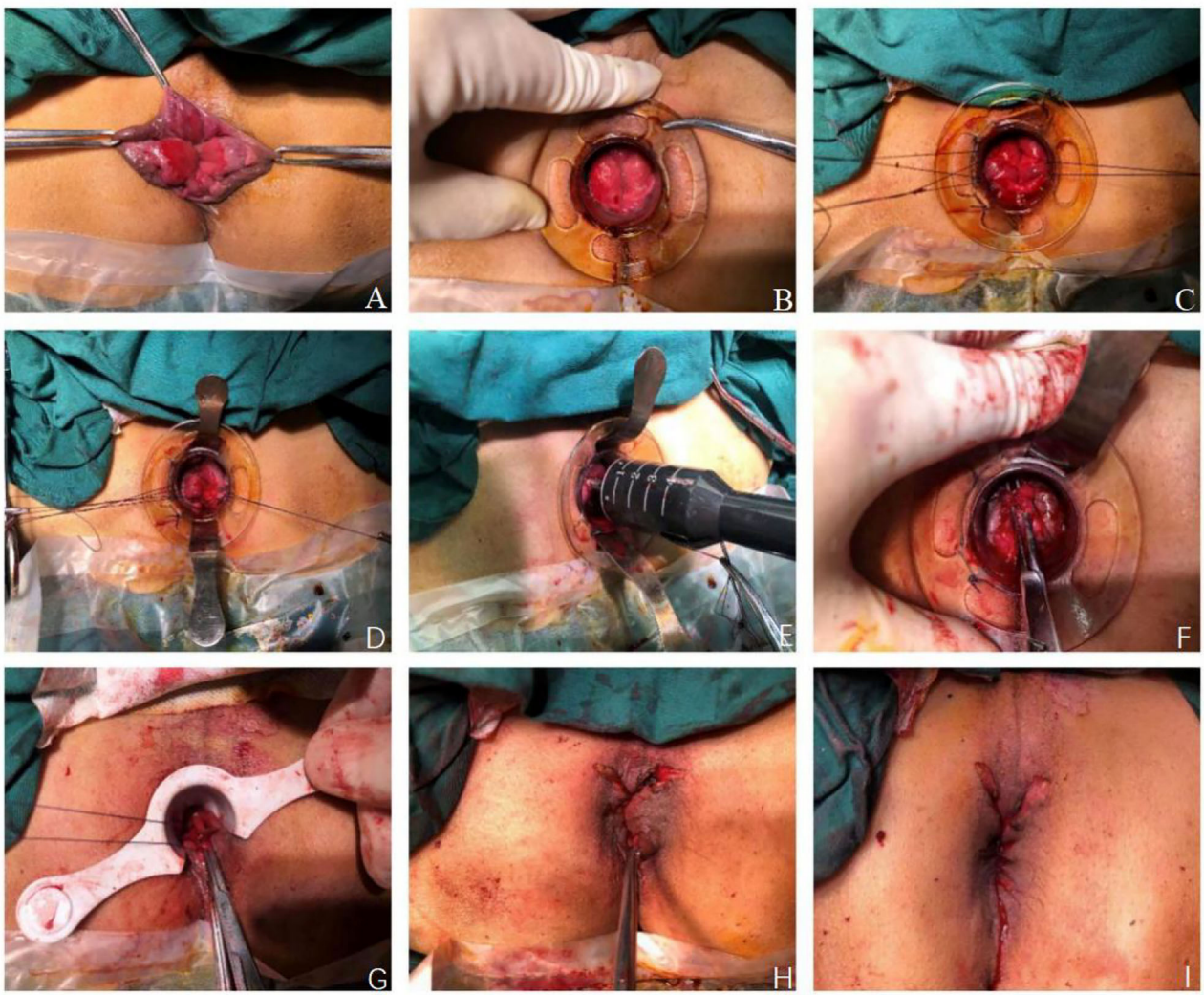

FIGURE 1 | Patients with prolapsing hemorrhoids treated with modified TST. **(A)** Exposing hemorrhoids with allis forceps. **(B)** An anoscope was inserted into the anus. **(C)** Purse string suture were made with 2-0 absorbable suture. **(D)** Two metal baffles were inserted. **(E)** Fired the stapler. **(F)** The bridges were separated. **(G)** The free ends of dissected mucosal bridges were ligated. **(H)** The external hemorrhoids were excised. **(I)** The perianal skin was repaired with absorbable sutures.

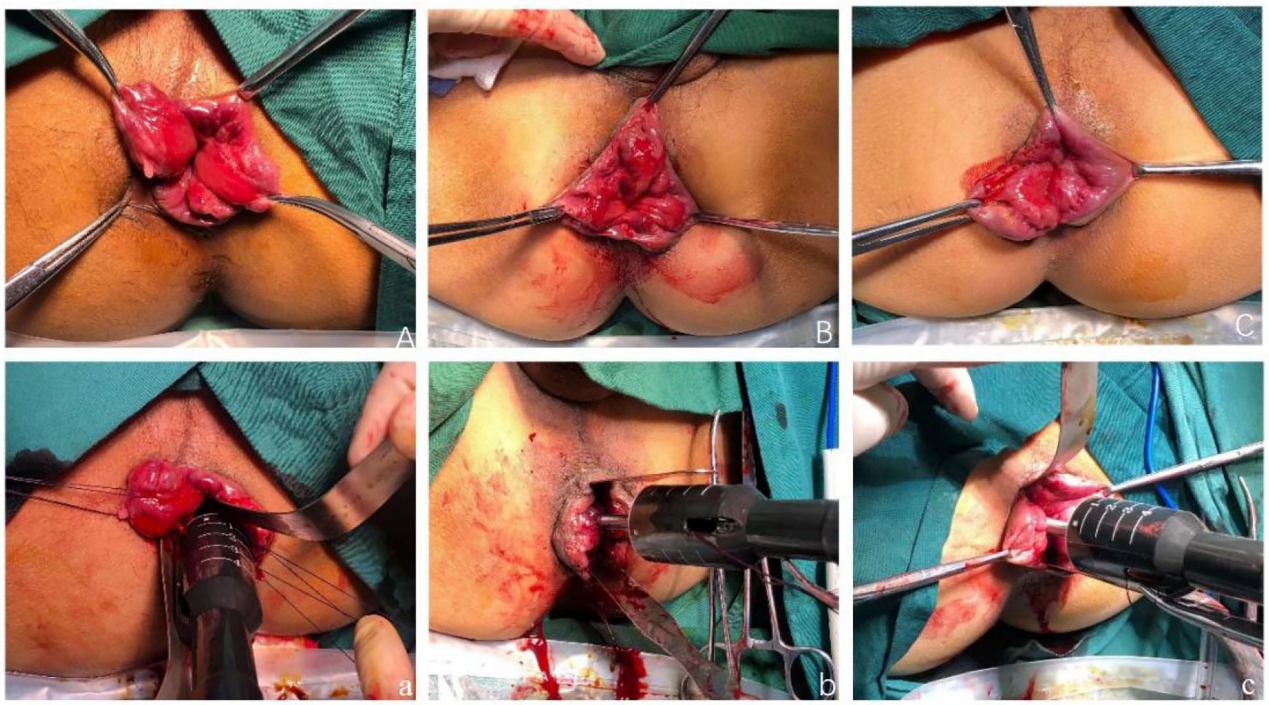

FIGURE 2 | (A) The left anterior and right posterior mucosal membranes were retained. The preoperative pictures of the patients in (a). **(B)** The anterior and posterior mucosal membranes were retained. The preoperative pictures of the patients in (b). **(C)** The right mucosa membrane was retained. The preoperative pictures of the patients in (c).

Thus, we developed a novel method based on the TST approach that we are calling modified TST to overcome the limitations of TST. The hemorrhoids were conformally and selectively removed according to their size and quantity, and the relatively normal anal pads were preserved to maintain the physiological function of the anus with the goal of minimizing the risk of anal stenosis and anal incontinence and reducing the impact of postoperative complications of the stapling technique. This clinical retrospective analysis was performed to observe and analyze the efficacy and complications associated with modified TST for prolapsing hemorrhoids.

MATERIALS AND METHODS

Participants

From January 2018 to January 2020, a total of 106 patients underwent modified TST at the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. The inclusion criteria were patients who were aged >18 y and < 75 y, had grade III–IV mixed prolapsing hemorrhoids according to the Goligher classification (12), had more than four consecutive o'clock sites of circumferential hemorrhoids, and planned to receive modified TST. The exclusion criteria were patients with severe primary diseases of the cardiovascular system, those who had other colorectal disorders and dysfunctions (e.g., tumor and inflammatory bowel disease), and those who had previously undergone surgery for mixed prolapsing hemorrhoids (traditional or stapled). The studies involving human participants were reviewed and approved by the Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. The participants provided written informed consent to participate in this study.

Data Collection

All data maintained in the computer database after the surgery were collected, retrospectively. The following parameters were recorded and analyzed: clinicopathological characteristics, including age, sex, body mass index (BMI), presenting symptoms, surgical duration, intraoperative blood loss, hospital stay, and hospital costs. Postoperative immediate complications, including the Numerical Rating Scale (13) and the additional use of analgesics, were collected. Postoperative digital anal and anoscopy examinations were conducted at our outpatient department every week until full recovery. Telephone follow-up was conducted every 3 months after surgery until 1 year. Patients were invited to the outpatient clinic for a final evaluation if any severe complications appeared during the follow-up period. Patient satisfaction and long-term complications (including anastomotic bleeding, persistent post stapler pain, anal stenosis, anal incontinence, anal discharge, anal tags, tenesmus, rectovaginal fistula and recurrence) were also recorded during the follow-up period.

Surgical Procedures

Modified TST was performed using the following steps: (1) The patient was placed in the lithotomy position after

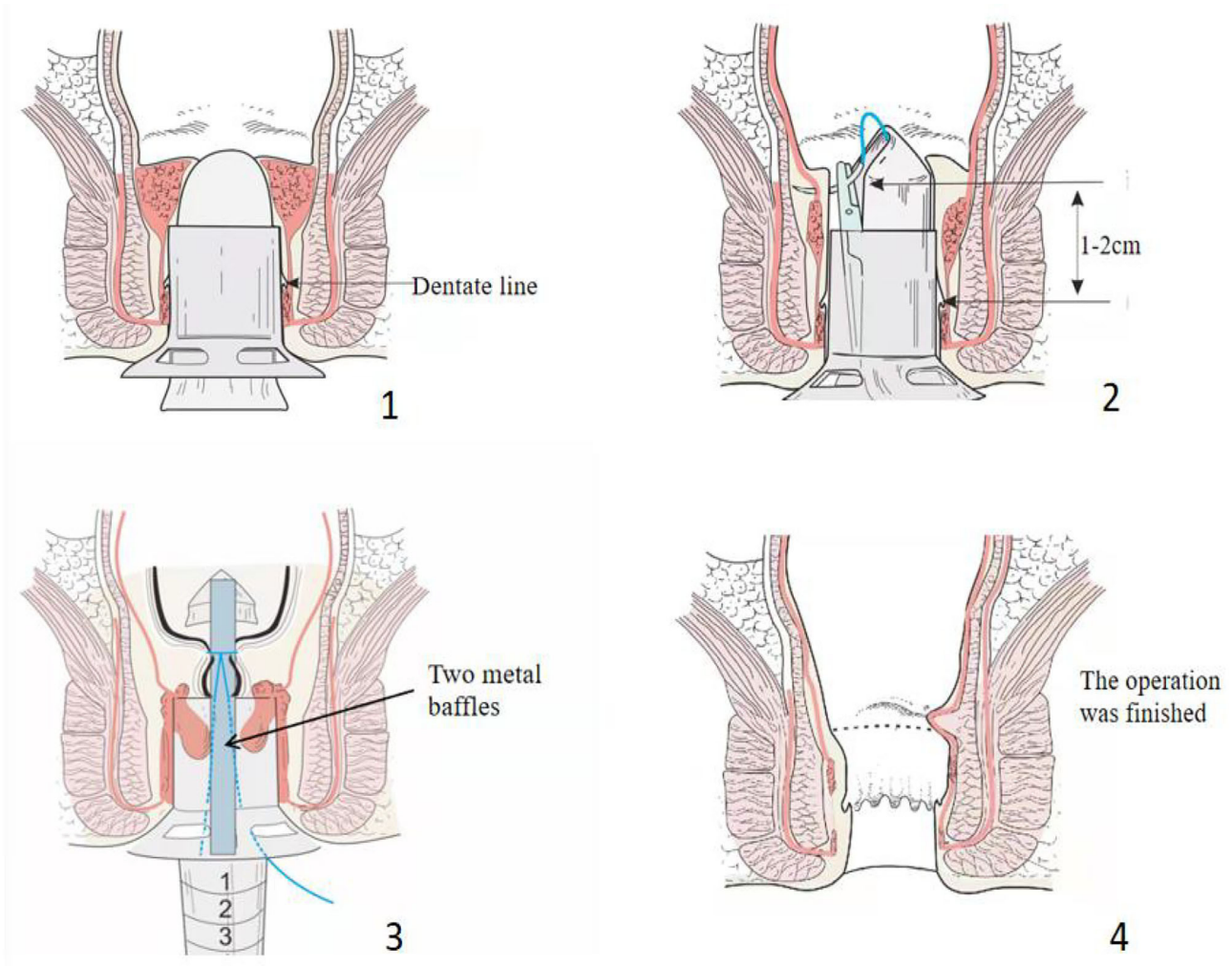

FIGURE 3 | The modified technique shown in drawings to allow for a correct reproduction of the technique.

general anesthesia, exposing the hemorrhoids with allis forceps, observing the distribution of the hemorrhoids and choosing the mucous membrane that needed to be maintained (**Figure 1A**). (2) An anoscope (YI LIAN) was inserted into the anus at a position where the upper half of the hemorrhoids was exposed (**Figure 1B**). (3) Purse string sutures were made on the mucosa and submucosa 1–2 cm from the dentate line. If the hemorrhoids were large, we performed double purse ring sutures (**Figure 1C**). (4) Two metal baffles were used to preserve the relatively normal mucosa in any direction. The anterior and posterior mucous membranes are shown in **Figure 1D**. The hemorrhoids were conformally and selectively removed according to the size and quantity of the hemorrhoids as shown in **Figure 2**. **Figures 2A–C** correspond to the preoperative pictures of the patients in **Figures 2a–c**, respectively. The left anterior and right posterior mucosal membranes are shown in **Figure 2a**. The anterior and posterior mucosal membranes are shown in **Figure 2b**. The right mucosa membrane shown in **Figure 2c** was retained. (5) The purse strings were tied to the stapler, and then the stapler was fired (**Figure 1E**). These bridges were separated, and the free ends of the dissected mucosal bridges were separately ligated (**Figures 1F,G**). (7) The external hemorrhoids were excised appropriately, and finally, the perianal skin was repaired with absorbable sutures (**Figures 1H,I**). We have provided drawings (**Figure 3**) and a video to help surgeons understand and achieve full reproduction of these procedures.

Postoperative Management and Follow-Up

Postoperative treatment consisted of standard nursing care and a semifluid diet. Patients experiencing postoperative pain within 1–3 days after the operation routinely received non-steroidal anti-inflammatory drugs (NSAIDs) twice a day as an analgesic. Patients were injected with additional opiates if necessary due to unbearable pain after routine analgesia.

Short-term postoperative complications were recorded during hospitalization: the frequency of additional injected postoperative analgesics were counted (0 indicating no

unbearable pain and 1 indicating unbearable pain), and the patients' postoperative pain was recorded at seven time points after the operation (Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, and Day 7), as assessed by the NRS score [0 indicating no pain and 10 indicating the worst pain (14, 15)].

A postoperative review was conducted at our outpatient department, and if the following symptoms appeared they were recorded: anastomotic bleeding (anastomotic hemorrhage found by anal examination, surgical intervention with 3#0 absorbable sutures were used for ligation and hemostasis); persistent post stapler pain as evaluated by NRS; anal stenosis [a condition in which the patients have difficulty in defecation and incomplete evacuation with a narrow stools caliber (16)]; anal incontinence [a lack of control over defecation, resulting in involuntary leakage of solid and/or liquid stool, with and without unintentional release of gas (17)]; anal discharge [perianal dampness or anal mucus secretion caused by the scar left by the surgery (18)]; anal tag [a perianal mass was pliable with an obvious foreign body sensation (11)]; tenesmus [the patient had a chief complaint of a sensation of rectal tenesmus (19)]; rectovaginal fistula [an opening allowing the passage of flatus and stool through the vagina (20)]; postoperative recurrence [continuous prolapse of perianal piles that recurred after hemorrhoidectomy (21)].

The efficacy was assessed 12 months after the operation, and the evaluation criteria (18) were defined as follows: marked effectiveness: the prolapse symptoms almost entirely disappeared; effectiveness: <50% prolapse symptoms remained compared with preoperative; ineffectiveness: >50% prolapse symptoms remained compared with preoperative. A patient satisfaction score (22) was obtained at 12 months by telephone follow-up. The scores ranged from 1 to 3, with 1 being satisfied with the outcome and 3 dissatisfied.

Statistical Analysis

The data were statistically analyzed. Normally distributed continuous variables are expressed as the means and standard deviation (SD), and non-normally distributed continuous variables are presented as the medians and interquartile range (IQR). Categorical variables are shown

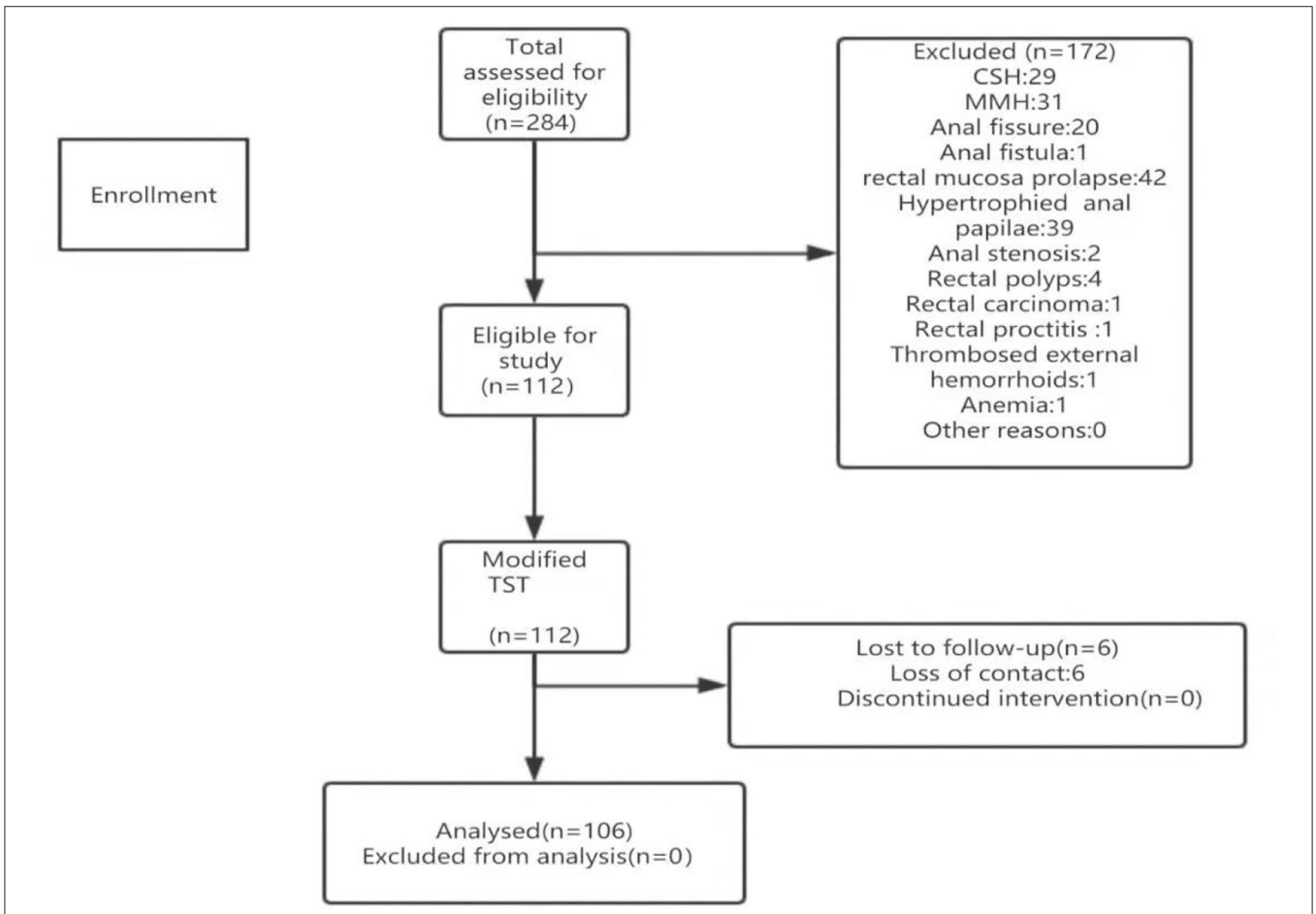

FIGURE 4 | Participant enrollment and follow-up. CSH, circumferential stapled hemorrhoidopexy; MMH, Milligan-Morgan hemorrhoidectomy; TST, Tissue selecting technique.

TABLE 1 | Patient demographics and clinical characteristics.

Factors	Total (n = 106)
Age, mean, (SD), y	49.24 (11.53)
Sex, *n* (%)	
Female	53 (50.00)
Male	53 (50.00)
BMI, mean, (SD), kg/m^2	23.46 (2.94)
Presenting symptoms, *n* (%)	
Hematochezia	4 (5.64)
Prolapse of hemorrhoids	12 (16.90)
Both of the above	83 (78.30)
Others	7 (9.86)
Intraoperative blood loss, median (IQR), ml	5 (7)
Operative time (SD), sec	55.01 (14.50)
Hospitalization stay, mean (SD), d	7.82 (2.38)
Hospitalization expenses, median (IQR), dollars	1938.95 (381.44)

BMI, Body mass index; SD, standard deviation; IQR, Interquartile range.

TABLE 2 | Efficacy assessment and patient satisfaction.

Results	Total (n = 106)
Efficacy assessment, *n* (%)	
Markedly effectiveness	92 (86.79)
Effectiveness	11 (10.38)
Ineffectiveness	3 (2.83)
Patients' satisfaction, *n* (%)	
Satisfied	97 (91.51)
Partially satisfied	6 (5.66)
Dissatisfied	3 (2.83)

The total effective rate = markedly effectiveness rate + effectiveness rate. The total satisfaction rate = satisfied rate + partially satisfied rate.

as numbers and percentages. All data were analyzed with SPSS statistical version 25.0.

RESULTS

Patient Characteristics and Clinical Data

A total of 112 eligible patients with grade III-IV prolapsing hemorrhoids were enrolled during the study period, with 106 undergoing modified TST (**Figure 4**). The follow-up period was 12 months. **Table 1** shows the analysis of the demographic characteristics and the clinical data of the patients. Their mean age was 49.24 y (range, 18–75 y), and there were 53 men and 53 women. Their mean body mass index (BMI) was 23.46 kg/m^2. The presenting symptoms of most patients were hematochezia and/or prolapse of hemorrhoids (99/106). The median operative time was 55.01 min (range, 25–95 min). The median intraoperative blood loss was 5 ml (range, 2–50 ml). The median hospitalization stay and hospitalization expenses were 7.82 d (range, 5–17 d) and 1938.95 dollars (range, 1415.93–3541.69 dollars), respectively.

Patient Satisfaction and Overall Efficacy

The majority of patients were satisfied with their surgery. Overall, 97.17% (103/106) of the patients reported being satisfied or partially satisfied by resolution of their troubling symptoms (score < 3) after the procedures. The total effective rate was achieved in 97.17% (103/106) of patients after modified TST. The total satisfaction rate and total effective rate of the patients are presented in **Table 2**.

Complications

Short-term postoperative complications, especially postoperative pain, were recorded by the NRS scores from the first day to the seventh day after the operation (**Figure 5**). The second day after the operation had the highest score, representing some patients experiencing intractable pain. The pain score was the lowest on the seventh day, indicating that the postoperative pain was relieved. Eight patients received an additional dose of analgesics (7.54%). Other complications were analyzed in detail (**Table 3**). The telephone follow-up and/or outpatient follow-up showed that no participants had anal incontinence, persistent post stapler pain, rectovaginal fistula (RVF) or anal stenosis. All complications were recorded, and the incidence of anal tags (4.72%) was the highest, followed by anastomotic bleeding (2.83%) (**Table 3**). Two of the 106 patients (1.89%) had symptomatic anal discharge and tenesmus. Two patients developed recurrent symptomatic hemorrhoids, leading to a yearly recurrence rate of hemorrhoids of 1.89% (2/106) (**Table 3**).

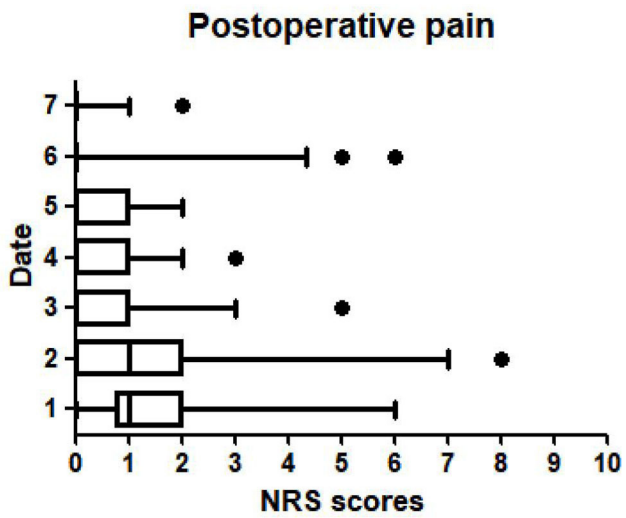

FIGURE 5 | Postoperative pain was recorded by the NRS scores from the first day to the seventh day after the operation.

DISCUSSION

The experience of clinical observation and medical research indicates that surgical resection combined with other therapeutic methods should be given priority for the treatment of grade III–IV mixed prolapsing hemorrhoids, although debate exists

as to which of the multitudinous surgical procedures is the most clinically effective (23). Pata et al. (24) described the two directions of surgical treatments for hemorrhoids in the first 20 years of the 2000s: modified traditional techniques and minimally invasive techniques. Based on the concept of minimally invasive surgery and reducing surgical trauma, this study introduced a modified procedure for the surgical management of hemorrhoidal disease. The surgeon innovatively used metal plates to readjust the surgical scope on the basis of the individual patient's clinical condition. The hemorrhoids were conformally selectively removed according to their size and quantity, and the relatively normal anal pads were preserved to maintain the physiological function of the anus.

The present study demonstrated that the modified TST technique achieved a superior effect compared to that of traditional TST in the management of prolapsing hemorrhoids. Lin et al. (21) reported that the 1-year recurrence rate of prolapsing hemorrhoids after traditional TST was 3.3%. It was speculated that this high recurrence rate might be associated with the patients not distinguishing between remnant prolapsed piles and anal tags from a recurrent prolapse (25). The patients therefore underwent a specialist examination to evaluate the actual cause of their recurrent symptoms. Ortiz et al. (26) also reported that the incidence of recurrent prolapsing hemorrhoids after PPH was as high as 25.9%. It was assumed that modified TST might decrease the recurrence rate. The recurrence rate of symptomatic hemorrhoids after MMH procedures were slightly higher (1.89% for modified TST vs. 2.6–2.7% for MMH) with a follow-up of 1 year, as shown in **Table 4**. The overall procedural complication rates of stapled hemorrhoidectomy ranged from 2 to 68% (29). We therefore believe that modified TST, compared with traditional TST, PPH, and MMH, conformally selectively excises the hemorrhoidal-bearing area, leading to a possible reduction in the recurrence rate. However, a few authors (34) have reported that stapled hemorrhoidopexy during the surgical procedures excluded a direct correlation with an increased rate of complications. The limitations of our study included the fact that it had a small sample size, lacked a control group, and was a retrospective study with a discrete sample number. Further investigation with a larger sample size, long-term postoperative follow-up and multicenter prospective studies is necessary to clarify this point.

It has been shown that surgical techniques and postoperative analgesics are associated with acute and chronic pain (35). This study found that the NRS scores of postoperative pain were low, and they were strongly correlated with the use of postoperative analgesics. This study routinely used non-steroidal anti-inflammatory drugs (NSAIDs) for analgesia twice a day to alleviate acute pain after the operation. The modified TST places the staple line 1 cm from the dentate line where there are fewer sensory nerves and far from the sensitive epithelium of the anal canal, which helped to relieve pain and prevent edema. The causes of postoperative pain in patients after stapled techniques have been reported to be a purse string suture placed deep and close to the levators, resulting in low-grade inflammation along with continuous stimulation, especially during the first postoperative defecation (30). A consensus statement (29) summarized the importance of comprehensive knowledge of the local anatomy and a proper choice of surgical techniques.

Residual anal tags were found after PPH in 1.8–80% of patients as reported in the literature, for which the incidence of

TABLE 3 | Complications, *n*.

Complications	Total ($n = 106$)
Short-term complications	
The frequency of additional injected postoperative analgesics, *n* (%)	8 (7.54)
Postoperative pain, median (IQR)	1 (1)
Long -term complications, *n* (%)	
Anastomotic bleeding	3 (2.83%)
Persistent post stapler pain	0
Anal stenosis	0
Anal incontinence	0
Anal discharge	2 (1.89%)
Anal tag	5 (4.72%)
Tenesmus	2 (1.89%)
Rectovaginal fistula	0
The 1-year recurrence rate	2 (1.89%)

SD, standard deviation; IQR, Interquartile range.

TABLE 4 | The incidence of postoperative complications of different surgical procedures.

Complications	Modified TST	TST	PPH	MMH
Anastomotic bleeding	2.85%	2.5% (22)	1–11% (7, 19)	1–2.6% (27, 28)
Persistent post stapler pain	0	0.9% (18)	1.4–8% (7, 19)	0–5.4% (18, 19)
Anal stenosis	0	0(9, 22)	0.2–7.5% (7, 9, 27, 29, 30)	2.6% (27)
Anal incontinence	0	1.4% (18)	3.2–31% (7, 19, 31)	7.2% (18)
Anal discharge	1.89%	1.4% (18)	38% (31)	10.4% (18)
Anal tag	4.72%	8.6% (11)	1.8–80% (27, 30, 32, 33)	3.7–21% (27, 33)
Tenesmus	1.89%	NR	14% (19)	8% (19)
Rectovaginal fistula	0	0(18, 21, 22)	0.2% (19)	0(18, 21)
The 1-year recurrence rate	1.89%	3.3% (21)	4.6–25.9% (7, 19, 26, 27, 32)	2.6–2.7% (21, 27)

NR, not reported; PPH, procedure for prolapse and hemorrhoids; MMH, Milligan-Morgan hemorrhoidectomy; TST, tissue selecting technique.

residual anal tags was the highest among the various procedures (4.72% for modified TST vs. 8.6% for traditional TST vs. 3.7–21% for MMH) (30, 32, 36). The modified TST preferentially removes the remaining circumferential external hemorrhoids and asymptomatic skin tags, which are considered to be sources of anal discomfort and itching. The present study showed that there was no significant difference in persistent post stapler pain between the modified TST and the other surgical procedures. This may be associated with retaining an appropriate mucosal bridge and full drainage to reduce postoperative anal edema.

The current study showed that anal incontinence was not encountered in any patients treated with modified TST, while the incidence of postoperative anal incontinence after MMH may be as high as 7.2% (18). It was speculated that modified TST retained the non-pathologic anal cushions without affecting anal function and maintained the continence function of the rectum and the anus, thereby avoiding fecal incontinence and urgency to a large extent (30). Sturiale et al. (10) found that stapled hemorrhoidopexy was associated with a high incontinence rate. This was found to be related to the unsuitable low position of the staples or possibly the excessive inflammatory response around the staple line after the operation. Mascagni et al. (37) suggested that defecatory urgency or gas/fecal incontinence may be caused by excessive resection. Therefore, maximal preservation of the normal mucosa and the anal sphincter is able to alleviate anal continence and urgency and increase defecation control (38, 39).

The incidence of anal stenosis after PPH and MMH reported in the literature is 0.2–7.5 and 2.6%, respectively (27, 29). The patients in the PPH group had higher rates of anastomotic stricture cases (40) and a higher incidence of fibrotic stenosis than the MMH group (41). In the present study, none of the patients developed postoperative anal stenosis after a modified TST procedure. This is associated with conformal selective resections of the rectal mucosa to preserve the mucosal bridges and the normal non-hemorrhoidal-bearing area. Injury of the underlying anal sphincter muscle may also lead to functional alterations (21, 29). Normal rectal compliance was maintained to reduce the risk of anal stenosis, leading to improved anal functional outcomes.

Although the differences in the incidences of anastomotic bleeding, anal discharge and rectovaginal fistula were not significant, modified TST had a lower recurrence rate and lower complication rate than TST (21). It was speculated that modified TST is a precise, conformal selective resection, not a full or partial circumference excision. The tissue between the mucosectomies and the protected tissue adjacent to the rectovaginal septum in women was untouched, leading to minimization of the risk for the development of anal stenosis and RVF formation (38).

It has been shown that modified TST solves the dilemma of choosing only single open, double open or triple open anoscopy in TST operations. In addition, it resects the abnormal tissues more accurately and retains more of the normal mucosa. The surgical process is brief, safe, and inexpensive, with fewer complications and a higher quality of life for the patients. We examined the database to analyze the operation cost of TST, and it was 469.2–625.6 dollars, while modified TST was only 156.4–234.6 dollars. Yang et al. (42) estimated that the overall expenditure on hemorrhoids in the US employer-insured population was $770 million annually. However, Chinese patients generally stay in the hospital longer and are discharged from the hospital with less pain, unobstructed stool and better recovery. The modified TST procedure reduced the financial stress on the patients during their longer hospital stay.

CONCLUSIONS

In summary, modified TST can be used to precisely resect prolapsing hemorrhoids and effectively preserve anal sphincter function and the normal perianal mucosa in patients. The technique is associated with fewer complications and lower recurrence rates. Modified TST is therefore considered a satisfactory and economical surgical procedure for prolapsing hemorrhoids.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CY performed the majority of the data analysis and wrote the article. CZho provided advice on the design and performance of the study. RX performed the follow-up and the initial data analysis. XJ performed ethical supervision and administrative support. CJ performed the majority of the clinical therapy. CZhe provided study materials or patients and is responsible for the article's reliability. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.838742/full#supplementary-material

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Which Role for Hyperbaric Oxygen Therapy in the Treatment of Fournier's Gangrene? A Retrospective Study

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Purpose: In Fournier's gangrene, surgical debridement plus antimicrobial therapy is the mainstay of treatment but can cause a great loss of tissue. The disease needs long hospital stays and, despite all, has a high mortality rate. The aim of our study is to investigate if factors, such as hyperbaric therapy, can offer an improvement in prognosis.

Methods: We retrospectively evaluated data on 23 consecutive patients admitted for Fournier's gangrene at the University Hospital "P. Giaccone" of Palermo from 2011 to 2018. Factors related to length of hospital stay and mortality were examined.

Results: Mortality occurred in three patients (13.1%) and was correlated with the delay between admission and surgical operation [1.7 days (C.I. 0.9–3.5) in patients who survived vs. 6.8 days (C.I. 3.5–13.4) in patients who died ($p = 0.001$)]. Hospital stay was longer in patients treated with hyperbaric oxygen therapy [mean 11 (C.I. 0.50–21.89) vs. mean 25 (C.I. 18.02–31.97); $p = 0.02$] without an improvement in survival ($p = 1.00$).

Conclusion: Our study proves that a delay in the treatment of patients with Fournier's gangrene has a correlation with the mortality rate, while the use of hyperbaric oxygen therapy seems to not improve the survival rate, increasing the hospital stay instead.

Keywords: Fournier's gangrene, hyperbaric therapy, fasciitis, perineum, necrosis

INTRODUCTION

Fournier's gangrene (FG) comprises all necrotizing fasciitis of the perineum, regardless of the etiology, with or without proven infection. It has an incidence rate of ∼1.6 per 100,000 males in western regions (1). The etiopathogenesis is debated between a primary ischemic process and infection because it is unclear if the disease represents an ischemic process complicated by infection from commensals or an infection finally causing the thrombosis of small subcutaneous vessels (2).

The related mortality ranges from 3 to 45%, with an overall rate of 16% proposed by a recent review (3). Deaths are due to severe sepsis, coagulopathy, acute renal failure, diabetic ketoacidosis and multiple organ failure.

The Fournier's gangrene severity index score (FGSIS) (**Table 1**) and the simplified FGSI score (SFGSI score) (**Table 2**), which includes only creatinine, hematocrit, and potassium are useful to stratify the disease (4, 5). In the low-risk group, according to the SFGSI, 1.3% of mortality has been reported, in contrast with 41% in the high-risk one (6).

Surgical debridement with broad spectrum antimicrobial therapy is the main treatment of FG (7). This broad- spectrum therapy is suggested regardless of the Gram stain and culture results, of course it can be reassessed when results are obtained (2).

In FG, the infection and edema reduce local blood circulation and tissue oxygenation, which increase the progression of necrosis, impair host defenses, and permit invasion of microorganisms. Tissue hypoxia is determined by two main factors: the reduction of blood flow in the amicted tissues and the concomitant proliferation of aerobic bacteria. Thus, this decrease in local oxygen concentration facilitates the seeding and spread of anaerobic bacteria, while causing thrombosis and tissue ischemia (8). Adequate debridement can cause a great loss of tissue, whose healing process can take a longer time, which is confirmed by the long hospital stays.

In this scenario, hyperbaric oxygen therapy (HBOT) could potentially be a therapeutic option to speed wound healing as it increases tissue oxygen tension to a level that inhibits and kills anaerobic bacteria, reduces systemic toxicity, limits the necrotizing fasciitis and enhances the demarcation of gangrene (9).

To investigate the role of HBOT in the treatment of FG, we retrospectively evaluated the patients admitted at the O.U. of General Surgery and Emergency of the University Hospital "P. Giaccone" of Palermo from January 2011 to November 2018.

Abbreviations: FG, Fournier's gangrene; FGSI, Fournier's gangrene severity index score; SFGSI score, Simplified Fournier's gangrene severity index score; HBOT, hyperbaric oxygen therapy; BMI, body mass index; ASA, American Society of Anesthesiologists score; HS, Hospital stay.

MATERIALS AND METHODS

Data on 23 consecutive patients admitted at the Urgent and General Surgery O.U. of the University Hospital "P. Giaccone" of Palermo who underwent surgical operations for FG were retrospectively collected. The patients were identified on admission by the diagnostic code of the ICD-9: 608.83. For each patient, we collected demographic data, admission characteristics, and management and treatment results from the charts of patients. Demographic data collected included age, sex, body mass index (BMI), comorbidities, American Society of Anesthesiologists (ASA) score, and delay from symptoms to admission.

Admission characteristics included laboratory values, radiological findings, and microbiological stains. The SFGSI score was calculated for each patient. Data on perioperative management included time until first operation, number and type of operative procedures, need for colostomy, type of anesthesia, type of antibiotic therapy and HBOT. As outcomes, we ultimately recorded length of hospital stay (HS) and 30-day mortality.

TABLE 1 | Fournier's Gangrene Severity Index (FGSI): >9 LRINEC = 75% probability of death; < 9 LRINEC = 78% probability of survival.

Variables	High abnormal values				Normal	Low abnormal values			
Points	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (C)	>41	39–40.9	–	38.5–35.9	36–38.4	34–35.9	32–33.9	30–31.9	<29.9
Heart rate	>180	140–179	110–139	–	70–109	–	56–69	40–54	<39
Respiration rate	>50	35–49	–	25–34	12–24	10–11	6–9	–	<5
Serum Na+ (mmol/l)	>180	160–179	155–159	150–154	130–149	–	120–129	111–119	<110
Serum K+ (mmol/l)	>7	6–6.9	–	5.5–5.9	3.5–5.4	3–3.4	2.5–2.9	–	<2.5
Serum Creatinine (mg/100 ml)(×2 for acute renal failure)	>3.5	2–3.4	1.5–1.9	-	0.6–1.4	–	<0.6	–	–
Hematocrit (%)	>60	-	50–59	46–49.4	30–45.9	–	20–29.9	-	<20
White blood count (total/mm^3 x 1,000)	>40	–	20–39	15–19.9	3–14.9	–	1–2.9	–	<1
Serum bicarbonate (venous, mmol/l)	>52	41–51.9	–	32–40.9	22–31.9	–	18–21.9	15–17.9	<15

TABLE 2 | Simplified Fournier's gangrene severity index (SFGSI): >2 = High risk patients; ≤2 = Low risk patients.

Variables	High abnormal values				Normal	Low abnormal values			
Points	+4	+3	+2	+1	0	+1	+2	+3	+4
Serum K+	>7	6–6.9	–	5.5–5.9	3.5–5.4	3–3.4	2.5–2.9	–	<2.5
Serum creatinine(x2 for acute renal failure)	>3.5	2–3.4	1.5–1.9	–	0.6–1.4	–	<0.6	–	–
% Hematocrit	>60	–	50–59	46–49.4	30–45.9	–	20–29.9	–	<20

Low risk patients: 1.3% of mortality. High-risk patients: 41.0% of mortality [LIN 2].

TABLE 3 | Patients' comorbidities.

Patients' comorbidities	
Tobacco consumption	50%
Alcohol abuse	15%
Diabetes	55%
COPD	13.1%
Cardiovascular diseases	34.8%
Inflammatory bowel disease	13.1%
Arthritis	8.7%
Cronic renal failure	13.1%
Cronic liver disease	8.7%
Cancer on chemotherapy	13%

Statistical Analysis

We conducted this statistical analysis to examine the potential relationship between the use of HBOT, length of hospital stay and mortality.

Descriptive data are presented as parametric and non-parametric data.

The relation between the simplified FGSI score and the use of HBOT, the need for a diverting stoma (colostomy) and the length of hospital stay were evaluated using the Chi-square test or the independent-sample *t*-test when appropriate.

Possible factors influencing mortality and specifically sex, age, BMI, comorbidities, ASA score, duration of symptoms, simplified FGSI score, use of HBOT, need for colostomy and need for several operations were investigated using the independent-sample *t*-test, Welch test or Fisher's exact test.

Statistical analysis was conducted using MedCalc statistical software (MedCalc Software, Ostend, Belgium).

RESULTS

A total of 23 patients (16 M and seven F with mean age 62.7 years, sd 13.1, C.I. 37–84) were admitted between 2011 and 2018 for FG and underwent surgery.

The comorbidities of patients are showed in **Table 3**. The average BMI was 29.4 kg/m^2 (sd. 6.5, C.I. 20.5–47.75).

The average duration of symptoms before admission was 11 days (sd 7.9, C.I. 3–30).

First location of symptoms was gluteal in five patients (21.7%), inguinal in four patients (17.4%), perineal in eight patients (34.8%) and scrotal in six patients (26.1%). The average white blood cell count at admission was 21,000 (sd 10,300), and average neutrophil count was 80.1% (sd. 17.9). C-reactive protein was > 1.25 mg/dl in 47% of patients. Fever was present in only three patients (18.8%) and bulging in seven patients (43.8%).

The diagnosis was supported by an ultrasound examination in eight patients (34.8%), and almost all patients received a CT evaluation. Air bubbles were found on CT in 69.5% of patients, fluid collections in 52.2% of patients, and soft tissue edema in 43.5% of patients.

The average delay between admission and surgery was 4 days (sd 4.4, C.I. 0.1–17); < 24 h in 30% of patients, 24–48 h in 22% of patients, 48–72 h in one patient and more than 72 h in 43.5% of patients.

The ASA score was I [0 patients], II (2), III (5), IV (8), V (1); six of the patients were managed only with local anesthesia.

Empiric broad-spectrum antibiotic therapy [penicillins (for gram positive), clindamycin or metronidazole (for anaerobes) and cephalosporine with aminoglycosides or fluoroquinolones (for gram negative) or, as alternative, monotherapy with carbapenems or piperacilline-tazobactam] was always administered and successively modified accordingly to the results of the samples (**Table 4**). The average length of antibiotic therapy was 22 days (sd 11, C.I. 10–60).

A colostomy was performed in four patients (17.4%). A total of 10 patients (43.5%) needed more than one surgical procedure. HBOT was offered to 13 patients (56.5%) using a scheduled session of 60 min daily.

An adverse event represented by dyspnea, sweating and agitation was reported during HBOT.

The average length of hospital stay was 26 days (sd. 17.9, C.I. 3–72). Mortality occurred in three patients (13.1%), two being treated with HBOT.

The length of hospital stay was influenced neither by the need for colostomy ($p = 0.21$) nor by SFGSI score > 2 ($p = 0.68$).

The use of HBOT did not improve the need for colostomy ($p = 0.50$) or several operations ($p = 1.00$).

HBOT use was not related to patients' severity of disease according to FSGI score ($p = 1.00$).

Hospital stay was longer in patients treated with HBOT [mean 11 (CI 0.50–21.89) vs. mean 25 (CI 18.02–31.97); $p = 0.024$].

Investigating factors related to mortality, the lapse between admission and surgical operation was the only statistically related to mortality, being 1.7 days (C.I. 0.9–3.5) in patients who survived vs. 6.8 days (C.I. 3.5–13.4) in patients who died ($p = 0.001$); other factors investigated, such as sex ($p = 0.20$), BMI ($p = 0.53$), renal failure ($p = 1.00$), diabetes ($p = 0.49$), age > 65 years old ($p = 0.55$), SFGSI score > 2 ($p = 0.05$), higher ASA score (≥ 4) ($p = 0.47$), symptoms lasting since more than 72 h before admission ($p = 0.28$), HBOT ($p = 1.00$), need for colostomy ($p = 0.06$), several operations ($p = 1.00$), and several operations plus HBOT ($p = 1.00$) did not show a relation.

DISCUSSION

There are different opinions and studies on the use of HBOT in this type of patient (**Table 5**) (7, 10–21). In a series of 11 patients, Pizzorno et al. attributed a 0% mortality rate to the adoption of HBOT (9).

Accordingly, none of the patients who underwent HBOT died in the series proposed by Ayan et al. (18). Another positive outcome came from a study done by Mehl et al., where patients with FG who were given HBOT with routine surgical treatment had a mortality rate of 11.5%, whereas the mortality rate was 35.7% for those who underwent only conventional surgical treatment. Thus, the study concluded that patients who were treated with HBOT had a lower mortality rate compared to conventional therapy alone (21).

TABLE 4 | Patient data.

	Sex	Age	Site	Signs	Lin-score	ASA	Anesthesia	Colostomy	Antibiotics	Bacterial isolation	HBOT	LOS	Death
1	M	68	Thigh root	fever and bulging	6	5	General	0	Daptomicina, metronidazol, Levofloxacin, meropenem	*Escherichia coli*	Not fit for	21	0
2	M	49	Perineum	Pain	11	3	Sedation	0	Clindamicin, imipenem cilastatin, daptomicin, vancomicin, meropenem, metronidazol	1	15	0	
3	F	61	Groin	Bulging and pain	10	4	General	0			0	44	0
4	M	72	Perineum	Fever	8	4	General	1	Metronidazol, daptomicin, meropenem		1	28	0
5	F	57	Thigh root	Fever	7	4	General	0	Clindamicin, pip-tazo, daptomicin	*Enterococcus fecalis*	1	20	1
6	F	69	Perineum	Pain and bulging	9	4	Sedation	0	Ceftazidim, metronidazol		1	47	0
7	F	76	Buttock	Fistulizing and bulging	12	4	General	1	Daptomicin, pip-tazo, metronidazol	*Stafilococco aureus, E. fecalis, E. coli*	1	21	1
8	M	84	Scrotum	Bulging	7	4	Sedation	0			1	37	0
9	M	72	Scrotum			-	Local	0			0	16	0
10	M	37	Scrotum/penis		10	-	Local	0			0	67	0
11	M	57	Scrotum	Pain and bulging	2	-	Local	0	Levofloxacin		0	7	0
12	F	55	Thigh root	Pain and bulging	9	4E	Sedation	0	Clindamicin, pip-tazo, Anidulafungin, linezolid	0	14	0	
13	M	57	Perineum		4	3	General	1			1	21	0
14	F	81	Buttock	Fistulizing	6	3	General	0	Teicoplanin, metronidazolo, Colimicin	*S. aureus*	1	31	0
15	M	64	Groin	Edema and erythema	1	2	General	0	Amoxicillin-clavulanat		1	13	0
16	M	42	Perineum			2	General	0			0	72	0
17	M	81	Perineum	Pain and edema	4	3	General	0	Clindamicin, ceftazidim, imipenem, vancomicin	*E. coli*, *Candida albicans*	1	27	0
18	M	71	Scrotum			-	Local	1			0	38	1
19	M	59	Perineum	Pain and bulging	4	-	Local	0	Cefixim, metronidazol		0	3	0
20	F	56	Buttock	Bulging	2	-	Local	0	Cefixim		0	5	0
21	M	73	Scrotum			4	General	0			0	15	0
22	M	63	Buttock	Pain	2	3	General	0	Linezolid, cefotaxim, clindamicin, ampicillin+sulbactam	*Streptococcus anginosus*	1	15	0
23	M	39	Perineum	Pain and bulging	6	2	Sedation	0	Clindamicin, daptomicin, tigeciclin, meropenem	*E. coli, Streptococccus sanguinis, Enterococcus fecalis*	0	20	0

Demogrhapics: sex, age, signs, Lin's score, ASA. Intervention: type of anesthesia, need for colostomy. Admistered antibiotics. Bacterial isolation. Post-surgical HBOT administration. Length of hospital stay. Mortality.

Interestingly, Hollanbaugh et al. observed that the use of HBOT was statistically significant in 26 cases of FG, where mortality rate was 7%, and the index increased five times in patients who did not receive HBOT (19).

In contrast, recently, Rosa and Guerreiro reported a mortality rate of 20.8% in a series of 34 patients treated with HBOT (22).

In a larger retrospective study, Mindrup et al. found no difference in length of hospital stay or mortality in relation to HBOT, and the authors cautioned against the routine use of HBOT based on the cost associated with the therapy, $600–$1,300 per treatment at their center (10).

TABLE 5 | Literature reports on the use of HBOT in Fournier's gangrene.

References	N. of patients	Days of hospital stay		Mortality		
		HBOT	Without HBOT	HBOT	Without HBOT	Total
Pizzorno et al. (9)	11	NR	–	0	–	0
Korhonen et al. (7)	33	36	–	9.1%	–	9%
Mindrup et al. (10)	42	21	25	26.9% (7/26)	12.5% (2/16)	21.4%
Wagner et al. (11)	41	23	–	0	–	0
Janane et al. (12)	70	6	–	11.4%	–	11.4%
Martinschek et al. (13)	8	NR	–	12.5%	–	12.5%
Li et al. (14)	28	31	31	12.5% (2/16)	33.3% (4/12)	21.43%
Hung et al. (15)	60			0	66.7% (32/48)	32/60
Milanese et al. (16)	6	NR	–	0	–	0
Ferretti et al. (17)	20	22	34	0 (0/4)	18.75% (3/16)	15%
Ayan et al. (18)	41			0 (0/18)	39% (9/23)	
Hollabaugh et al. (19)				7%	42%	
Baraket et al. (20)	20	NR	NR	0 (0/4)	25% (4/16)	20%
Our study	23	25	11	15.4% (2/13)	10% (1/10)	13%

Shupak et al. pointed out through their study that HBOT, when used as a complementary treatment for necrotizing fasciitis, does not offer the advantage of decreasing morbidity and mortality. The outcome in their study among patients treated with HBTO showed a mortality rate of 36% for the treated group, while the untreated group had a mortality rate of 25%; the average number of episodes of surgical debridement per patient was also lower in the untreated group when compared to that in the treated group (23).

Similar outcomes were reported by Tharakaram and Keckes who also observed a lower number of episodes of surgical debridement in the untreated group. On the contrary, in their study, the mortality rate was lower in the group treated with HBOT vs. the group not treated with HBOT [12.5% (2/16) and 33.3% (4/12), respectively] (24).

In a study proposed by Stanley, analyzing 636 patients, the mortality rate of patients was reported to be 10.1% and was related to older age, higher BMI and lower WBC and platelet counts in a multivariate analysis. No data on the use of HBOT were reported in their analysis (25).

Differing from the high mortality rate found by a recent study by Rosa and Guerreiro (22), as well as from the no difference in length of hospital stay with the use of HBOT stated by Mindrup et al. (10), our study showed an increase in length of hospital stay in patients treated with HBOT [mean 11 (CI 0.50–21.89) vs. mean 25 (CI 18.02–31.97); $p = 0.02$] and no advantages in terms of mortality as assessed in 15.4% of patients in the HBOT group and 10% of patients in the non-HBOT group ($p > 0.05$).

In our study, the factor that adversely affected the prognosis was a delay more than 72 h between the emergency admission and the surgical debridement. The causes of delay can be due to missed diagnoses, theater availability, surgeons availability or initial conservative treatment with antibiotics only.

The progression of the disease is described by Horta as a four-step process with a first phase of 24–48 h of non-specific symptoms associated with local hardening, edema and erythema; a second phase that is considered invasive and presents with local and regional inflammatory manifestations; a third necrotic phase with a rapid worsening of the general state evolving into septic shock in 50% of the cases; and a fourth phase of healing or spontaneous restoration (26). The rapidity of progression of the gangrenous area is considered to be 2–3 cm/h (27).

Our data are in accordance with the ones reported by Lin et al. who suggest that early surgical interventions allow to maximize the survival benefit. Although the Authors recommend even shorter interval of times since they found that in high-risk patients (SFGSI score >2) mortality rate was 26.32% within 12 h, 40% between 12 and 24 h and 69.23% >24 h; early surgical interventions performed within 14.35 h from hospital arrival allowing to maximize the survival benefit (6).

So, when approaching patients, we have to remember that tenderness, erythema and swelling can mimic less severe infections, such as cellulitis and erysipelas; however, pain out of proportion to clinical examination should alert the clinician to the strong possibility of necrotizing fasciitis (28).

Our results are supported from the data reported by Yeniyol et al. in a study on 25 patients, where the authors report that mortality was related to both the FGSI and the difference in the duration of symptoms before admission, being 1.9 +/– 0.7 days in patients who survived and 4.1 +/– 1.4 days in patients who died (29).

Altarac reported that the median duration of symptoms before admission was a day longer in patients who not survived (4 days compared to 3 days), but this was not statistically associated with higher mortality ($p = 0.11$) (30).

Similar data have been reported by Basoglu et al.; in their study, the duration of the symptoms prior to gangrene in the survivors was 6.2 days (range 2–20 days) in comparison to 7.5 days (range 5–10 days) for the non-survivors ($p > 0.05$) (31).

Ersay et al. state that the median duration of symptoms at presentation was 7.00 days in survivors, but it was 8 days in non-survivors. The time from the onset of symptoms to presentation was not significantly different in survivors and non-survivors ($p > 0.05$) (32).

However, with the delay between symptoms and admission not being carefully predictable, our study focused the problem of prompt surgical treatment when patients are admitted. Thus, in our series, mortality was related to the delay of in-hospital treatment rather than on the delay between symptoms and admission. Of course, both delays are important for the cure rate, but only one of them being related in our series.

These data should underline the concept of the urgent situation when approaching a case of suspected FG and should encourage aggressive treatment each time the suspicion arises in a patient urgently admitted to the surgical department.

The current study has several limitations. It was retrospective and the number of patients was quite small, but this can be explained by the rarity of the disease. The gravity of the disease was evaluated with the SFGSI score instead of the FGSI because not all the data to calculate this score were present.

CONCLUSIONS

In our study, patients treated with HBOT showed an increase in length of hospital stay, and HBOT did not offer an improvement in mortality when added to surgical debridement plus antibiotic therapy.

As previously suggested, the incoming necrosis has to be promptly stopped when the suspicion of FG first arises, because the delay in treatment seems to be the most important factor causing an increase in mortality and the only factor in our study that worsened the prognosis of patients.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RT and FC have given substantial contributions to the conception or the design of the manuscript. GR, GSc, GSa, and GM have given substantial contributions to the acquisition, analysis and interpretation of the data. RT, FC, and GR have participated to drafting the manuscript. GG, SB, MS, MM, and GC revised it critically. All authors read and approved the final version of the manuscript.

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OPINION
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Defunctioning Ileostomy to Prevent the Anastomotic Leakage in Colorectal Surgery. The State of the Art of the Different Available Types

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INTRODUCTION

Defunctioning ileostomy (DI) is a surgical procedure adopted for fecal diversion in colorectal surgery to prevent the most important complication, i.e., anastomotic leakage (AL). It could be defined as a defect in the intestinal wall integrity at the suture site leading to a communication between the inside and outside compartments such as pelvic abscess close to the anastomosis and recto-vaginal fistula (1). Most surgeons suggest the use of fecal diversion in patients undergoing low anterior resections of rectal tumors followed by ultra-low colorectal or coloanal anastomoses at high risk for anastomotic failure. Although a stoma does not always prevent AL, it may reduce the incidence of sepsis in the event of leakage and decreases the rate of emergency reoperation (2–4). Fecal diversions have been associated with poor quality of life, stoma-related complications from 3 to 33%, and perioperative risk of stoma closure later on or a reversal of stoma not happening because of patients at high risk of complications (5). In the past decade, most techniques have been described as variants of the conventional loop ileostomy or as novel technical notes, changing the site of stoma or using tubes to perform it. With the advent of minimally invasive surgery, new techniques have been developed in an attempt to maintain the concept of less invasiveness for the patients. The aim of our paper is to give a snapshot of the current literature on the available types of DI to prevent AL in colorectal surgery, searching by three different electronic databases, namely Pubmed/Medline, Web of Science (WOS), and EMBASE, using a combination of the following MESH terms: "loop ileostomy," "cannula ileostomy," "tube ileostomy," "defunctioning ileostomy," "diverting loop ileostomy," "colorectal surgery," "anastomotic leak," and "fecal diversion." The references of the retrieved articles were screened to find further studies. We chose to not describe "Ghost ileostomy" and "Hidden ileostomy," because these are not ostomies but considered as alternative procedures to DI, so cannot be included in the group of fecal diversions.

"TURNBULL" LOOP ILEOSTOMY

The more popular technique used to perform a conventional loop ileostomy is that described for the first time by Turnbull and Weakley (6) around the late 1960s. The intestinal loop is pulled out through an abdominal transparietal circular opening at the level of the right iliac fossa and fixed with four interrupted sutures between the parietal fascia, peritoneum, and seromuscular layer of

the bowel, in order to avoid postoperative prolapse. A rod is used to pull out and keep the loop in place to avoid retraction and to exclude the efferent loop from the transit of the bowel content. After the opening of the stoma, interrupted mucocutaneous stitches with absorbable materials are used to complete stoma fixation to the skin. The ileostomy takedown is made with a peristomal skin incision, complete mobilization of the bowel loop, intestinal anastomosis, and abdominal wall reconstruction. In the past decades, many variants of classic techniques have been reported. The changes have consisted of eliminating the use of the rod, trying new material for the rod, suturing the efferent loop, and changing the site of ostomy (7–10) (**Figure 1A**).

SKIN BRIDGE LOOP ILEOSTOMY

This is the most recent variant of the classic loop ileostomy technique, consisting of using a skin flap as a rod (17). The skin is incised, creating a rectangular skin bridge about 3 cm long and 1 cm wide, and the subcutaneous fat is divided. This flap is passed through an avascular window opened in the mesentery at the apex of the chosen ileal loop and then secured with separate stitches of 2/0 absorbable suture to the distal edge of the opening, determining the exclusion of the efferent loop of the stoma. The afferent and the efferent loops are fixed to the skin with a 3/0 absorbable suture to prevent retraction and dislocation. Some recent papers (12, 18) demonstrate that the skin bridge loop ileostomy may significantly reduce the early postoperative stoma-related complications, the frequency of exchanged ostomy bags, and patient medical costs after hospital discharge if compared with a conventional loop ileostomy. The ostomy closure follows the same techniques of conventional loop ileostomy (**Figure 1B**).

UMBILICAL ILEOSTOMY

Used for the first time in pediatric patients with Hirschsprung's disease or imperforate anus (10), this technique has increased in use together with the rise of laparoscopic surgery in order to maintain the concept of minimal invasiveness of the surgical procedures. The loop of the ileum designated for the ileostomy was brought out without tension through the umbilical port site with a vertical skin incision just below the umbilicus. It is important to widen the fascial incision to allow for a 5 cm gap as for the conventional ileostomy, and the intestinal serosa and fascia were fixed. Three points of the serosal muscular layer were sutured on the caudal side and on both lateral sides to prevent retraction. The intestinal tract was opened, and the umbilicus is fixed to the incision end of the stoma to assist in the elevation of the intestinal tract. Ostomy reversal is performed through a full mobilization of the stoma including the umbilicus, followed by the anastomosis. Finally, the skin is fixed to the muscle layer subcutaneously with two needles to form a new umbilicus (19–25) (**Figure 1C**).

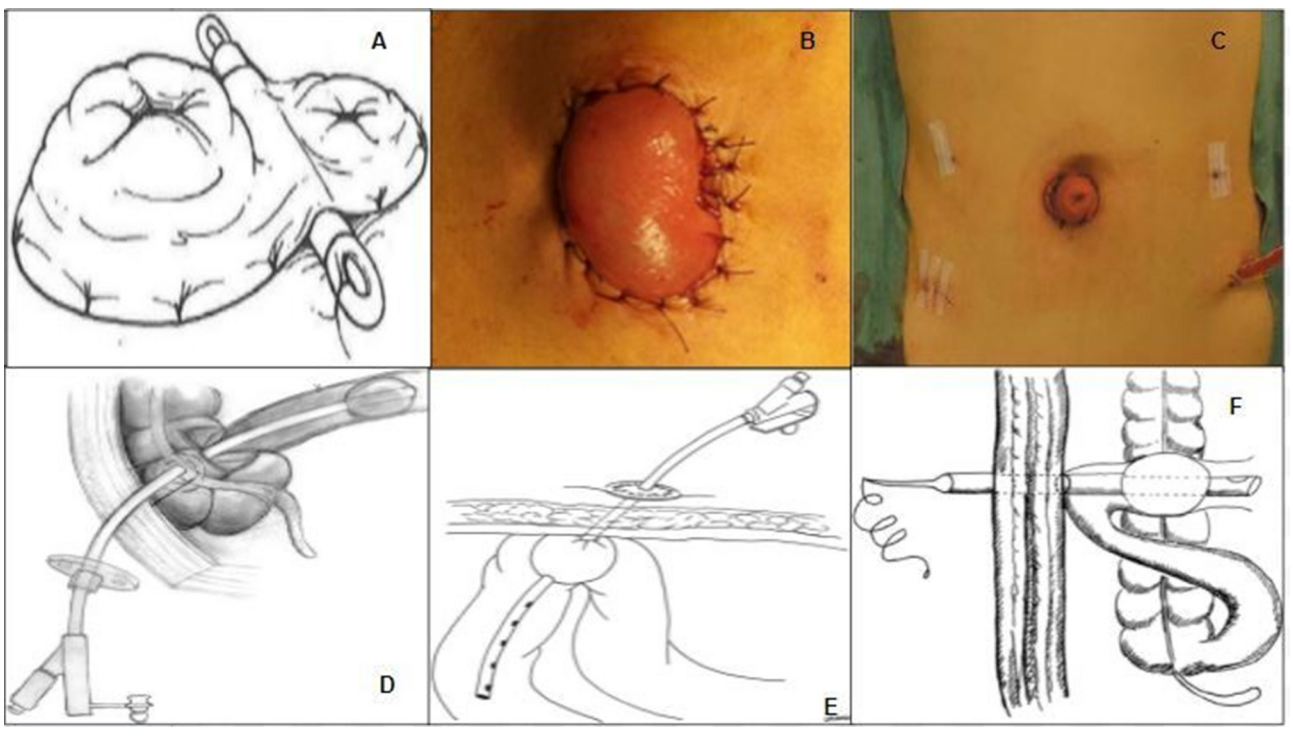

FIGURE 1 | (A) Classic Turnbull loop ileostomy, from Whitehead and Cataldo (11). **(B)** Skin bridge loop ileostomy, from Ye et al. (12). **(C)** Umbilical ileostomy, from Eto et al. (13). **(D)** Transcaecal ileostomy, from Monzòn-Abad et al. (14). **(E)** Percutaneous ileostomy, from Rondelli et al. (15). **(F)** Cannula ileostomy from Hua et al. (16).

TRANSCECAL ILEOSTOMY

Simpson and Srivastava (26) described this technique of ileal diversion in 1975 to allow a complete colonic lavage and ileal decompression in elective colonic surgery. A Foley catheter (26, 27) or a gastrostomy tube (14) is inserted through the cecum in the ileocecal valve and then the balloon is inflated. The catheter and the cecum are fastened with a single or double purse-string suture to the parietal peritoneum and abdominal wall. Ostomy closure is performed by a gradual deflation of the balloon started at postoperative day 5 (27) or at postoperative day 7 (14), and when is complete, the catheter is removed (**Figure 1D**).

PERCUTANEOUS ILEOSTOMY

After the performance of colorectal anastomosis, a modified 18 or 20 Fr jejunostomy tube is placed into the distal ileum about 40 cm proximal to the ileocecal valve by ensuring that the distal part of the tube was in the afferent loop to optimize the drainage (15). The jejunostomy balloon was inflated with 7–10 ml of normal saline then the catheter is fixed in the ileal loop with a purse-string and was brought out through the abdominal wall in the right inferior quadrant also by using a port incision in laparoscopic and robotic surgery. Between the 8th and the 11th postoperative days, a CT scan with a trans-anal enema of hydrosoluble iodate contrast is performed to assess the integrity of the anastomosis, and the catheter can be removed by deflating progressively the balloon. Finally, the abdominal orifice is kept open and connected to a urostomy bag (**Figure 1E**).

TUBE/CANNULA ILEOSTOMY

The endotracheal tube can be used to perform fecal diversion after the colorectal anastomosis; some authors named this technique "cannula" ileostomy (16) and some others "tube" ileostomy (28, 29). A double row of concentric purse-string sutures is placed onto the ileum wall with absorbable sutures and the tracheal cannula is inserted into the distal ileum through a small incision within the inner purse-string, after which the inner and then the external purse-string sutures are tied. Thereafter, normal saline is injected into the balloon and the tube is pulled out through the abdominal wall. The loop is secured to the same location at the parietal peritoneum, near the tube end with seromuscular stitches. The cannula is then pulled tight, and sutures at the fixation site are tightly knotted. The procedure ends with or without a reversible single row of staples across the whole width of the terminal ileum about 10 cm distal to the site of tube insertion. The tube is removed 2 days after the anal function of the patient resumes, during which the tube is blocked with the deflated balloon to ensure that the passage of bowel content continues after its removal between the 20th and the 75th postoperative days.

Chowdri et al. (30) described the same procedure but using a 26 Fr three-way self-retaining Foley catheter, and they also named it "tube ileostomy." In the postoperative period, the management of ostomy requires a regular check of the free flow of contents by washing the tube with normal saline. The tube is deflated between the 5th and 7th postoperative days, clamped after the second week, and finally removed after the third week of surgery to obtain a controlled fistula (**Figure 1F**).

Table 1 shows the characteristics of the main included studies.

TABLE 1 | Characteristics of the main included studies.

References	Type of ileostomy or comparison
Turnbull and Weakley (6)	Loop ileostomy
Flati et al. (7)	Loop ileostomy
Pace et al. (17)	Skin bridge loop ileostomy
Fitzgerald et al. (10)	Umbilical ileostomy
Hada et al. (19)	Umbilical ileostomy
Ishiguro et al. (20)	Umbilical ileostomy
Mushaya et al. (21)	Umbilical ileostomy
D'Alessaandro et al. (22)	Umbilical ileostomy
Miyo et al. (24)	Umbilical ileostomy
Seow-En et al. (25)	Umbilical ileostomy
Simpson and Srivastava (26)	Transcaecal ileostomy
Winslet et al. (27)	Transcaecal ileostomy
Monzòn-Abad et al. (14)	Transcaecal ileostomy
Rondelli et al. (15)	Percutaneous ileostomy
Hua et al. (16)	Cannula ileostomy
Sheng et al. (29)	Tube ileostomy
Chowdri et al. (30)	Tube ileostomy
Dzki et al. (8)	Loop ileostomy vs. skin bridge ileostomy
Carranante et al. (18)	Loop ileostomy vs. skin bridge ileostomy
Ye et al. (12)	Loop ileostomy vs. skin bridge ileostomy
Eto et al. (23)	Loop ileostomy vs. umbilical ileostomy
Eto et al. (31)	Loop ileostomy vs. umbilical ileostomy
Zhou et al. (28)	Loop ileostomy vs. tube ileostomy
Rondelli et al. (32)	Loop ileostomy vs. percutaneous ileostomy
Hanju et al. (33)	Loop ileostomy vs. cannula ileostomy

DISCUSSION

Defunctioning ileostomy is a surgical procedure adopted for the fecal diversion in colorectal surgery to prevent AL. The perfect technique to perform an ileostomy does not exist and any one of the available procedures could be best suited for the patient. All the techniques described could be adopted in open or minimally invasive surgery by using the laparoscopic port incisions adapted as needed, except for the umbilical ileostomy that can be performed only in laparoscopic surgery for obvious intrinsic technical reasons. We aimed to give a snapshot of the current literature on the available types of DI in colorectal surgery. The most important characteristic of a fecal diversion is to be really "defunctioning" as much as possible, without stoma-related complications and with only some or no discomfort for the patients. Moreover, a temporary ileostomy should be easy to take down spontaneously if possible, as described for some techniques (15, 16). In our study, we described the different

available techniques that could not have been compared, but some have been compared to the conventional Turnbull loop ileostomy (8, 12, 18) in terms of stoma-related complications and ostomy management. Carannante et al. (18) compared the conventional technique with a plastic rod to the skin bridge one, showing an improvement of stomal infection, dermatitis, and ulcers in the second group. Besides, the average number of exchanged stoma wafers per week resulted in more than half with statistical significance. No studies investigated eventual differences in the ostomy take-down outcomes that seem to be the same for both techniques. Eto et al. (23, 31) compared the conventional ileostomy and umbilical ileostomy after the laparoscopic anterior resection for rectal cancer. The studies demonstrated a lower wound infection rate in the group of conventional loop ileostomy with better surgical outcomes, but a significantly lower incidence of incisional hernia and relative risk for its development in the umbilical ileostomy group. The temporary percutaneous ileostomy seems to be a valid alternative to the classic loop ileostomy after low anterior resection and extraperitoneal anastomosis, offering a more comfortable and complete fecal diversion with fewer stoma-related and surgical complications if compared with a conventional DI (32). The real novelty is that this ostomy does not require surgery for its closure. The comparison between tube/cannula ileostomy and conventional loop ileostomy has shown no statistical difference in terms of anastomotic dehiscence, stomal complications, and pain. The main differences are the longer hospital stay for the traditional loop ileostomy group and the need for a second surgery for its closure (28, 33). In daily practice, no one technique leads to superior performance than another, and no evidence supports to advise the use of one routinely; the confidence and the expertise of the surgeons in performing a DI and the characteristics of patients play a key role in the choice of the technique to adopt. Further prospective studies with multiple arms of investigation are needed to compare the different techniques of DI to prevent AL in colorectal surgery.

CONCLUSION

The perfect technique to perform a DI does not exist; different techniques can be performed and every patient should receive the proper tailored one. The surgeon should know every one of these available choices and use them as the arrows in the quiver of an archer when needed.

AUTHOR CONTRIBUTIONS

DC and FLT have designed the study. DC, II, and CD have performed the literature search and extracted data. DC has written the manuscript and is responsible for the financial support. FLT, APu, APa, and PAG have critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Preliminary Results of the First 50 Patients Undergoing Sclerotherapy for II-Degree Hemorrhoidal Disease Using an Automated Device

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Background: Sclerotherapy is defined as the injection of sclerosant agents causing fibrosis and scarring of the surrounding tissue. It is currently employed for the treatment of I-III degree hemorrhoidal disease (HD). The aim of this study is to investigate the use of a new automated device for the injection of 3% polidocanol foam.

Methods: This is an observational study including 50 patients who underwent a sclerotherapy procedure with 3% polidocanol foam for II-degree HD according to Goligher classification. Patients were evaluated through validated scores [Giamundo score, Hemorrhoidal Disease Symptom Score (HDSS), Short Health Scale (SHS-HD) and Vaizey score]. Follow-up was conducted until 3 months from the procedure.

Results: Complete resolution of bleeding was achieved in 72% and 78% of patients, respectively, at 1 week and after 3 months from the procedure. Forty eight percent of patients were symptom free after the last follow-up visit (HDSS = 0). No major surgical complications were reported. Three patients out of 36 successfully treated, recurred, and needed a second sclerotherapy injection, which was successful in 2 of them.

Conclusion: These preliminary results of 3% polidocanol foam injection on 50 patients suggest the efficacy and reproducibility of the technique with this new device in the short-term follow-up.

Keywords: hemorrhoidal disease, sclerotherapy, 3% polidocanol foam, bleeding haemorrhoids, symptomatic haemorrhoids

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BACKGROUND

Hemorrhoidal disease (HD) represents a common clinical condition in the Western world among the adult population (1). During the last years, its impact on the quality of life and on the patients' daily activities has been largely discussed in the scientific literature due to its high incidence, multifactorial aetiology, and the absence of a strict consensus regarding diagnosis and therapeutic assessment (2).

Historically, HD has been classified according to the Goligher classification, even though this last one is, today, considered incomplete, and it requires other methods of grouping (3). However,

the choice of treatment today, going from conservative to surgical ones, is guided on the severity of disease presentation and related symptomatology.

Several studies demonstrated successful results after sclerotherapy in terms of remission of the symptomatology, complication rates, and cost-effectiveness in those patients who presented with I-III degree of HD (4, 5). Sclerotherapy is defined as the injection of sclerosing agents at the apex of the internal hemorrhoidal complex, above the dentate line, leading to scarring, fibrosis, and fixation of the hemorrhoids (2). The aim of this study is to investigate the efficacy, safety, and reproducibility of a new technique by the means of a newly introduced automated device (Varixio © VB Devices, Barcelona, Spain) for the injection of a 3% polidocanol foam.

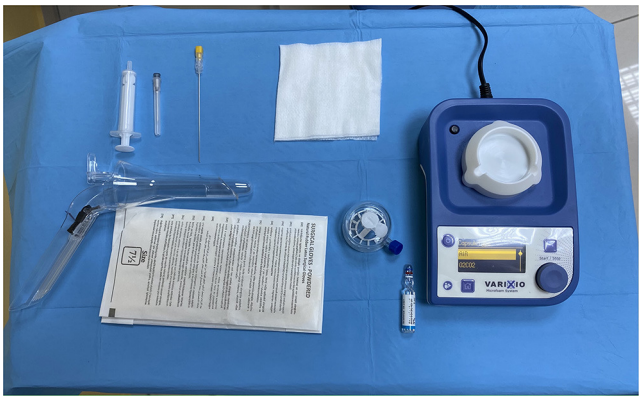

FIGURE 1 | The equipment needed to perform the procedure: an automated device, open-ended anoscope, a 20 Gauge needle, a 5-ml syringe, and polidocanol 3% liquid.

METHODS

This is an observational study including 50 patients who underwent an elective sclerotherapy procedure for II-degree HD according to Goligher classification. All patients failed conservative treatment.

Results were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies (6).

The patients were enrolled between August and October 2021; their follow-up continued until January 2022. All the patients underwent elective surgical treatment on an outpatient basis by an experienced colorectal surgeon.

All the patients who underwent treatment with sclerotherapy, reaching at least 3 months of follow-up, were included in the analysis. Indeed, during the study period, other 19 procedures were performed without achieving the required follow-up.

The second sclerotherapy session was performed at least 4 weeks after the first injection. The same criterion was used for any subsequent repetitions.

Surgery was performed only after a complete work-up including the patient's history, stratification of the patient in degrees of severity by means of validated scores, and physical proctological examination through anoscopy.

Colonoscopy was performed in suspicious cases for rolling out other colorectal disorders.

The procedure was performed in the Sims position on an outpatient setting without any sedation or local anaesthesia as previously described (7, 8). It consisted of the injection of a 3% polidocanol foam using a new automated device (Varixio © VB Devices, Barcelona, Spain) (**Figure 1**). This device allows a continuous foam injection reducing, at minimum, the human error. It is composed of a dome-shaped capsule, with a luer lock both for injection and removal of the sclerosing agent and a magnetic stirrer on top. The foam demonstrated to have a stable consistency and a higher 1.5-x/2-x half life with respect to the liquid sclerosant used in the Tessari method. Moreover, the device allows the use of different percentages of composition, maintaining a liquid/gas ratio between 1:5 and 1:7. It constantly re-emulsifies the foam during the whole duration of the procedure and reduces the human error so drastically to be now considered an operator-independent technique. The emulsified foam has a bubble diameter (μm) of 116 ± 24 with a half-life of 5.2 ± 0.6 min (9). A total of 2 ml of 3% polidocanol foam was used for each of the three classical piles (3, 7, and 11 o'clock).

After the procedure, the patients were asked to walk and were discharged 20 min later, after a safety check. Stool softeners and flebotonics were administered in the post-operative period.

Time of procedure was considered as a baseline (T0) and after that, the patients underwent follow-up visits, which consisted of external clinical evaluation after 1 week (T1), and a complete proctological evaluation, including digital rectal examination and anoscopy after 4 weeks (T2) and 3 months (T3). The patients were evaluated by validated scores. Giamundo score was utilised for the evaluation of bleeding at the baseline, and all follow-up visits (0 = absence of bleeding, 1 = < 1 episode per month, 2 = 1 episode per week, 3 = 1–3 episodes per week and 4 = 4 or more episodes per week) (10).

Symptom severity and quality of life were assessed using a five-item questionnaire: the Hemorrhoidal Disease Symptom Score (HDSS). This score evaluates pain, itching, bleeding, soiling, and prolapse on a 5-point scale (0 = never, 1 = less than one time a month, 2 = less than one time a week, 3 = 1–6 days per week, 4 every day or always). Another used score was the Short Health Scale for HD (SHS-HD) score, including 4 questions with a 7-point Likert scale for each question minimum score = 0, 7 = maximum score = 0 at T0, and T3 (11). Anal continence was evaluated through the Vaizey incontinence score (minimum score = 0, perfect continence/maximum score = 24, totally incontinent) at T0, T2, and T3 (12).

Visual analogue scale (VAS) score was used to evaluate peri-procedural pain (VAS) score (minimum score = 0, maximum score = 10).

The primary outcome was defined as the complete resolution of bleeding episodes 1 week after the procedure based on the Giamundo bleeding score.

TABLE 1 | Patient characteristics and procedural results.

Male (*N*°, %)	31/50 (62%)
Mean age (years)	48.3 ± 17.2 (range: 18–75)
Mean operation time (minutes)	5.5 ± 1.7 (3–10)
Post-operative Pain (VAS > 0)	3/50 (6%) 0 (0–0)
Success Rate after 1 week (T1)	36/50 (72%)
Overall Success Rate (T5)	39/183 (78%)
Recurrence	3/36 (8.3%)
Adverse Events	None

Recurrences were defined as the new onset of bleeding after T1 in the successfully treated patients, always based on Giamundo score assessment, from a bleeding score of 0 to at least 2 at any time point between T2 and T3.

Eligibility Criteria

Patients aged between 18 and 75 years with symptomatic II-degree HD according to the Goligher classification were considered eligible for the present study.

The patients with a history of cardiac disease, blood disorders, gastrointestinal tract oncological or inflammatory disorders, other proctological diseases, previous anal surgical procedures, recurrency of the pathology after sclerotherapy or rubber band ligation in the last 12 months, pregnancy or lactation, infectious disease, or previous pelvic radiotherapy were excluded. The inability to return for postoperative control visits was also considered an exclusion criterion.

Safety

Safety and toxicity of the procedure were investigated by reporting the adverse events (AE) after foam injection and using the WHO toxicity scale, respectively (13). AEs were reported according to the probability of occurrence as none, remote, possible, probable, or not assessable.

Statistical Analysis

Categorical variables were analysed and reported as counts and percentages, and as the mean ± SD (range) for continuous normally distributed variables, whereas ordinal categorical variables, and continuous not normally distributed variables were reported as median [interquartile range (IQR)]. The chi-square test was used for cross tabulations. The results associated with a $p < 0.05$ were considered statistically significant.

RESULTS

Most of the population enrolled in the study was male, consisting of 31 patients out of 50 (62%), whereas the rest, the other 19 patients out of 50 (38%), were females. The mean age of the population was 48.3 ± 17.2 (range: 18–75) years. The mean operation time was 5.5 ± 1.7 (range: 3–10) min (**Table 1**).

At the baseline (T0), Giamundo score had a mean of 3.18 ± 0.63 (range: 2–4), meaning that the majority of the patients, graded II according to the Goligher classification of HD, referred 1–3 episodes of bleeding per week before treatment. After 1 week, the complete resolution of bleeding was achieved in 36 out of 50 patients (72%), whereas only 12 patients reported an episode of bleeding (Giamundo score = 1) with a mean of.32 ± 0.55 (range: 0–2) with respect to the total population.

TABLE 2 | Differences among the mean of the Giamundo score at baseline (T0) and follow-up visits.

Mean	T0	T1	T2	T3	*P*-value
Giamundo score	3.18	0.32	0.56	0.3	<0.0001

TABLE 3 | Differences among the median values of Hemorrhoidal Disease Symptom Score (HDSS) and Short Health Scale (SHS) between baseline (T0) and 3 month follow up (T3).

Median	T0	T3	*P*-value
HDSS	11	1.5	<0.0001
SHS	16	0	<0.0001

Giamundo score maintained stable values even at the second follow-up visit after 1 month from the procedure (T2). It reported a mean value of 0.56 ± 0.93 (range: 0–3) with 17 patients referring at least one bleeding episode in the last month.

However, the analysis at the third and last follow-up visits at 3 months from the procedure confirmed values stable in time for the Giamundo score with only 11 patients reporting a score equal or higher than 1 with a mean value of 0.3 ± 0.68 (range: 0–3) with an overall success rate of 78% (39/50). The differences of the Giamundo score were highly statistically significant ($p < 0.0001$) (**Table 2**).

In 2 patients (4%), there was worsening of the Giamundo score at T2, from 1 to 3. For these patients, a second sclerotherapy session has been successfully performed. One patient got worse at T3, from 1 to 3, and a second sclerotherapy session has been planned but not included in the results.

About 3 out of 36 (8.3%) successfully treated patients recurred according to the primary outcome, and, after the second sclerotherapy session, one patient became successful, one patient improved from 3 to 1, and one patient failed (remaining at Value 3 from preoperative to postoperative examination).

Vaizey score at the baseline was considered completely negative with a median value of 0 (IQR: 0–1). It demonstrated to maintain the same results (median of 0, IQR: 0–0) at a T2 follow-up visit with a statistically significant *p* value ($p < 0.021$).

On the other side, median HDSS was 11 preoperatively (IQR: 9–12), considerably improving at the T3 follow-up to a median value of 1.5 (IQR: 0–3); the difference was statistically significant ($p < 0.0001$). Forty eight percent of patients were symptom free (HDSS = 0) after the last follow-up visit.

Similarly, improvement of the SHS-HD was statistically significant ($p < 0.0001$) from a median value of 16 (IQR: 14–18) to a reported value of 0 (IQR: 0–5) (**Table 3**).

Only three patients referred to peri-procedural pain on the VAS score (<3), with a median value of 0 (IQR 0–0). No other intraoperative complication was registered.

DISCUSSION

The results of this preliminary analysis on the treatment of HD with polidocanol 3% foam demonstrated the safety as well as the efficacy of the procedure performed through a new automated device (Varixio © VB Devices, Barcelona, Spain). Indeed, neither intraoperative nor postoperative complications occurred. Our results reported a great improvement of bleeding symptoms for the majority of the population. Over 78% of the patients maintained a therapeutical success at 3-month follow-up, and almost half of the entire population was symptom free at the last follow-up visit based on the HDSS score. The severe standardisation of the procedure as well as the use of validated scores allowed to objectify the results, avoiding a difficult interpretation of the latter.

The patients who suffer from HD generally bear a great psychological discomfort because of recurrent presentation of symptomatology, not responding to medical therapy, feeling of shame, and fear of surgery; therefore, there is a high number of patients that seek the help of the physician when the disease is already advanced in its severity. Nevertheless, those patients who present to medical attention with I-II and, sometimes, III-degree HD might be successfully treated on the outpatient clinics, with minimally invasive procedures like sclerotherapy or rubber band ligation. The spread of this less-invasive procedure may lead to the general population to consult their general practitioner earlier.

Sclerotherapy is currently recognised as an efficacious method of treatment in I and II-degree HD through the injection of sclerosing materials with benefits for the patients in terms of recovery and minimal discomfort that allow normal continuation of daily-life activities. Moreover, this technique is safe, cheap, and easy to run, permitting its application also in tough cases and in III-degree HD, who failed conservative treatment (2). In fact, in cases in which the patient has many comorbidities and is not fit for anaesthesia, or is waiting for a more invasive therapy, he/she may benefit from a damage-control assessment. For example, in case of severe acute anal bleeding, a bridge to surgery through sclerotherapy might be the most appropriate choice of treatment (14).

Recent studies have demonstrated the higher efficacy of foam injection with respect to the one involving liquid sclerosing agent (5). This new device (Varixio © VB Devices, Barcelona, Spain) allows the injection of a continuously re-emulsified foam and reduce at minimum the success variability related to the different operators. The present study is the first one reporting the procedural results after 3% polidocanol foam injection using an automated device.

Over the last few years, there has been an increasing attention and appreciation of sclerotherapy with 3% polidocanol foam (4, 15, 16).

Lobascio et al. (4) published similar results of the therapeutical success rate in a limited population with a longer follow-up of 12 months. The authors reported 78.8% of success after a single-ST session with around 20% of recurrences in the first 6 months treated with a second ST injection (with a success rate of 86%) or with mucopexy.

Salgueiro et al. (15) published the first randomised trial regarding the comparison between rubber band ligation and sclerotherapy with 3% polidocanol foam injection. The authors registered a rate of success of sclerotherapy similar to ours, even though the two studies are not comparable due to the different study designs and primary endpoints. They reported a higher complete success rate in the sclerotherapy group with respect to the rubber band ligation, particularly in the 88.3 and 66.7% ($p = 0.009$) of the patients, respectively. Moreover, the recurrence rate (16.1 vs. 41.1%; $p = 0.004$), and complications (10 vs. 30%; $p = 0.01$) were inferior in case of sclerotherapy.

The conclusions of both studies agree with ours. In addition to this confirmation, the new device that we utilised during this study contributes to the efficacy and reproducibility of the procedure with technical improvements related specifically to the instrument. Indeed, the variability of foam consistency is completely abolished, thanks to the continuous emulsification of the foam during the procedure, as already explained. The real strength of this method is that the whole operation is made faster and reproducible by every surgeon, limiting human error to a minimum. However, this technique deserves further studies in a wider sample of patients to better evaluate the efficacy and the long-term results. Limitations of the present study are the retrospective analysis of the data, even though the enrolment has been prospective, the limited sample of the patients, and the limited duration of follow-up until 3 months.

CONCLUSION

Sclerotherapy is a valid therapeutical option in case of bleeding HD.

Preliminary results of polidocanol injection with this new device on 50 patients suggest the efficacy of the technique in the short-term follow-up. This technique is safe and repeatable, useful in case of a bridge to surgery and in damage control emergency procedures. However, other investigations in a broader population sample and with a longer follow-up are needed.

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 Regione Calabria–Comitato Etico Sezione Area Centro. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MG and GG: substantial contributions to the conception and design of the work, acquisition, analysis, interpretation of data for the work, drafting the work, revising it critically for

important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved. CN, PA, ED, and MT: substantial contributions to the conception and design of the work, acquisition, analysis, interpretation of data for the work, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved. All the authors contributed to the article and approved the submitted version.

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MINI REVIEW
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Management and Treatment of External Hemorrhoidal Thrombosis

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Background: External hemorrhoidal thrombosis (EHT) is a common complication of hemorrhoidal disease. This condition causes extreme pain, likely resulting from internal anal sphincter hypertonicity, which traps the hemorrhoids below the dentate line thus leading to congestion and swelling. The choice of treatment remains controversial and both conservative and surgical options have been proposed in the last decades.

Methods: This mini-review focuses on the most relevant studies found in literature evaluating conservative and surgical management of EHT. Special conditions such as pregnancy and EHT in elderly patients have been considered.

Results: Traditionally, symptoms duration represents the discriminant in the choice between medical and surgical treatment. Several Coloproctological Societies considered conservative treatment as the first-line approach to EHT and a variety of options have been proposed: wait and see, mixture of flavonoids, mix of lidocaine and nifedipine, botulinum toxin injection and topical application of 0.2% glyceryl trinitrate. Meanwhile, different surgical treatments are recommended when EHT fails to respond to conservative management or when symptoms onset falls within the last 48–72 h: drainage with radial incision, conventional excision, excision under local anesthesia and stapled technique.

Conclusion: The management and treatment of EHT is still controversial since no specific guidelines have been published. Both medical and surgical treatment have been proven effective but randomized clinical trials and structured consensus-based guidelines are warranted.

Keywords: hemorrhoidal disease, external hemorrhoidal thrombosis, hemorrhoidectomy, surgery, pregnancy

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INTRODUCTION

Hemorrhoidal thrombosis is one of the most frequently diagnosed complication of hemorrhoidal disease that can involve both the internal and the external hemorrhoidal plexus (1).

External hemorrhoidal thrombosis (EHT) commonly occurs in young adults of both sexes (2), representing distended vascular tissue in the anal canal, distal to the dentate line, covered by richly

innervated anoderm (3). This condition causes extreme pain, likely resulting from internal anal sphincter hypertonicity, which traps the hemorrhoids below the dentate line thus leading to congestion and swelling (2, 3).

Etiology of EHT is still a matter of debate. It is linked to an increased intravenous pressure in the hemorrhoidal plexus which leads to rupturing of the endothelial lining initiating thrombosis (4, 5). Young age, hard stool, constipation, excessive physical effort and use of dry toilet paper combined with wet cleaning methods after defecation appear to promote EHT development, whereas the use of bathtub or shower before sleep seem to have a protective role (4, 5). Pregnancy, commonly considered a risk factor for EHT, has no significant relationship, except for childbirth (5). Occasionally, recurrent EHT could be associated with administration of L-asparaginase, in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (6).

There is neither a classification nor a consensus agreement for evaluating the presence and severity of EHT. For this reason, the choice of the type of treatment remains controversial (7).

The decision-making process usually depends on timing since symptom onset, with surgical treatment being favored with symptoms onset occurring in the preceding 72 h (8, 9). Severity of symptoms and patient preference should also be considered (10). Conservative treatment is mainly symptomatic, with use of analgesics, nifedipine or glyceryl trinitrate (GTN), activity reduction and laxatives (11). Surgical treatment options include incision and evacuation of the thrombus (12) or excision of the thrombosed hemorrhoid (10).

METHODS

Published literature was searched using PubMed to identify publications reporting the treatment and the clinical assessment of EHT between January 1, 2000 and January 1, 2022.

Key words for the search were: "external hemorrhoidal thrombosis", "thrombosed hemorrhoids", "acute thrombosed hemorrhoids", "external thrombosis hemorrhoids", and "acute hemorrhoids".

Screening of articles was performed at the abstract level by four authors (AP, AD, GT, and MR), excluding studies not meeting eligibility criteria (i.e., medical and surgical treatments, outcomes in patients affected by EHT, EHT during pregnancy and in elderly patients) where these could be readily determined from the abstract alone.

Study characteristics and outcome data were extracted independently onto a Microsoft Excel spreadsheet. The following data were extracted for each study: first author, year of publication, authors' country, study design and length (in years), number of patients, patients' demographics (gender, age), type and duration of symptoms, etiology of EHT, type of medical or surgical treatment, recurrence rate.

CLINICAL ASSESMENT

The diagnosis of EHT is clinical, based on accurate collection of anamnestic data and on proctological examination. When collecting anamnestic data, patients usually refer an episode of straining with constipation, physical effort or diarrhea (3). Classic symptoms of this condition are acute and invalidating anal pain with appearance of a perianal lump (11, 13). Patients with EHT complain of sudden onset of anal pain with appearance of a visible, bluish perianal lump and a certain degree of internal anal sphincter hypertonia. Bleeding is infrequent and occurs only when the thrombus leads to ulceration of the underlying skin (14) (**Figure 1A,B**). Pain associated with EHT can be extremely intense and debilitating for the patient, requiring immediate management. If left untreated, symptoms may take several days or weeks to resolve (2, 15). The anorectal examination is fundamental for

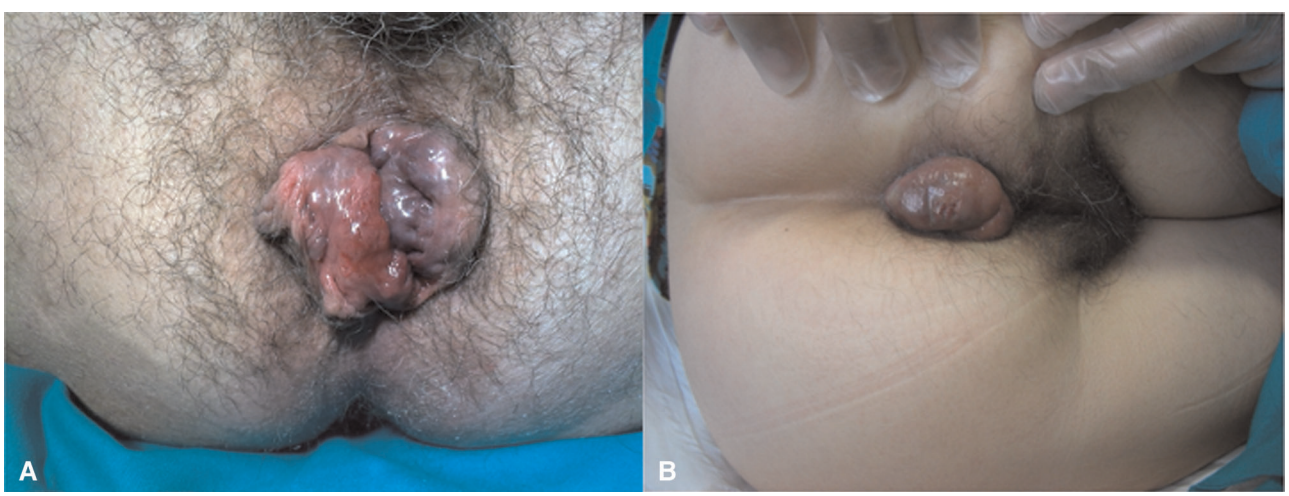

FIGURE 1 | (**A**,**B**) External thrombosed hemorrhoids and anal lump.

correct diagnosis and is typically performed with the patient lying in left lateral decubitus position. It consists of visual inspection, digital examination and anoscopy. Inspection, in case of EHT, allows identification of a bluish perianal lump, which must be differentiated from complicated internal hemorrhoids and pigmented anal melanoma. EHT are covered by anoderm, whereas complicated internal hemorrhoids are covered by anal mucosa. Pigmented anal melanoma can be excluded in case of sudden appearance of the bluish perianal discoloration (11). Digital rectal examination allows evaluation of the resting sphincter tone, which is usually increased in patients with acute hemorrhoidal crisis (16).

CONSERVATIVE MANAGEMENT AND OUTCOMES

Several Coloproctological Societies considered conservative treatment as the first-line approach to EHT (16, 17).

Traditionally, the most important discriminant in the choice between medical or surgical treatment is symptoms duration when reaching medical attention. Medical approach is reserved to patients experiencing symptoms beyond 48–72 h from onset (3, 11, 12, 18). However, there is no evidence in literature that conservative management is best used in cases of early onset of symptoms. It seems to be based on clinical experience handed down over the years. Sammarco et al. and Chan et al. recommended to base the choice of approach not only on timing since onset of symptoms but also on the severity of patient's symptoms and needs (10, 14).

A variety of conservative treatment options have been proposed (16). The first level of treatment is "wait and see" and includes a combination of local hygiene measures, ointments, sitz baths, high-fiber diets, increased oral intake of fluid, stool softeners, oral and topical analgesics (15–17). Gebbensleben et al. (19) proposed a strict management policy: no water, showering, washcloth use, wet wipes, soap or shower gel for hygiene after defecation, but only use of a smooth dry sheet of toilet paper for one to two weeks. Patients were asked to complete a questionnaire at study entry and six months later. At follow-up, 62.5% described themselves as "healed" or "ameliorated", a recurrence was suspected in 21.3%, and 45.8% reported persistence of at least one symptom (i.e., itching, pain, sore anus, bleeding and burning).

A recent randomized, controlled, triple blind trial demonstrated the efficacy of oral intake of a mixture of diosmin, troxerutin and hesperidin in the treatment of acute hemorrhoid crisis (20). The mixture of flavonoids showed a significant and rapid reduction in anal pain, bleeding and itching compared to placebo. Furthermore, after 42 days of follow-up, the intake of painkillers was significantly lower, with a lower occurrence and persistence of oedema and thrombosis compared to the placebo group.

Physical examination of patients with EHT often reveals internal anal sphincter hypertonia, which seems to play a causal role in pain. In fact, according to the World Society of Emergency Surgery (WSES) and of the American Association for the Surgery of Trauma (AAST) guidelines on anorectal emergencies, topic muscle relaxant are suggested (21). Currently there is no evidence of benefit and no indication to the subcutaneous administration of low molecular weight heparin (22).

In this context, Perotti et al. prospectively compared the use of 1.5% topical lidocaine alone and combination of 1.5% topical lidocaine and topical 0.3% nifedipine. The evaluation on the 98 randomized patients showed in the combined nifedipine-lidocaine group a higher pain control at day 7 (86 vs. 50%, $p < 0.01$), decreased use of oral analgesia (8 vs. 54%, $p < 0.01$) and complete resolution of EHT after 14 days (92 vs. 46%, $p < 0.01$). No patient treated with nifedipine showed any systemic side effect, but only a slight local hyperemia in 4%, which disappeared with interruption of the application (23). Moreover, a prospective randomized study by Patti et al. (2) evaluated the efficacy and safety of intrasphincteric injection of botulinum toxin for pain relief in patients with EHT. The 30 randomized patients received an intrasphincteric injection of either 0.6 mL saline or 0.6 mL of a solution containing 30 units botulinum toxin. Pain intensity was significantly reduced in the botulinum group within 24 h of injection ($p < 0.001$), whereas in the placebo group a reduction was noted only from day 7. The latter group also needed a higher amount of daily analgesic tablets compared to the botulin group (2.3 vs. 1.6, $p = 0.008$). No systemic or local side-effects or anal incontinence was recorded in any patients (2).

Gallo et al. suggested the use of a polysaccharide complex, eg mesoglycan, with antithrombotic and profibrinolytic properties with the aim of reducing the post-operative thrombosis of the mucocutaneous bridges after excisional hemorrhoidectomy (24, 25). The same authors suggested the combined use of mesoglycan with local nifedipine or GTN, stool softeners, increased oral intake of fluid, oral and/or topical analgesics (12). However, further prospective studies are needed to validate its use in EHT.

SURGICAL MANAGEMENT AND OUTCOMES

Surgical treatment is recommended when EHT fails to respond to conservative management or, traditionally, when symptoms have been present for up to 48–72 h (10). Drainage with a radial incision and complete excision of EHT are considered the two conventional methods (3, 12), although various strategies and techniques have been attempted to reduce post-operative pain and recurrence rate.

Jongen et al. (1) retrospectively reviewed 340 patients who underwent outpatient excision of EHT under local anesthesia using a solution of mepivacaine 1%, epinephrine 0.0005% and sodium bicarbonate 8.4%. The 0.3% of these patients had post-operative bleeding controlled under local anesthesia and 2.1% developed a fistula or anal abscess. Twenty-two (6.5%) developed a recurrent EHT $\geq$2 months after the initial excision. After 17.5 months of follow-up, 66.4% had no anorectal complaints, 21% pruritus ani, 9.4% anal pain and

5.4% anal bleeding. Ninety-eight percent of patients were satisfied of outpatient treatment and in 79% local anesthesia was felt acceptable for another excision.

In literature two studies compared surgical and conservative managements of EHT. Greenspon et al. (15) retrospectively reviewed 231 patients with EHT, 51.5% of them were treated conservatively and the remaining 48.5% surgically (97.3% with excision and the rest with incision and evacuation of thrombus). Resolution of symptoms (pain, bleeding and perianal tumefaction) was achieved earlier by the surgical group (3.9 vs. 24 days, $p < 0.0001$). The conservative group had a higher frequency of recurrence (25.4 vs. 6.3%, $p < 0.0001$) with also a shorter time span to recurrence (7.1 vs. 25 months, $p < 0.0001$) (15). The second trial is the prospective study by Cavic et al., that randomized 150 patients into three treatments groups: topical application of 0.2% GTN, incision and excision of EHT. Comparison of postoperative pain scores revealed a less severe intensity of pain provided by classical excision, followed by topical application of GTN. However, no difference in symptomatic relief was found at 1-month follow-up between the groups, but at 1-year the percentage of patients without symptoms and recurrence was significantly higher in the excision group (26).

Two prospective randomized trials by Brown et al. and Wong et al. (27, 28) evaluated the role of stapled technique for EHT compared with conventional hemorrhoidectomy. The stapled

TABLE 1 | Main studies reporting surgical and conservative treatment in patients affected by EHT.

Study	Design	Patients No.	Mean Age	Conservative treatment	Incision	Open/closed hemorrhoidectomy	Stapled hemorrhoidopexy	Recurrence
Eberspacher	Retrospective	87	80.9	36 pts. (A): stool softeners, oral, topical analgesics, flavonoid mixture (diosmin, hesperidin)	31 pts. (B): incision	20 pts. (C): hemorrhoidectomy		12.5 months A. 19.4% B. 16.1% C. 0%
Greenspon	Retrospective	231	43.2 (A) 41.9 (B)	119 pts. (A): conservative treatment	3 pts. (B): incision	109 pts.(B): excision of the thrombosed vessel		A. 25.4% (7.1 months) B. 6.3% (25 months)
Brown	Prospective randomized	30	44–46			15 pts: hemorrhoidectomy	15 pts: stapled mucosectomy with PPH technique	
Gebbensleben	Prospective cohort study	48	43	No water, shower, bath, washcloth, wet wipes, soap, shower gel. Only smooth dry toilet paper for anal cleaning for 2 weeks.				6 months 21.3%
Perrotti	Prospective randomized	98	35	50 (study): topical 0.3% nifedipine every 12 h for 2 weeks 48 (control): topical lidocaine ointment every 12 h for 2 weeks				
Patti	Prospective randomized	30	40	15 pts. (A): Botulinum toxin injection 15 pts. (B): Placebo				12 months A. 20% B. 26%
Jongen	Retrospective	340				Excision under local anaesthesia		24 months 6.5%
Cavcic	Prospective randomized	150		50 pts.(A): 0.2% glycerlyl trinitrate ointment	50 pts. (B): Incision	50 pts. (C): Excision		12 months A. 21% B. 24% C. 5%
Wong	Prospective randomized	41	47 (A) 53 (B)			20 pts. (A): Hemorrhoidectomy	21 pts. (B): Stapled hemorrhoidectomy	12 months A. 25% B. 0%
Giannini	Prospective randomized	66	49	Mixture of diosmin, troxerutin and hesperidin (Triade H)				42 days 10%

procedure was burdened by significantly longer operation time and pain at discharge (5 vs. 1 at VAS); however, the median stay was not significantly different between the groups. In the first postoperative weeks the conventional group complained of persistent bleeding and reported significantly higher pain score, particularly on passing stool. The stapled group required a significantly shorter period to become analgesic/pain-free with a shorter time required for wound healing. This group also resumed work or activities of daily living sooner than the conventional group. At 1 year follow-up in both groups none of the patients complained of incontinence, whereas 25% of patients in the conventional group developed recurrent symptoms. The stapled group had a significantly better overall symptom improvement and were more satisfied with surgical outcomes during follow-up (**Table 1**).

EHT MANAGEMENT IN ELDERLY

Geriatric patients tend to be at high risk of complications because of their comorbidities (e.g., cardiovascular diseases) and frequent assumption of anticoagulants, which favor conservative management over surgical treatments. Only one study retrospectively evaluated the differences between conservative and surgical treatment (i.e., incision with evacuation of thrombosis and Milligan Morgan's hemorrhoidectomy) for EHT in elderly (age >75). The group treated with incision reported immediate pain relief (2.6 day) followed by the excision group (7.3 days). However, the incision group was the only one that reported bleeding in 16% of patients for an average duration of 1.4 days. No recurrence was found in the excision group, with a similar recurrence between incision and conservative group (16 vs. 19% respectively) after 10 months. No major complication or anal stenosis were reported in all groups (29).

EHT MANAGEMENT DURING THE PREGNANCY

EHT is one of the most important sources of anal pain during pregnancy. Around 8% of pregnant females will experience EHT, especially during the 2nd and 3rd trimesters. Risk factors are vaginal delivery, constipation, high birth weight, traumatic and /or instrumental delivery (30–32). Prevention and conservative management (fibers, stool softeners, sitz baths and topical creams) are considered the initial treatment, reserving surgical management for postpartum period. There has been reluctance in performing surgical excision, especially under general anesthesia, due to technical difficulties encountered with patient positioning as well as fear of inducing premature labor (31). Mirhaidari et al. demonstrated the safety and effectiveness of EHT excision under local anesthesia in outpatient setting. Forty pregnant females with an average gestational age of 31.7 weeks underwent excisional treatment. Twenty-one patients were complicated by a recurrence, fissure and/or hemorrhoidal tag. The recurrence rate of EHT was 32.5%, only 10% of which occurred during pregnancy. No spontaneous abortion or admission for preterm labor occurred (31).

CONCLUSIONS

This mini review exclusively considered articles published in the last 20 years. Medical treatment has been proven effective for pain control and swelling. Different surgical treatments are recommended when EHT fails to respond to conservative management, or when symptom onset has occurred no later than 72 h from reaching medical attention. Surgical management provides rapid symptom relief, lower incidence of recurrence and longer remission interval when compared to medical treatment. Future studies and consensus-based guidelines are needed to determine the optimal treatment of EHT, particularly in special circumstances (e.g., pregnancy and elderly).

AUTHOR CONTRIBUTIONS

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The Role of Indocyanine Near-Infrared Fluorescence in Colorectal Surgery

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Purposes: The aim of this study was to evaluate the importance of Indocyanine Green in control of anastomosis perfusion and on anastomotic leakage rates during laparoscopic and robotic colorectal procedures.

Methods: A retrospective review of patients who underwent elective minimally invasive surgery for colorectal cancer from 1 January 2018 to 31 December 2020 was performed. All patients underwent Near-Infrared Fluorescence-Indocyanine Green system in two moments: before performing the anastomosis and after completing the anastomotic procedure. Primary outcomes were the rate of intraoperative change in the surgical resection due to an inadequate vascularization and the rate of postoperative anastomotic leakage. Secondary outcomes were the postoperative complications, both medical and surgical (intra-abdominal bleeding, anastomotic leakage).

Results: Our analysis included 93 patients. Visible fluorescence was detected in 100% of the cases. In 7 patients (7.5%), the planned site of resection was changed due to inadequate perfusion. The mean extension of the surgical resection in these 7 patients was 2.2 ± 0.62. Anastomotic leakage occurred in 2 patients (2.1%). Other complications included 8 postoperative bleedings (8.6%) and 1 pulmonary thromboembolism.

Conclusions: The intraoperative use of Near-Infrared Fluorescence-Indocyanine Green in colorectal surgery is safe, feasible, and associated with a substantial reduction in postoperative anastomotic leakage rate.

Keywords: indocyanine green, colorectal cancer, perfusion, minimally invasive surgery, nearinfrared fluorescence

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INTRODUCTION

Anastomotic leakage (AL) is defined as a dehiscence of the intestinal wall at the anastomotic site, that could require a surgical revision, and it represents one of the most common complications in colorectal surgery. The incidence of AL in ileocolic, colo-colic, and colorectal or coloanal anastomoses is 1–4%, 2–3%, and 5–19%, respectively (1, 2). In most cases, the development of AL depends on the state of perfusion, the surgical technique, and the anastomotic procedure.

Data reported from the literature showed that there is no difference in the AL rate between open surgery and minimally invasive techniques; regarding the anastomotic technique, anastomosis with stapling devices is associated with a higher incidence of AL with respect to non-stapled anastomosis, as confirmed by a recent study conducted by Wurtz et al (3). Complications following surgery can be due to technical errors such as insufficient blood supply and increased tension to the anastomosis, technical failure of the stapler, and inadequate suturing. Advances in technology have introduced near-infrared (NIR) fluorescence imaging with indocyanine green (ICG) to evaluate the perfusion of colorectal anastomosis.

The aim of this study was to evaluate the role of ICG in control of perfusion to the anastomosis and on AL rates during minimally invasive colorectal surgery.

MATERIAL AND METHODS

After the approval of the Institutional Review Board of the "Federico II" University of Naples, a retrospective chart review of the minimally invasive colorectal resection for cancer from 1 January 2018 to 31 December 2020 was performed.

All patients received an elective laparoscopic or robotic operation and they underwent previously a complete history and physical examination with blood tests, cross-sectional imaging (4), and colonoscopy. After the admission, the patients underwent bowel preparation with a combination of osmotic laxative, potassium and sodium salts if possible, preoperative antibiotics, and heparin prophylaxis according to the current literature (5–8).

Surgical Technique

All operations were performed by expert surgeons. In order to reduce the bias related to the different surgical techniques, only procedures performed according to the standardized criteria were included in the study.

All the patients were operated on under general anesthesia (9). In right colectomy, once identified the ileocolic pedicle, the peritoneum of the mesentery just inferior to the vessel should be opened with the creation of a mesenteric window. Thus, Toldt's fascia was separated from Gerota's plane, with identification and preservation of the right ureter, duodenum, and pancreatic head. After ligation of the ileocolic pedicles at their origin, the right colon was completely mobilized laterally from the right parietocolic gutter. The mesentery was dissected medially, with consequent ligation of the right colic vessels and the right branch of the middle colic vessels. After performing the right hemicolectomy with a linear stapler, the ileo-colic anastomosis was performed intracorporeally in a side-to-side isoperistaltic fashion. In the left colectomy, after the colo-epiploic detachment and the complete mobilization of the splenic flexure, the Inferior Mesenteric Vein (IMV) and the Inferior Mesenteric Artery (IMA) were isolated, clipped, and divided at their roots. After the detachment of the Toldt's fascia from the Gerota's plane, with the preservation of the retroperitoneal elements, left hemicolectomy was performed with a linear stapler and a colorectal end-to-end anastomosis was performed according to Knight–Griffen technique. In the case of anterior rectal resection, after the complete mobilization of the left colon as described, the intervention proceeded with a Partial or Total Mesorectal Excision (PME or TME). In segmental splenic flexure resection, after the mobilization of the descending and transverse colon, the left branches of the middle colic vessels and the left colic artery were isolated, clipped, and ligated at their origin. Finally, for transverse colon resection, both the colic flexures were completely mobilized and a wedge resection of the mesentery, including the branches of the middle colic artery, was performed. In the case of segmental resections, the colo-colic anastomosis was performed intracorporeally in a side-to-side isoperistaltic way.

All patients underwent NIR/ICG system according to a standardized technique at two different moments: before performing the anastomosis to control the adequate vascularization of the stumps and after completing the anastomosis to control its perfusion (**Figure 1**). In detail, before the colonic or rectal resection, the anesthesiologist administered a bolus of 0.2 mg/kg of ICG, and after a median time of 25 seconds, an adequate vascularization was visible (if present). The same procedure was repeated after performing the anastomosis.

Data Collection and Outcomes Assessment

Data were prospectively collected and included gender, age, Body Mass Index (BMI), American Society of Anesthesiologists (ASA) Score, conversion rate, and intraoperative complications.

Primary outcomes included the rate of intraoperative change in the surgical resection due to an inadequate vascularization at the NIR/ICG system and the rate of postoperative anastomotic leakage. In case of intraoperative changes due to an inadequate vascularization, the extension of the surgical resection was measured in centimeters and registered.

Secondary outcomes were the postoperative complications according to the Clavien–Dindo classification.

Anastomotic leakage was suspected based on fever, abdominal pain, fecal matter in abdominal drainage, abscess and gas around the anastomotic site at the computed tomography, and the presence of a communication between inside and outside the intestinal tract at the contrast enema. Anastomotic leakage was considered as a complication when a surgical re-intervention was necessary.

Statistical Analysis

Statistical analysis was performed using the SPSS 26 system (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean ± SD; categorical variables were expressed as %. Furthermore, a multivariate analysis was performed to assess if any patients' or surgical characteristics (age, gender, BMI, ASA Score, the presence of diabetes or hypertension, the adoption of robotic or laparoscopic approach) could significantly impact on anastomotic leakage or bleeding rate. Results of the multivariate analysis were expressed by Odds Ratio (OR) and 95% Confidence interval (95% CI).

RESULTS

Our analysis included 93 patients; all patients underwent elective minimally invasive surgery (laparoscopic or robotic surgery) for malignant colorectal cancer. Of these, 40 were female and 53 were male (43% and 57%, respectively).

Demographic data are reported in **Table 1**. Mean age was 69.81 ± 12.06, mean BMI was 25.81 ± 4.29, and mean ASA Score was 2.54 ± 0.52. Of the included patients, 16 (17.2%) were smokers, 12 (12.9%) were obese, 20 (21.5%) were affected by diabetes, and 56 (60.2%) by hypertension. 24 patients (25.8%) underwent previous abdominal surgery.

Intraoperative data are reported in **Table 2**. Of the included procedures, 62 (66.6%) were laparoscopic and 31 (33.4%) robotic. 41 were right hemicolectomy (44.1%), 24 (25.8%) left hemicolectomy, 23 (24.7%) were rectal anterior resection (with or without protective loop ileostomy), 4 (4.3%) splenic flexure resection, and 1 (1.1%) was a segmental resection of the transverse colon. Intraoperative complications included 3 intraoperative bleeding, with no conversion needed. After the injection of the ICG, no adverse events were registered.

Visible fluorescence was detected in 100% of the cases and the meantime from ICG injection to visible fluorescence was 25 seconds. In 7 patients (7.5%), the planned site of resection

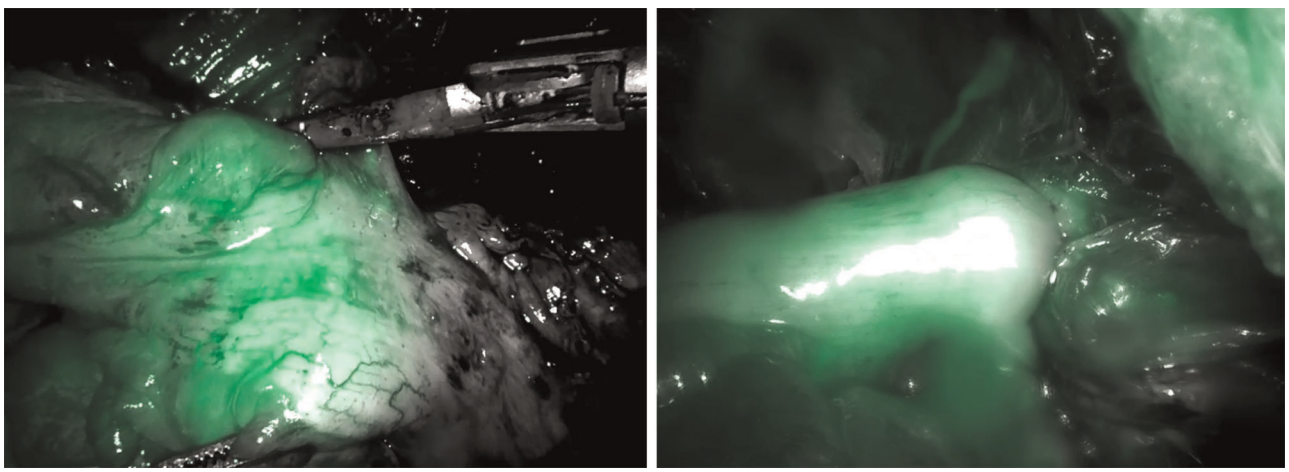

FIGURE 1 | Pre- (**A**) and post-anastomotic (**B**) application of the Indocyanine Green technology.

TABLE 1 | Demographic data of the included patients.

Patients (*N*)	**93**
Gender	
M	53 (57)
F	40 (43)
Age (years)	69.81 ± 12.06
BMI	25.81 ± 4.29
ASA score	2.54 ± 0.52
I	1 (1)
II	41 (44.1)
III	51 (54.9)
Smokers	16 (17.2)
Comorbidity	
Hypertension	56 (60.2)
Diabetes	20 (21.5)
Obesity	12 (12.9)
Previous abdominal intervention	24 (25.8)

Categorical variables are expressed as number and (percentage); continuous variables are expressed as mean ± standard deviation (SD). BMI, Body Mass Index.

TABLE 2 | Intraoperative data.

Intraoperative data	***N***
Surgical technique	
Laparoscopic	62 (66.6)
Robotic	31 (33.4)
Type of resection	
Right hemicolectomy	41 (44.1)
Left hemicolectomy	25 (25.8)
Rectal anterior resection	23 (24.7)
Splenic flexure resection	4 (4.3)
Transverse colon resection	1 (1.1)
Intraoperative complications	3
Intraoperative bleeding	3 (3.2)
Conversion	0
ICG characteristics	
Detection	93 (100)
Change in planned resection	7 (7.5)
Extension of the modified surgical resection	2.2 ± 0.62

Categorical variables are expressed as number and (percentage). Continuous variables are expressed as means ± standard variation (SD). ICG, Indocyanine Green.

was changed due to inadequate perfusion at NIR/ICG system. The mean extension of the surgical resection in these 7 patients was 2.2 ± 0.62.

After performing the anastomosis, the NIR/ICG system detected no cases of inadequate perfusion in the performed anastomoses.

Postoperative complications are summarized in **Table 3**. Anastomotic leakage occurred in 2 patients (2.1%), in which a protective loop ileostomy was performed. Other complications included 8 postoperative bleedings (8.6%), which required blood transfusion, and 1 pulmonary thromboembolism, which required implementation of anticoagulant therapy. Postoperative complications are defined according to the Clavien–Dindo classification, which consists of five severity grades. Grade 1 includes minor postoperative complications, not requiring therapy and none of the patients enrolled in the study is included in this group. Grade 2 complications require pharmacological treatment and eight patients with intra-abdominal bleeding are included in this group. Grade 3 complications, requiring surgical or radiological intervention, are recorded in 2 patients with anastomotic leakage, while Grade 4 complications, requiring an intensive care management for single or multiorgan disfunction, are recorded in 1 patient with pulmonary thromboembolism. Grade 5 indicates the death of the patient and it did not occur in any patients enrolled in the study (10).

Table 4 reported results classifying patients according to precise categories: sex, age, obesity, defined as BMI > 30, presence of diabetes, hypertension, and previous abdominal intervention. For each category, the surgical technique, intraoperative complications, postoperative complications, and ICG detection were reported.

Table 5 showed the results of the multivariate analysis. Specifically, none of the patients' characteristics or the adoption of robotic or laparoscopic approaches significantly impacted on the rate of anastomotic leakage and bleeding.

TABLE 3 | Postoperative complications.

Postoperative complications	*N*
Clavien–Dindo Classification	
I	0
II	8 (8.6)
Intra-abdominal bleeding	8 (8.6)
III	
Anastomotic leakage	2 (2.1)
IV	1 (1.1)
Pulmonary thromboembolism	1 (1.1)
V	0

Categorical variables are expressed as number and (percentage).

DISCUSSION

Although the benefits of the minimally invasive surgery in the treatment of the colorectal pathologies are well known (11–15), anastomotic leakage (AL) remains one of the most common complications in colorectal surgery. It increases morbidity and mortality, healthcare costs, and worsening long-term oncological outcomes. The risk factors for AL include: preoperative findings, such as tumor size and stage (16, 17), radiation, chemotherapy, male sex (18), nutrition (17), and comorbid condition such as obesity (19, 20), diabetes mellitus, cardiovascular disease; intraoperative factors, including the state of bowel perfusion, the level and the tension of anastomosis (21, 22), blood loss and operation time (16, 19, 23, 24); postoperative factors, such as the presence of diverting stoma (21), placement of abdominal drainage tube (16), and changes of intestinal microbes (25). Malignant involvement of local mesenteric lymph nodes could lead to mesenteric lymphadenopathy and increase the risk of complications, including AL, as reported also for several types of tumors (26).

TABLE 4 | Surgical technique, complications, and ICG detection according to patient categories.

	N	Laparoscopic surgery	Robotic surgery	Intraoperative complications	Postoperative complications	ICG detection
Male	53	37 (70%)	16 (30%)	3 (5.7%)	9 (17%)	53 (100%)
Female	40	25 (62.5%)	15 (37.5%)	0 (0%)	2 (5%)	40 (100%)
Age >60 y.o.	73	49 (67.1%)	24 (32.9%)	3 (4.1%)	8 (11%)	73 (100%)
Age >60 y.o.	20	13 (65%)	7 (35%)	0 (0%)	3 (15%)	20 (100%)
Obesity	12	8 (66.7%)	4 (33.3%)	0 (0%)	1 (8.3%)	12 (100%)
No obesity	81	54 (66.7%)	27 (33.3%)	3 (3.7%)	10 (12.3%)	81 (100%)
Diabetes	20	17 (85%)	3 (15%)	0 (0%)	3 (15%)	20 (100%)
No Diabetes	73	45 (61.6%)	28 (38.4%)	3 (4.1%)	8 (11%)	73 (100%)
Hypertension	56	33 (58.9%)	23 (41.1%)	2 (3.6%)	9 (16.1%)	56 (100%)
No hypertension	37	29 (78.4%)	8 (21.6%)	1 (2.7%)	2 (5.4%)	37 (100%)
Previous abdominal intervention	24	15 (62.5%)	9 (37.5%)	1 (4.2%)	3 (12.5%)	24 (100%)
No previous abdominal intervention	69	47 (68.1%)	22 (31.9%)	2 (2.9%)	8 (11.6%)	69 (100%)

Categorical variables are expressed as number and (percentage). ICG: Indocyanine Green; y.o: years old.

TABLE 5 | Results of the multivariate analysis.

Characteristics	Leakage OR and (95% CI)	Leakage *p*-value	Bleeding OR and (95% CI)	Bleeding *p*-value
Gender	0.825 (0.037–18.416)	0.903	1.467 (0.312–6.903)	0.628
Age	0.942 (0.820–1.081)	0.396	1.002 (0.929–1.080)	0.963
BMI	1.214 (0.713–2.066)	0.475	0.966 (0.821–1.136)	0.675
Diabetes	4.889 (0.11–216.793)	0.412	0.983 (0.154–6.271)	0.986
Hypertension	0.802 (0.031–20.704)	0.894	0.843 (0.167–4.252)	0.836
ASA Score	2.610 (0.101–67.395)	0.563	0.535 (0.081–3.532)	0.516
Robotic/laparoscopic intervention	0.842 (0.070–10.186)	0.892	0.814 (0.237–2.801)	0.744

The surgical technique and the state of perfusion are known to be important factors for the occurrence of AL. For years, anastomotic blood perfusion is assessed by the surgeons with visual evaluation of the resection margins, even if it has been reported to be a subjective analysis. In the last years, several studies have suggested that NIR has emerged as a promising method for a more accurate assessment of tissue perfusion during colorectal surgery, following intravenous infusion of indocyanine green (ICG).

ICG is a tricarbocyanine compound with a molecular mass of 776 Da, soluble in water. After its intravenous injection, ICG is quickly fixed to plasmatic proteins and, from the blood circulation, is carried to the liver, where ICG is extracted unchanged. In the case of extravenous injection, ICG is found in macrophages located in lymphatic vessels and lymph nodes.

ICG is captured by a system that activates its fluorescence with the light emitted by a led. Once excited, ICG sends fluorescent signals that have the ability to cross about 10 mm of the human soft tissue. From the intravenous injection, the spread of ICG to peripheral vessels is very rapid, in terms of few seconds. The reduction of the blood flow in a tissue leads to a decrease in ICG fluorescence emission. The evaluation of blood perfusion using ICG fluorescence imaging is applied not only to colorectal resection but also to breast reconstruction and coronary artery bypass grafting.

Several studies have reported the efficacy and the feasibility of the ICG injection in patients who underwent different surgical interventions under election for colorectal cancer (1, 27–33).

Impellizzeri et al. (1) showed that the intraoperative use of NIR/ICG for evaluation of anastomosis perfusion was safe for colorectal surgery and it significantly reduces the AL incidence. They conducted a retrospective study including 196 procedures of which 98 were without the use of ICG imaging and 98 were with the use of ICG imaging. In the first group, six patients developed AL, in the second no one. Similar encouraging results have been shown by other studies. Boni et al. (27) and Jafari et al. (28) conducted two case-control analyses, showing that the use of NIR/ICG for low anterior rectal resections, where the risk of AL is higher than in other large intestinal resection, demonstrated inadequate blood perfusion on the anastomosis site in 5%–19% of cases, thus the colonic transection point was changed, and it was associated with a reduction in AL rate (5%–12%), in comparison to the control group. The use of NIR/ICG in right and left hemicolectomy, segmental resection and anterior rectal resection reported a change of section line in 3.7%–7.9% of cases following NIR/ICG, with an AL incidence of 0.9%–1.4% (34, 35). Morales-Conde et al. (29), in their study, enrolled 192 patients who underwent different colorectal surgical procedures to evaluate in which one fluorescence angiography with indocyanine green (ICG-FA) was more effective in the anastomosis assessment, changing the section line level. The most significant value was observed in left hemicolectomy (25.9%), followed by anterior rectal resection (25.7%), segmental resection of the splenic flexure (11.1%), and right hemicolectomy (6%). Hasegawa et al. (2) conducted a retrospective study on 844 patients who underwent laparoscopic sphincter-sparing surgery: among them, 141 patients underwent ICG-FA to identify AL, and they were compared to 703 patients in whom ICG-FA was not performed. The incidence of AL was 2.8% in the first group and 12.4% in the second one. Also, Ishii et al. (31) evaluated the role of ICG-FA in their retrospective analysis, including 488 patients with colorectal cancer who underwent surgical intervention. ICG-FA was performed in 233 patients and they showed that the incidence of AL was no significantly different between the two groups in patients with colon cancer, while, in patients with rectal tumor, the incidence of AL was lower in the ICG group than in the no-ICG group (3.5% vs 10.5%). The retrospective case–control study by Brescia et al. (32) confirmed that the use of ICG-FA in patients managed with ERAS perioperative protocol was feasible, safe, and reduced the anastomotic leakage. They enrolled 182 patients who underwent laparoscopic colorectal surgery and divided them into two groups: a first group (A) including 107 patients managed with ERAS perioperative protocol and a second group (B) including 75 patients managed not only with ERAS pathway but also with the use of ICG-FA. 6 (5.6%) clinically relevant AL occurred in group A while there was none in group B. In a retrospective study, Kin et al. (33) evaluated the use of ICG-FA for the assessment of anastomosis perfusion in patients underwent colorectal surgery, but they did not find any advantage from the use of NIR/ICG, showing that the pelvic radiation therapy and the anastomosis proximity from anal verge were independent predictors of AL. However, they evaluated with NIR/ICG only the proximal point of transection. Thus, we believe that to reduce the AL rate, it is important to evaluate with NIR/ICG the perfusion of both the transection point and of the anastomosis once completed.

However, there is no unified system for the quantitative analysis of the fluorescence signal, thus it is not possible to

reproduce and compare results from various studies. Moreover, there are some technical aspects of fluorescence imaging that we have to consider. Firstly, fluorescence intensity depends on the distance between the emission source and the target tissue. Moreover, ICG circulates dynamically in the tissues according to perfusion and this often leads to an underestimation of ischemic zones. Actually, few studies regarding the quantitative evaluation of perfusion in the colorectal anastomotic site are reported in literature. One of them is the study by Amagai et al. (36), where authors, in the evaluation of intestinal perfusion during colorectal surgery, considered four areas of interest: two proximal intestinal areas, one where the fluorescence was higher (proximal-high) and the other where it was lower (proximal-low), and two distal intestinal areas, one where the fluorescence was higher (distal-high) and the other where it was lower (distal-low). In each area, they considered the time from the intravenous injection of ICG to the maximum fluorescence (T_{max}) and the time from the start of dyeing to the T_{max}, which is defined as ΔT, and they found a correlation between T_{max} e ΔT. Wada et al. (37) showed a correlation between the maximum fluorescence value (Fmax) and AL. On the contrary, Hayami et al. (38), analyzing Fmax data in their results, hypothesized a correlation with breath excursions, especially in minimally invasive surgery. For this reason, they considered Fmax as an unstable factor and it cannot be considered a feasible indicator of AL. Thus authors focused on the relationship between the period from the intravenous infusion of ICG to the beginning of fluorescent emission (T0) and AL and showed that patients with AL had longer T0 than those without AL. In another report, Son et al. (39) showed a correlation between time from first fluorescence increase to half of the maximum and AL and a correlation between the time ratio (time from first fluorescence increase to half of the maximum/ the time from the start of dyeing to the maximum fluorescence) and AL. D'Urso et al. (40) demonstrated that fluorescence-based enhanced reality (FLER) can be an accurate method to quantify fluorescence signal in augmented reality and to provide a feasible evaluation of intestinal perfusion.

During colorectal resections, ICG imaging also provides to facilitate vascular dissection when the vascular anatomy of tumor site is unclear and identifies the ureter to prevent iatrogenic injury. Santi et al. (41) prospectively enrolled 38 patients for a standard surgical treatment of laparoscopic colorectal resection, in six cases they used ICG imaging to identify vascular anatomy and to perform vascular dissection, in one case they used ICG imaging to identify the ureter which was tightly attached to the tumor.

In our study, we use indocyanine near-infrared fluorescence in two moments: before performing the anastomosis to control transection points and after completing the anastomotic procedure to control its perfusion. In 7.5% of the cases, the planned site of transection was changed because the demarcation line defined by NIR/ICG system was different from the point established by the surgeon's visual inspection. AL developed only in 2.1% of the cases. In conclusion, the results of this retrospective analysis suggest that the intraoperative use of NIR/ICG in colorectal surgery is safe and feasible, both before performing the anastomosis to control the site of resection than after performing the anastomosis to evaluate the perfusion of the anastomotic site, regardless of patients' characteristics and the surgical approach. Furthermore, the use of ICG did not result in allergic reactions and prolonged surgery time, and postoperative complications were not consequential to the additional technique. However, major limitations of this study have to be addressed. Being a retrospective cohort analysis, the bias related to the absence of randomization and of a control group clearly constituted a concern. For this reason, randomized prospective trials on intraoperative NIR/ICG use are necessary to confirm these data.

Therefore, despite there are several questions to be discussed and more high-quality large sample size randomized prospective trials are necessary to confirm the benefits of NIR/ICG in colorectal surgery, we believe that the assessment of an adequate vascularization by the use of NIR/ICG should be considered a key point to reduce the incidence of AL.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants, in accordance with the local legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

MF: conception, design, interpretation of the data and drafting of the article; MM, CA, VS, AP, DA, MA, SC, CG, MR, DS, DN, GN, DSG, SG: acquisition, analysis, and interpretation of the data; MM and DPGD: interpretation of the data and critical revisions; MM and DPGD: critical revisions and final approval. All authors contributed to the article and approved the submitted version.

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Correlation Between Poor Defecation Habits and Postoperative Hemorrhoid Recurrence

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Background: The relationship between hemorrhoid recurrence and poor defecation habits is poorly understood. This study aimed to analyze the effects of poor defecation habits on postoperative hemorrhoid recurrence.

Materials and Method: We performed a retrospective study on 1,162 consecutive patients who underwent a surgical procedure for hemorrhoids at the Sixth Affiliated Hospital of Sun Yat-Sen University from December 2016 to May 2020. All patients were followed for 12 months post-operatively. Patients were monitored for disease recurrence. Patient defecation habits were assessed using an obstructive defecation syndrome (ODS) score.

Results: Patients with a score of 0–4 had a mild defecation disorder, 5–8 a moderate defecation disorder, and 9 or more ODS. Of the 1,162 patients, 1,144 (98.45%) had a mild defecation disorder, 13 (1.12%) had a moderate defecation disorder, and 9 (0.43%) had ODS. Older patients were significantly more likely to have worse defecation habits ($P < 0.001$). A higher ODS score correlated with a higher maximum anal squeeze pressure ($P = 0.07$) and a more severe inability for the anus to relax during simulated evacuation ($P = 0.002$). The maximum rectum threshold was also found to be the highest in ODS patients ($P = 0.010$). The proportion of Procedure for prolapsing hemorrhoids (PPH) was the highest in the moderate defecation disorder group (53.85), followed by the ODS group (40.00) and the mild defecation disorder group ($P = 0.023$). Recurrence occurred in 5.51% of patients in the mild defecation disorder group, 38.46% of the moderate defecation disorder group, and 60% of the ODS group ($P < 0.001$). Multivariate analysis confirmed a higher ODS score ($P < 0.001$) was an independent predictor of recurrence. Furthermore, patients who occasionally exercised ($P = 0.01$) and patients who exercised regularly ($P = 0.021$) were less likely to have a recurrence.

Conclusion: Patients with unresolved defecation disorders are more likely to have their hemorrhoids recur and are unlikely to be satisfied with surgical management.

Keywords: defecation habit, obstructive defecation syndrome, hemorrhoid, recurrence, risk factors

INTRODUCTION

Hemorrhoids are the most common anorectal disease and have a considerable impact on health care expenditure (1). The prevalence of hemorrhoids in the general population is as high as 50% (2), affecting a considerable proportion of adults of all ages and genders (3). Current causes of hemorrhoids include chronic straining during defecation, lack of physical exercise, diarrhea, pregnancy, and inadequate fiber intake (4). There is a close link between hemorrhoids and constipation (5, 6). Hard or large stools and exertion during defecation are associated with an increased prevalence of hemorrhoids. Bowel habit regulation is essential to managing hemorrhoids (7–9). For instance, oral fiber is adjusted for constipation symptoms (5, 10) and flavonoids decrease the risk and recurrence rate of hemorrhoids (11).

Patients diagnosed with obstructive defecation syndrome (ODS) usually have long-standing constipation. The surgical treatment of defecation disorders is still very controversial, with unacceptable effects on patient quality of life (12). Hemorrhoid management is usually conservative, and only 20% of patients require surgical management (13). Similarly, before developing hemorrhoidal symptoms patients usually suffer from difficulty defecating (14). Many patients undergo surgery for this, often without treating the underlying cause of their symptoms. Unsurprisingly, the postoperative recurrence rate of hemorrhoids is still high (15, 16), with multiple studies attributing recurrence to surgical technique (17, 18).

Although surgical technique is widely accepted as the main reason for hemorrhoid treatment failure, the relationship between poor defecation habits and hemorrhoid recurrence is poorly understood. This study aimed to analyze the effects of poor defecation habits on postoperative hemorrhoid recurrence. We hypothesized that patients with more severe defecation disorders would be more likely to see their hemorrhoids recur following surgery. Patients with a severe defecation disorder are less likely to be satisfied with their surgical outcome regardless of the method used to perform the surgery.

MATERIALS AND METHODS

Study Design and Participant Selection

The unit protocol and study format were approved by the Sixth Affiliated Hospital of Sun Yat-Sen University (Approval code: 2022ZSLYEC-096). This retrospective study was performed on 1,162 consecutive patients who underwent a surgical procedure for hemorrhoids from December 2016 to May 2020 (**Figure 1**). All patients were followed for 12 months post-operatively. Inclusion criteria were age > 18 and ≤80 years old, a clinical diagnosis of hemorrhoids, and surgery performed by a surgeon with at least 5 years of experience with all three common surgical techniques. Exclusion criteria were previous hemorrhoidal surgical management, malignancies, fecal incontinence, pregnancy, and severe psychiatric disorders.

Preoperative Preparation, Surgical Methods

All patients underwent routine pre-operative bloodwork, electrocardiograms, and chest X-rays to rule out surgical contraindications. They also underwent a pre-operative colonoscopy to exclude more serious diseases such as

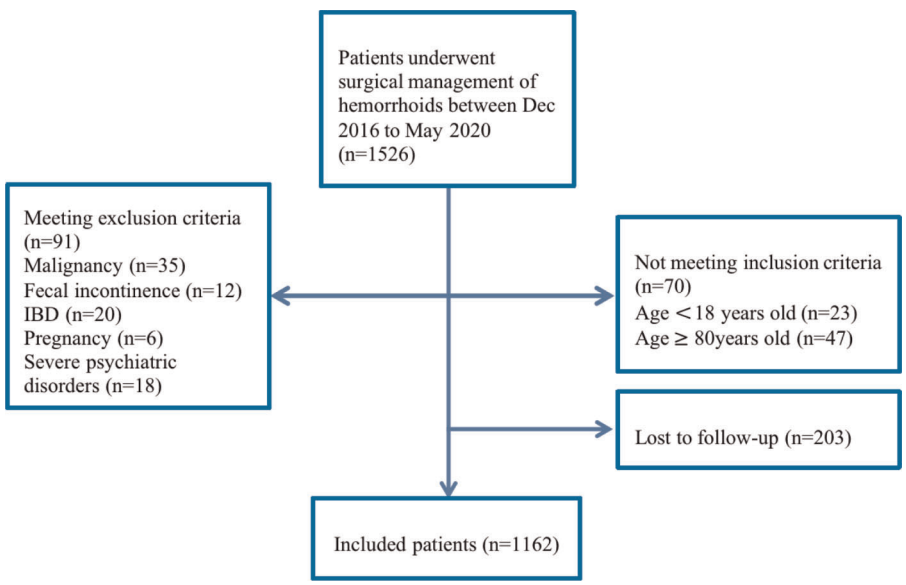

FIGURE 1 | Flow diagram study sample selection.

inflammatory bowel disease, proliferative polyps, and colorectal cancer. All patients underwent pre-operative anorectal manometry, which was preceded by a phosphate enema. Anorectal manometry was performed with patients in the left lateral position with their hips flexed. Anorectal manometric parameters such as anorectal pressure, rectal sensation, and neural reflexes were recorded. All patients received a pre-operative bowel enema the night before surgery, and a prophylactic antibiotic was injected 30 min before the surgical procedure was started. Most patients had spinal anesthesia and were placed in the jackknife or left lateral position. Tape was attached to both sides of the buttocks to expose the anus.Some other patients underwent local anesthesia, because these patients were able to tolerate the relatively simple procedure under local anesthesia. General anesthesia was performed in some patients because of lumbar lesions, coagulopathy, or psychosomatic disorders.

Surgical Modalities

Many patients had a combination of surgical therapies. The Goligher classification is the most widely used classification for HD. Surgical management was performed based on the Goligher Classification of hemorrhoids (19), the type of health insurance patient's choice. Patients with bleeding hemorrhoids underwent either Hemorrhoid injection sclerotherapy (IS)or rubber band ligation (RBL), which was performed either in the treatment room using 1% lidocaine as a local anesthetic or in the operation theater under spinal anesthesia. IS and RBL were used for the treatment of I, II, and III-degree HD. A recent multicentre study showed that Sclerotherapy with 3% polidocanol foam is a safe, effective, painless, repeatable and low-cost procedure in patients with bleeding hemorrhoids, especially in the treatment of 2nd-degree hemorrhoids (20). After a thorough digital rectal examination (DRE), an anoscope was inserted to fully expose the hemorrhoids. Sclerotherapy was mainly performed if the patient suffered from hemorrhoidal bleeding. It was done using "Shaobei" (Taifeng, Henan, China) and lidocaine in a 1:1 ratio. The mixture was injected into the submucosa of each hemorrhoid tissue, paying attention to avoid any blood vessels. The total injection volume was generally less than 20 mL. Rubber band ligation was used on patients with bleeding hemorrhoids. It was performed using a ligation device to ligate the hemorrhoid, bleeding point, or tissue superior to the hemorrhoid. There were generally less than four ligation sites. Procedure for prolapsing hemorrhoids (PPH) and the Milligan-Morgan hemorrhoidectomy (MMH) was indication for symptomatic III- and IV-degree HD. Preoperative clinical evaluation is essential for HD patient treatment and outcome and classification systems are useful for the therapeutic choice (21). Our patients with obvious protrusions underwent PPH or MMH, which were usually performed under spinal anesthesia. Endotracheal anesthesia was used in patients who had any contraindications to spinal anesthesia, such as a coagulopathy. The patient was usually in the prone jackknife position or the lithotomy position during surgery. After a thorough DRE and insertion of an anal speculum, the surgeon identified the hemorrhoids that were to be excised. PPH was performed as previously described (22). For MMH, tissue forceps were used to grasp and lift the external hemorrhoid towards the surgeon at the mucocutaneous junction. Monopolar electrocautery or a pair of scissors were used to make a V-shaped incision in the skin around the base of hemorrhoid. The dissection continued into the submucosal space to peel the entire hemorrhoid from its bed. The pedicle was ligated, and the distal part of the hemorrhoid was excised. All of the other hemorrhoids were similarly treated, leaving a skin bridge in-between to avoid stenosis. Large wounds were closed and sutured with 3-0 absorbable thread for aesthetic reasons. An absorbable sponge dressing was placed in the anal canal when the procedure was completed. Post-operatively, the patient was advised to take an adequate amount of dietary fiber and water.

Follow-Up

All cases were followed for at least 12 months from the date of surgery for any disease recurrence. Recurrence was defined as unresolved bleeding or prolapse at the site where surgical management was performed. It is difficult for patients to accurately describe their defecation habits. Given the anatomic, functional, and sometimes psychological factors involved in defecation there may be a variety of clinical presentations of ODS. We therefore used the ODS severity index to evaluate patients' defecation habits (12). The ODS score (23, 24) was chosen to assess these patients' defecation habits (**Table 1**). A score of 0–4 was classified as a mild defecation disorder, 5–8 as a moderate defecation disorder, and 9 or more as ODS.

Statistical Methods

The statistical analyses were performed using SPSS 26.0 (Armonk, NY, USA). All tests were two-way, and $P < 0.05$ was considered statistically significant. Mean ± standard deviation was used to describe continuous variables, frequency and frequency were used to describe categorical variables, and the analysis of variance or chi-square tests were used to identify statistically significant differences between groups. Univariate logistic regressions were used to identify correlations between various factors and hemorrhoid recurrence. The univariate results were included in a multivariate logistic regression model for further analysis, and stepwise regression was used to screen variables.

RESULTS

Patient Demographics

A total of 1,162 consecutive patients underwent a hemorrhoidectomy at our institution and followed up for at least 12 months. Of the 1,162 patients, 1,144 (98.45%) had a mild defecation disorder, 13 (1.12%) had a moderate defecation disorder and 9 (0.43%) had ODS. Older age was significantly correlated with worsen defecation habits ($P < 0.001$) (**Table 2**).

TABLE 1 | Obstructed defecation score.

Frequency of defecation	
1–2 defecations every 1–2 days	0
2 defecations/week or 3 defecations or attempts/day	1
1 defecation/week or 4 defecations or attempts/day	2
<1 defecation/week or >4 defecations or attempts/day	3
Intensity of straining	
No or light	0
Moderate	1
Intense	2
Duration of straining	
Short	1
Prolonged or many times	2
Incomplete evacuation	
Never	0
≤1 time/week	1
2 times/week	2
>2 times/week	3
Rectoperineal discomfort	
Never	0
≤1 time/week	1
2 times/week	2
>2 times/week	3
Reduction of activities	
None	0
<25%	2
25%–50%	4
>50%	6
Laxatives	
Never	0
<25% of defecations	1
25%–50% of defecations	3
>50% of defecations	5
Always	7
Enemas	
Never	0
<25% of defecations	1
25%–50% of defecations	3
>50% of defecations	5
Always	7
Digitation	
Never	0
<25% of defecations	1
25%–50% of defecations	3
>50% of defecations	5
Always	7

TABLE 2 | Patient demographics.

Variable	Mild defecation disorder	Moderate defecation disorder	ODS	Statistic	*P*
Number of cases	1144 (98.45)	13 (1.12)	5 (0.43)	–	–
Gender					
Male	533 (46.59)	6 (46.15)	1 (20.00)	1.303	0.630
Female	611 (53.41)	7 (53.85)	4 (80.00)		
Age (years)	40.91 ± 12.25	56.92 ± 17.58	58.20 ± 24.34	15.510	**<0.001**
Height (m)	1.65 ± 0.08	1.65 ± 0.07	1.58 ± 0.06	1.784	0.168
Weight (kg)	51.05 ± 11.32	57.23 ± 8.50	55.30 ± 6.20	1.374	0.253
BMI (kg/m^2)	22.46 ± 3.38	21.05 ± 3.05	22.33 ± 3.46	1.115	0.328
Smoking habit					
No	963 (84.18)	9 (69.23)	5 (100.00)	2.586	0.251
Yes	181 (15.82)	4 (30.77)	0 (0.00)		
Alcohol consumption					
Rarely	1005 (87.85)	13 (100.00)	5 (100.00)	1.250	0.494
Often	139 (12.15)	0 (0.00)	0 (0.00)		
Physical activity					
Rarely	375 (32.78)	4 (30.77)	2 (40.00)	3.823	0.408
Seldom	555 (48.51)	4 (30.77)	2 (40.00)		
Regular exercise	214 (18.71)	5 (38.46)	1 (20.00)		
Average daily working hours					
<5 h	226 (19.45)	4 (30.77)	2 (40.00)	2.916	0.554
5–8 h	610 (53.32)	7 (53.85)	2 (40.00)		
>8 h	308 (26.92)	2 (15.38)	1 (20.00)		
Taste preference					
Not partial	487 (42.57)	3 (76.92)	0 (0.00)	5.348	0.054
Partial addiction	657 (57.43)	10 (23.08)	5 (100.00)		
Amount of drinking water					
≤2,000 mL/day	566 (49.48)	6 (46.15)	3 (60.00)	0.377	0.933
>2,000 mL/day	578 (50.52)	7 (53.85)	2 (40.00)		
Dietary condition					
Low fiber diet	765 (66.87)	8 (61.54)	4 (80.00)	0.540	0.847
High fiber diet	379 (33.13)	5 (38.46)	1 (20.00)		

The bold values has Statistically significant P value.

Pre-Operative Anorectal Manometry

We aimed to understand the effects of poor defecation habits on pre-operative anorectal function (**Table 3**). A higher ODS score correlated with a higher maximum anal squeeze pressure ($P = 0.07$) and a more severe inability for the anus to relax during simulated evacuation ($P = 0.002$). ODS patients also had the highest maximum rectum threshold ($P = 0.010$).

Goligher Classification and Surgical treatment

1 RBL procedure and 11 IS procedures were done spinal anesthesia due to lumbar lesions, coagulopathy, or psychosomatic disorders. 5 MMH procedures were performed under local anesthesia because these patients were able to tolerate the relatively simple procedure under local anesthesia. Endotracheal intubation was performed in 12 combined PPH and MMH procedures, 9 combined MMH and RBL procedures, and 5 MMH procedure because of lumbar lesions, coagulopathy, or psychosomatic disorders. The other 1,119 patients routinely received spinal anesthesia.

Most of the low defecation disorder patients underwent an MMH procedure (77.54%) while sclerotherapy was least utilized (7.97%). Only the use of PPH was statistically significant between groups. The proportion of PPH was the highest in the moderate defecation disorder group (53.85%), followed by the ODS group (40.00%) and the mild defecation disorder group ($P = 0.023$). The proportion of single operation and combined operation was 185 (15.92%) and 977 (84.08%) respectively. The proportion of single operation and compound operation in each group of defecation disorder was almost the same. ($P = 0.876$). Results are shown in **Table 4**. There was no statistical significance observed on the use of single or combined surgeries ($P = 1.000$). No statistical significance was observed among the four surgical methods _ PPH ($P = 0.943$), MMH ($P = 0.649$), RBL ($P = 0.499$), IS ($P = 0.332$). There was also no statistical significance observed between Goligher grade and recurrence rates ($P = 0.944$) (**Table 5**).

TABLE 3 | Physiological and biochemical indices.

Variable	Mild defecation disorder	Moderate defecation disorder	ODS	F	P
Albumin g/L	43.46 ± 5.72	42.97 ± 2.71	42.68 ± 2.11	0.091	0.913
Hemoglobin g/L	128.67 ± 25.59	126.32 ± 24.75	111.90 ± 19.13	1.123	0.326
Platelets (109L)	248.97 ± 66.55	226.71 ± 63.46	231.52 ± 107.71	0.882	0.414
Mean anal resting pressure (MERP) (mmHg)	90.97 ± 24.49	82.10 ± 14.79	108.28 ± 49.36	2.092	0.124
Length of the anal canal (cm)	3.61 ± 2.26	3.70 ± 0.33	3.44 ± 0.60	0.025	0.975
Maximum anal squeeze pressure (MSP) (mmHg)	210.08 ± 63.01	240.75 ± 94.91	285.60 ± 78.08	4.991	**0.007**
Anal relaxation rate (ARR) during simulated evacuation (%)	28.09 ± 17.40	25.92 ± 17.82	0.20 ± 0.18	6.505	**0.002**
First sensation (FST) (mL)	39.62 ± 15.21	44.62 ± 12.66	50.00 ± 10.00	1.850	0.158
First defecation threshold (mL)	57.87 ± 21.28	60.77 ± 18.47	68.00 ± 21.68	0.682	0.506
Maximum tolerable threshold of the rectum (mL)	115.61 ± 31.53	110.77 ± 26.91	158.00 ± 47.65	4.656	**0.010**

The bold values has Statistically significant P value.

Unresolved Poor Defecation Habits and Hemorrhoids Recurrence

We assessed the impact of an unresolved defecation habit on hemorrhoidal recurrence using linear regression (**Table 6**). Recurrence occurred in 5.51% of the mild defecation disorder group, 38.46% of the moderate defecation disorder group, and 60% of the ODS group ($P < 0.001$).

Analysis of Factors Influencing Hemorrhoids Recurrence

We aimed to identify factors associated with hemorrhoid recurrence. In a univariate analysis (**Table 7**), ODS score ($P < 0.001$), physical activity ($P = 0.001$), and BMI ($P = 0.014$)) were significantly associated with hemorrhoid recurrence. There was no statistical significance observed between recurrence and surgical modality ($P = 0.919$). Multivariate analysis (**Table 8**) confirmed that ODS score (OR = 1.380, $P < 0.001$) was independent risk factor for hemorrhoid recurrence. Every increment in the ODS score resulted in an increased risk of

TABLE 4 | Correlation between surgical modality and defecation habits.

Surgical modality	Total number of cases	Mild defecation disorder	Moderate defecation disorder	ODS	χ^2	P
PPH						
No	896 (77.11)	887 (77.53)	6 (42.15)	3 (60.00)	7.442	0.023
Yes	266 (22.89)	257 (22.47)	7 (53.85)	2 (40.00)		
M-M						
No	261 (22.46)	257 (22.46)	3 (23.08)	1 (20.00)	0.185	1.000
Yes	901 (77.54)	887 (77.54)	10 (76.92)	4 (80.00)		
RBL						
No	391 (33.65)	381 (33.30)	8 (61.54)	2 (40.00)	4.626	0.085
Yes	771 (66.35)	763 (66.70)	5 (38.46)	3 (60.00)		
IS						
No	1081 (93.03)	1064 (93.01)	12 (92.31)	5 (100.00)	0.279	0.730
Yes	81 (7.97)	80 (6.99)	1 (7.69)	0 (0.00)		
Surgical modality						
Only one	185 (15.92)	182 (15.91)	2 (15.38)	1 (20.00)	#	0.876
Combined	977 (84.08)	962 (84.09)	11 (84.62)	4 (80.00)		

hemorrhoid recurrence of 1.38 times. Interestingly, the recurrence risk of patients who exercised occasionally was 0.445 and that of for those who exercised regularly was 0.337, implying that physical activity has a protective effect against hemorrhoid recurrence.

DISCUSSION

The primary aim of this study was to understand if patients with unresolved poor defecation habits are at a higher risk of recurrence following hemorrhoidectomy. Our results show 1,144 (98.45%) had a mild defecation disorder, 13 (1.12%) had a moderate defecation disorder, and 9 (0.43%) had ODS. Older patients were significantly more likely to have worse defecation habits ($P < 0.001$). A higher ODS score correlated with a higher maximum anal squeeze pressure ($P = 0.07$) and a more severe inability for the anus to relax during simulated evacuation ($P = 0.002$). The maximum rectum threshold was also found to be the highest in ODS patients ($P = 0.010$). The proportion of (PPH) was the highest in the moderate defecation disorder group (53.85), followed by the ODS group (40.00) and the mild defecation disorder group ($P = 0.023$). Recurrence occurred in 5.51% of patients in the mild defecation disorder group, 38.46% of the moderate defecation disorder group, and 60% of the ODS group ($P < 0.001$). Multivariate analysis confirmed a higher ODS score ($P < 0.001$) was an independent predictor of recurrence. Furthermore, patients who occasionally exercised ($P = 0.01$) and patients who exercised regularly ($P = 0.021$) were less likely to have a recurrence.

TABLE 5 | Effects of surgical modality and goligher grade on hemorrhoid recurrence rates.

	All $N = 1162$	No Recurrence $N = 1091$	Recurrence $N = 71$	*P*
PPH				0.943
No	896 (77.11%)	842 (77.18%)	54 (76.06%)	
Yes	266 (22.89%)	249 (22.82%)	17 (23.94%)	
M-M				0.649
No	261 (22.46%)	243 (22.27%)	18 (25.35%)	
Yes	901 (77.54%)	848 (77.73%)	53 (74.65%)	
RBL				0.499
No	391 (33.65%)	364 (33.36%)	27 (38.03%)	
Yes	771 (66.35%)	727 (66.64%)	44 (61.97%)	
IS				0.332
No	1081 (93.03%)	1017 (93.22%)	64 (90.14%)	
Yes	81 (6.97%)	74 (6.78%)	7 (9.86%)	
Surgical modality				1.000
Only one	185 (15.92%)	174 (15.95%)	11 (15.49%)	
Combined	977 (84.08%)	917 (84.05%)	60 (84.51%)	
Goligher grade				0.944
1	42 (3.61%)	39 (3.57%)	3 (4.23%)	
2	251 (21.60%)	237 (21.72%)	14 (19.72%)	
3	675 (58.09%)	633 (58.02%)	42 (59.15%)	
4	194 (16.70%)	182 (16.68%)	12 (16.90%)	

The pathophysiology of hemorrhoids is not fully understood. A recent genome-wide association study (GWAS) analysis of 944,133 individuals found that hemorrhoids, which is a partially inherited disease, could be affected by functional gastrointestinal diseases (FGID) through genotype-driven modulation of Caja interstitial cell (ICC) function (25). ICCs are present throughout the human gastrointestinal tract and help in normal intestinal function and peristalsis. Few studies have shown differences in ICC distribution between ODS and non-ODS patients (26, 27), implying that patients with FGID are more likely to suffer from hemorrhoids.

It is difficult for patients to accurately describe their defecation habits. Given the anatomic, functional, and sometimes psychological factors involved in defecation there may be a variety of clinical presentations of ODS. It is therefore recommended that the ODS severity index is used evaluate patient defecation habits (12). ODS score describes a series of complex symptoms such as repeated straining, difficulty evacuating, using laxatives or an enema to defecate, using digital means, spending an excessive amount of time on the toilet during defecation, feelings of incomplete evacuation, perineal pain, and rectal discomfort (23, 24). Our results show that the defecation disorder score is an independent predictor for hemorrhoidal recurrence. Every one-point increment increased the risk of hemorrhoid recurrence by 1.38 times ($P = <0.001$). Furthermore, risk of hemorrhoid recurrence in the moderate defecation disorder group was 10.72 times higher, and 25.74 higher in the ODS group ($P < 0.001$). According to previous literature reports, key components of the pathogenesis and aggravation of hemorrhoids are rectal mucosal prolapse and increased anal pressure (28). Defecation disorder and pelvic floor disease cause the disintegration of the muscle fibers of Treitz (29). Straining during defecation may lead to excessive intra-abdominal pressure, rendering defecation ineffective and therefore multiple evacuations are required. Straining also impairs venous drainage of the

TABLE 6 | Effects of poor defecation habits on hemorrhoid recurrence.

Group	Recurrence	β	Standard Error	Wald	*P*	OR (95% CI)	*P*-trend
Mild defecation disorder	63 (5.51)	–	–	–	–	1.00	**<0.001**
Moderate defecation disorder	5 (38.46)	2.373	0.585	16.468	**<0.001**	10.72 (3.41, 33.73)	
ODS	3 (60.00)	3.248	0.922	12.409	**<0.001**	25.74 (4.22, 156.82)	

The bold values has Statistically significant P value.

TABLE 7 | Univariate analysis for hemorrhoid recurrence.

Variable	*β*	Standard Error	Wald	*P*	OR (95%CI)
ODS score	0.431	0.073	5.873	**<0.001**	1.539 (1.338, 1.787)
Gender					
Female	–	–	–	–	1
Male	−0.369	0.252	−1.465	0.143	0.691 (0.417, 1.125)
Age (years)	−0.008	0.01	−0.759	0.448	0.992 (0.972, 1.012)
BMI (kg/m^2)	−0.102	0.042	−2.453	**0.014**	0.903 (0.83, 0.977)
Smoker					
No	–	–	–	–	1
Yes	0.104	0.328	0.318	0.751	1.11 (0.558, 2.037)
Alcohol consumption					
No	–	–	–	–	1
Yes	0.071	0.369	0.191	0.848	1.073 (0.488, 2.105)
Physical activity					
Rarely	–	–	–	–	1
Seldom	−0.925	0.268	−3.446	**0.001**	0.397 (0.231, 0.666)
Often	−1.075	0.398	−2.702	**0.007**	0.341 (0.146, 0.707)
Daily sitting habit					
<5h	–	–	–-	–	1
5–8h	0.616	0.396	1.556	0.12	1.852 (0.897, 4.328)
>8h	0.815	0.418	1.951	0.051	2.26 (1.038, 5.461)
Taste preference					
Partial	–	–	–	–	1
Specific	−0.298	0.274	−1.089	0.276	0.742 (0.441, 1.296)
Water consumption					
≤2,000 mL/day	–	–	–	–	1
>2,000 mL/day	0.2	0.246	0.811	0.417	1.221 (0.755, 1.988)
Diet					
Low fiber	–	–	–	–	1
High fiber	−0.228	0.25	−0.913	0.361	0.796 (0.49, 1.31)
Mean resting pressure of anal sphincter (mmHg)	0.003	0.005	0.532	0.594	1.003 (0.993, 1.012)
High-pressure zone (cm)	−0.072	0.092	−0.775	0.438	0.931 (0.725, 1.057)
Maximum anal sphincter pressure (mmhg)	0.001	0.002	0.774	0.439	1.001 (0.998, 1.005)
Anal relaxation rate (%)	−0.009	0.006	−1.685	0.092	0.991 (0.98, 1.002)
Initial sensory threshold (mL)	0.003	0.008	0.457	0.648	1.003 (0.988, 1.018)
Initial defecation threshold (mL)	0.009	0.005	1.827	0.068	1.009 (0.999, 1.018)
Maximum tolerance threshold (mL)	0	0.004	0	1	1.00 (0.992, 1.007)
Duration course (Months)	0.001	0.002	0.538	0.59	1.001 (0.998, 1.004)
Goligher grade					
1					1
2	−0.264		0.659	0.689	0.768 (0.237–3.44)
3	−0.148		0.620	0.812	0.863 (0.296–3.669)
4	−0.154		0.669	0.818	0.857 (0.257–3.89)
Surgical modality					
Only one	–	–	–	–	1
Combined	0.034	0.338	0.102	0.919	1.035 (0.554, 2.114)
PPH					
No	–	–	–	–	1
Yes	0.063	0.287	0.218	0.828	1.065 (0.59, 1.831)
MMH					
No	–	–	–	–	1
Yes	−0.17	0.282	−0.602	0.547	0.844 (0.494, 1.505)
RBL					
No	–	–	–	–	1
Yes	−0.203	0.253	−0.805	0.421	0.816 (0.50, 1.354)
IS					
No	–	–	–	–	1
Yes	0.408	0.416	0.98	0.327	1.503 (0.61, 3.188)

The bold values has Statistically significant P value.

hemorrhoids (30). Avoiding forced defecation has been shown to limit the prolapse of hemorrhoids (31).

We also found that physical activity has a protective effect against hemorrhoidal recurrence. Patients who exercised occasionally ($P = 0.01$) or regularly ($P = 0.021$) were less likely to have a recurrence. Mild physical activity can accelerate gastrointestinal transit and increase the stimulation of abdominal muscles, therefore aiding in the movement of stool into the rectum (32). However, high-intensity exercises can often lead to gastrointestinal distress when associated with either

TABLE 8 | Multivariate analysis of hemorrhoid recurrence.

Variable	β	Standard Error	Wald	P	OR(95% CI)
ODS score	0.322	0.089	3.605	**<0.001**	1.380 (1.157, 1.651)
BMI (kg/m^2)	−0.037	0.049	−0.762	0.446	0.963 (0.872, 1.054)
Physical activity					
Rarely	–	–	–	–	1.00
Seldom	−0.809	0.312	−2.592	**0.01**	0.445 (0.239, 0.817)
Often	−1.088	0.473	−2.302	**0.021**	0.337 (0.126, 0.814)

The bold values has Statistically significant P value.

dehydration or increased intra-abdominal pressure (33). As noted by Marco et al. (5), we recommend that hemorrhoidal patients abandon a sedentary lifestyle and practice mild exercises such as walking, swimming, and yoga. This approach can result in improved circulation, strengthen the pelvic floor muscles, improve anorectal function, and prevent a defecation disorder.

We also found that older patients were more likely to have worse defecation habits ($P < 0.001$). The physiologic changes that result from poor defecation habits are not fully understood (34). Aging is associated with a higher prevalence of constipation (35) and impaired collagen quality. The ratio of connective tissue to muscle tissue increases with age and may play a role in the development of rectal mucosal or rectal prolapse in the elderly (36). This imbalance would result in the inability of the muscles to adequately contract to support the internal hemorrhoidal plexus (37). These factors would lead to sliding of the anal cushion, relaxation of the cushion's connective tissue, and reduced venous return to the middle rectal vein and the superior rectal vein (38). A recent study (39) by Stanford Medical School showed that elderly patients had more severe prolapse symptoms than younger patients. With respect to anorectal function, we found that a higher ODS score was associated with a higher maximum anal squeeze pressure ($P = 0.07$), a more severe inability for the anus to relax during simulated evacuation ($P = 0.002$), and a higher maximum rectum threshold ($P = 0.010$). Increased maximum anal resting pressure, (40) increased internal anal sphincter activity, and a higher maximum rectum threshold (41) are common in patients with hemorrhoids and ODS.

Our results show a hemorrhoid recurrence rate of 6.11% following surgery, which is consistent with recurrence rates of 2% to 8% cited by previous clinical studies (42–44). There was no significant difference in recurrence rate based on the surgical procedure performed, which is consistent with the review by Naldini et al. (45). Patients with a moderate defecation disorder or ODS were more likely to undergo PPH. This is because these patients were more likely to have a higher degree of protrusion compared with mild defecation disorder patients.

Our findings are in line with those of a recent systematic review that reported that functional evacuation disorder, dyssynergic defecation, and abnormal balloon expulsion were more frequent in patients with hemorrhoids compared with healthy subjects ($P < 0.0001$) (46). The review concluded that it would be more effective to treat functional constipation instead of repeating RBL procedures. Pelvic floor physiotherapy was also deemed necessary to improving the long-term results of hemorrhoid treatment (14). We believe that it is necessary to evaluate the bowel habits of hemorrhoidal patients prior to surgery. We recommend performing preoperative anorectal manometry if the ODS score is 5 or more. Patients with defective anorectal function should be treated preoperatively conservatively or through biofeedback (47, 48). Patients should also be regularly followed for their symptoms. If poor defecation habits persist, defecation habit scores should be re-evaluated. Once these habits are improved, surgical management can be considered.

This study has several limitations. First, this is a retrospective study that has a small sample size of patients with a moderate defecation disorder or ODS. Prospective randomized controlled clinical trials need to be performed in the future. Secondly, we did not investigate whether there is a causal relationship or co-disease mechanism between ODS and hemorrhoids. Neural pathways and the role of the anal sphincter and pelvic floor muscles during defecation needs to be further studied. Further basic research projects on genetic and molecular mechanisms will be considered in future work.

CONCLUSION

The defecation habits of patients with hemorrhoids should be scored both perioperatively and postoperatively. They should be encouraged to normalize their defecation habit and pick the right exercise routine. A scoring system will help guide the preoperative conversation, analyze the patient's prognosis, managing the patient's post-operative expectations, and reduce hemorrhoid recurrence.

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 The Sixth Affiliated Hospital of Sun Yat-Sen University (Approval code: 2022ZSLYEC-096). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QL: Conception, data analysis, drafting the manuscript, review of the literature. RG: Conception, data acquisition,

interpretation of data, drafting the manuscript. LL: Conception, data acquisition, interpretation of data. HZ: Conception, data collection, revision. DZ: Critical revision of the manuscript and factual content. HQ: Interpretation of manuscript revision, critical revision of the statistical analysis. DR: critical revision of the manuscript and factual content. DS: Conception and design, data acquisition, critical manuscript review. All authors have agreed to the final revision of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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Effectiveness and Validation of the Italian Translation of the Low Anterior Resection Syndrome Score in an Italian High-Volume University Hospital

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Background: The low anterior resection syndrome (LARS) score is a validated questionnaire developed in Denmark to measure the severity of bowel dysfunction after low anterior resection. This retrospective study aimed to assess the effectiveness of the LARS score in the Italian language in a population of Italian patients who underwent low anterior resection for rectal cancer. The convergent and discriminative validity and the test-retest reliability of the score were investigated.

Methods: A cohort of two hundred and five patients treated with low anterior resection were enrolled in an Italian high-volume university hospital between January 2000 and April 2018. The Italian version of the LARS score (tested twice), as translated from English original version, a single question on quality of life and the EORTC QLQ-C30 questionnaire were submitted to patients.

Results: A high proportion of patients showed a perfect or moderate fit between the LARS score and QoL categories (convergent validity, $p < 0.0005$). All differences regarding the items of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) functional scales were statistically significant ($p < 0.0005$). The LARS score was able to discriminate between groups of patients who received or did not receive preoperative chemoradiotherapy ($p < 0.0005$) and those who received total or partial mesorectal excision ($p < 0.0005$). The test-retest reliability was excellent (intraclass correlation coefficient 0.96).

Conclusion: The Italian translation of the LARS score is an easy and reliable tool for assessing bowel dysfunction after low anterior resection and its routine use in clinical practice should be recommended.

Trial registration number at www.clinicaltrials.gov: NCT04406311.

Keywords: rectal cancer, low anterior resection, low anterior resection syndrome, quality of life, functional outcomes

INTRODUCTION

Colorectal cancer represents the third most common neoplasm in men (12.0%) and the second in women (11.2%) in Italy, with 43,700 new diagnoses expected in 2020 (23,400 in men and 20,300 in women) (1). The rectum is the most frequently involved site among colorectal tumours (approximately 35% of cases).

Increasing attention has been recently paid to the outcomes of surgical treatment in terms of patient anorectal function and quality of life (QoL). Currently, the majority of patients affected by rectal carcinoma undergo a sphincter-sparing procedure, avoiding a permanent colostomy.

Up to 80% of patients undergoing low anterior resection (LAR) will have at least some degree of bowel dysfunction (2–4); for this reason, the term low anterior resection syndrome (LARS) has been coined to describe this complex functional condition (3). The main symptoms included in this syndrome are as follows: incontinence of gas and/or liquid or solid stools, constipation, urgency, fragmentation and frequent bowel movements. In addition, a worsening of QoL has been observed in patients with severe LARS symptoms (5).

Due to the importance and high prevalence of this condition, the so-called LARS score has been introduced (6) to identify a reliable tool for assessing severity and determining the type of treatment (7). The score has been validated in several languages, including English (8), Chinese (9), Lithuanian (10), Swedish, Spanish, German, Danish (in a consolidated international validation) (11), Dutch (12) and many others (13, 14).

The primary aim of this study was to assess the effectiveness of the LARS score in the Italian language in a population of Italian patients who underwent LAR for rectal cancer. Moreover, the study provided the opportunity to investigate convergent and discriminatory validity and to retest the reliability of the score.

METHODS

This retrospective, observational study included rectal cancer patients treated by LAR with total mesorectal excision (TME) or partial mesorectal excision (PME) between January 2000 and April 2018. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies (15) and was approved by the local Ethical Committee (Protocol ID 3358). The present study was registered at www.clinicaltrials.gov (NCT04406311) on May 2020, when a validated Italian translation of the LARS was not yet available. All patients provided written informed consent.

Translation

The validated English version of the LARS questionnaire was translated into the Italian language. The translation was performed by two independent professional translators. The translators discussed any discrepancies between their translations until an agreed-upon version was reached. A third native English translator translated the Italian version into English. Subsequently, the two English versions (the initial version and the new version) were compared, and the final version in Italian was elaborated (**Figure 1**).

Data Collection and Participants

Six surgical units of the "Fondazione Policlinico Universitario A. Gemelli, IRCCS" of Rome participated in the data collection. The inclusion criteria were as follows: diagnosis of rectal cancer (between 0 and 15 cm from the anal verge); treatment with anterior rectal resection surgery (open, laparoscopic, robotic or transanal approach) with total or partial mesorectal excision (TME or PME); if a stoma has been created, intestinal continuity must have been restored for at least 24 months (by April 2018). The exclusion criteria were: dementia; metastatic or recurrent disease; other intestinal diseases (including Crohn's disease, ulcerative colitis); patients with a stoma or with intestinal continuity restored for less than 24 months; and patients with problems understanding the Italian language. Eligible patients received an invitation to complete the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30), two copies of the LARS questionnaire (administered 1–2 weeks apart), and a single question about QoL, which was added for validation purposes.

Each surgical unit was responsible for the truthfulness of the data collected and provided.

Patient-Reported Outcome Measures

Lars Score

The LARS questionnaire translated into Italian was administered to all patients enrolled in the study. The LARS score was originally developed in Denmark with a population of rectal cancer patients. The score is based on five questions regarding bowel dysfunction that were selected from 26 candidate items on the basis of their high correlation with patient-reported QoL. The scores of the five subscales are summed to produce a total score ranging from 0 to 42 points. Patients were classified into three groups according to their total score: 0–20 points: no LARS; 21–29 points: minor LARS; and 30–42 points: major LARS (6).

Single Question on Qol

A single question on QoL was added to the LARS score to investigate convergent validity. The question, "Complessivamente, in che modo la sua funzione intestinale influisce sulla sua qualità della vita?" (in English, "Overall, how does bowel function affect your quality of life?"), was answered with one of the following options: "per niente", "un po'", "parecchio", "moltissimo" (in English, "not at all", "a little", "quite a bit", "a lot"). This question was previously used for the development and validation of the LARS score in other countries (6, 11, 12). To evaluate the degree of agreement between the 3 LARS score categories and the single QoL question, the last question was grouped as follows: "not at all" = no impact on QoL; "a little" = minor impact on QoL; "quite a bit" + "a lot" = major impact.

L'obiettivo di questo questionario è di valutare la sua funzionalità intestinale. Per favore, contrassegni soltanto una casella per ogni domanda. Potrebbe risultare difficile selezionare una sola risposta, dato che i sintomi di alcuni pazienti tendono a variare di giorno in giorno. La preghiamo di scegliere una risposta che descriva al meglio la sua vita quotidiana. *Se è stato affetto recentemente da un'infezione che colpisce la normale funzionalità intestinale, la preghiamo di non tenerne conto e di concentrarsi sulla risposta alle domande riferendosi alla sua solita, quotidiana, funzionalità intestinale.*

D.1: Le capita mai di non riuscire a trattenere i gas? (aria)

☐ No, mai	0
☐ Sì, ma meno di una volta alla settimana	4
☐ Sì, almeno una volta alla settimana	7

D.2: Le capita mai di perdere feci liquide in maniera involontaria?

☐ No, mai	0
☐ Sì, ma meno di una volta alla settimana	3
☐ Sì, almeno una volta alla settimana	3

D.3: Con che frequenza va di corpo?

☐ Più di 7 volte al giorno (24 ore)	4
☐ 4-7 volte al giorno (24 ore)	2
☐ 1-3 volte al giorno (24 ore)	0
☐ Meno di una volta al giorno (24 ore)	5

D.4: Le capita mai di dover andare di corpo una seconda volta entro un'ora dalla prima evacuazione?

☐ No, mai	0
☐ Sì, ma meno di una volta alla settimana	9
☐ Sì, almeno una volta alla settimana	11

D.5: Le capita mai di dover correre in bagno per la sensazione di estrema urgenza di dover evacuare?

☐ No, mai	0
☐ Sì, ma meno di una volta alla settimana	11
☐ Sì, almeno una volta alla settimana	16

Sommare i punteggi di ognuna delle cinque risposte per ottenere un punteggio finale.
Interpretazione: 0-20 = LARS assente 21-29 = LARS minore 30-42 = LARS maggiore

FIGURE 1 | The Italian version of the low anterior resection syndrome (LARS) score questionnaire.

EORTC QLQ-C30

The EORTC QLQ-C30 questionnaire (16, 17) is a validated and specific tool for evaluating the QoL of cancer patients. It consists of 30 questions that provide a global QoL scale, five functional scales (i.e., physical, role-playing, emotional, cognitive, social), three symptom scales (fatigue, nausea and vomiting, pain) and six individual factors (dyspnoea, insomnia, loss of appetite, constipation, diarrhoea, financial difficulties). The scores for each scale are combined to produce a score ranging from 0 to 100. For the purpose of this study, only the functional scales and the global QoL scale were used. A high score on a functional scale represented a good level of function.

Statistical Analysis

Based on previous validation studies conducted in other countries (8–12), it was determined that the sample should

include at least 200 patients. The clinical and demographic features of the sample are described using descriptive statistics. Quantitative variables are described using the following measures: mean and standard deviation. Qualitative variables are summarized as absolute and percentage frequencies.

Convergent Validity

The LARS score data are presented as the median and interquartile range (IQR). Based on the responses to the single QoL question, the patients were grouped into three categories: no impact, minor impact or some/major impact of bowel function on QoL. The fit between the QoL category and LARS score category was investigated and was considered perfect when patients reported no LARS and no impact on QoL, minor LARS and a minor impact on QoL, or major LARS and some/major impact on QoL. A box and whisker plot analysis was used to illustrate the differences in the numerical LARS score among QoL categories, and any difference was tested by the Kruskal-Wallis test. Convergent validity was explored by investigating the association between the LARS categories and the five functional subscales and the global QoL scale of the EORTC QLQ-C30. EORTC QLQ-C30 scores were calculated. The Kruskal-Wallis test was used to perform all comparisons.

Discriminative Validity

The ability of the LARS score to differentiate among groups of patients was evaluated with the Mann-Whitney test. Similar to previous validation studies (6, 8, 11, 12), the clinically relevant subgroups were based on preoperative chemoradiotherapy (CRT), type of surgery (TME/PME), and age (cut-off of 69 years).

Test-Retest Reliability

Test-retest reliability is a key aspect of all health measures (18). To examine the test-retest reliability of the LARS score, all patients were sent a second LARS questionnaire 1–2 weeks after they completed the first one, and they all were asked to complete the questionnaire again. Agreement between tests for each of the five LARS score items and for the LARS score classification is presented as the proportion with 95% CI. A Bland-Altman plot with 95% limits of agreement is also presented, as is the intraclass correlation coefficient (ICC). An ICC above 80 is considered excellent agreement. A p-value less than 0.05 was considered statistically significant.

All statistical analyses were performed using SPSS® version 25.0 for Windows® software (SPSS, Chicago, IL, USA).

RESULTS

Two hundred five patients (117 males, 88 females; mean age 67.7 ± 11.0 years) were enrolled in the study and returned a completed LARS score questionnaire. Only 42.0% of the respondents underwent preoperative CRT, and 77.6% of them had undergone TME. 53.2% of the patients underwent a laparoscopic approach; the others 18.6%, 14.1% and 14.1% underwent an open, robotic and transanal approach respectively. According to the LARS score, 74 (36.1%) patients had major LARS, 55 (26.8%) had minor LARS, and 76 (37.1%) had no LARS. A detailed description of the patients' characteristics is provided in **Table 1**. Seventy-two patients (35.1%) were followed up in the outpatient clinic, 66 patients (32.2%) were followed up by e-mail, and 67 (32.7%) completed a telephone interview.

Convergent Validity

The proportion of patients with a perfect fit between the QoL category and the LARS score category was 64.3%; a moderate

TABLE 1 | Baseline characteristics of patients ($N = 205$).

Gender (*n*, %)		
Males	117	57.1
Females	88	42.9
Age (mean, SD)	67.7	11
Distance of the cancer from the anal verge (cm) (mean, SD)	8.95	4
Distance of the anastomosis from the anal verge (cm) (mean, SD)	4.72	3
Neoadjuvant radiotheraphy (*n*, %)		
NO	119	58.0
YES	86	42.0
Resection type (*n*, %)		
TME	159	77.6
PME	46	22.4
Surgical Approach (*n*, %)		
OPEN	38	18.6
LPS	109	53.2
ROBOTIC	29	14.1
TaTME	29	14.1
Stoma creation (*n*, %)		
NO	81	39.5
YES	123	60.0
LARS SCORE AT QUESTIONNAIRE #1 (median, IQR)	27	19
LARS SCORE CLASSES #1 (*n*, %)		
No LARS	76	37.1
Minor LARS	55	26.8
Major LARS	74	36.1
LARS SCORE AT QUESTIONNAIRE #2 (median, IQR)	25.5	19
LARS SCORE CLASSES #2 (*n*, %)		
No LARS	76	37.1
Minor LARS	54	26.3
Major LARS	74	36.1
No response	1	0.5
QOL SINGOLA (*n*, %)		
Not at all	55	26.8
Very little	50	24.4
Somewhat	74	36.1
A lot	26	12.7

Abbreviations: TME, Total mesorectal excision; PME, partial mesorectal excision; LARS, low anterior resection syndrome; LPS, laparoscopic; TaTME, transanal total mesorectal excision.

fit was found for 29.8%, and no fit was found for 5.9% (**Table 2**). For respondents who reported that bowel problems had no impact on QoL ($n = 55$), the median (IQR) LARS score was 9 (4–18), whereas for those who reported that it had a minor impact on QoL ($n = 50$), the median (IQR) LARS score was 24.5 (17.5–29). Patients who reported that bowel problems had some/a major impact on QoL ($n = 100$) had a median (IQR) LARS score of 34 (27–39). Differences in the LARS score among QoL categories were highly significant ($p < 0.0005$) (**Figure 2**). The three LARS categories were also compared with the EORTC QLQ-C30 functional scales (Physical functioning, Emotional functioning, Role functioning, Cognitive functioning, Social functioning) and the global health score. **Table 3** presents the main results of these comparisons; all differences regarding all items of the EORTC QLQ-C30 functional scales were statistically significant.

TABLE 2 | Fit between LARS category and QoL category.

	No impact on QoL	Minor impact on QoL	Major impat on QoL
No LARS	46 (22.4%)	20 (9.8%)	10 (4.9%)
Minor LARS	7 (3.4%)	22 (10.7%)	26 (12.7%)
Major LARS	2 (1.0%)	8 (3.9%)	64 (31.2%)

Perfect fit: 64.3%.
Moderate fit: 29.8%.
No fit: 5.9%.

Discriminative Validity

As shown in **Figure 3**, the LARS scores of patients who underwent preoperative CRT ($n = 86$; median = 31, IQR = 21–37) were significantly higher than those of patients who proceeded directly to surgery ($n = 119$; median = 24, IQR = 9–31)

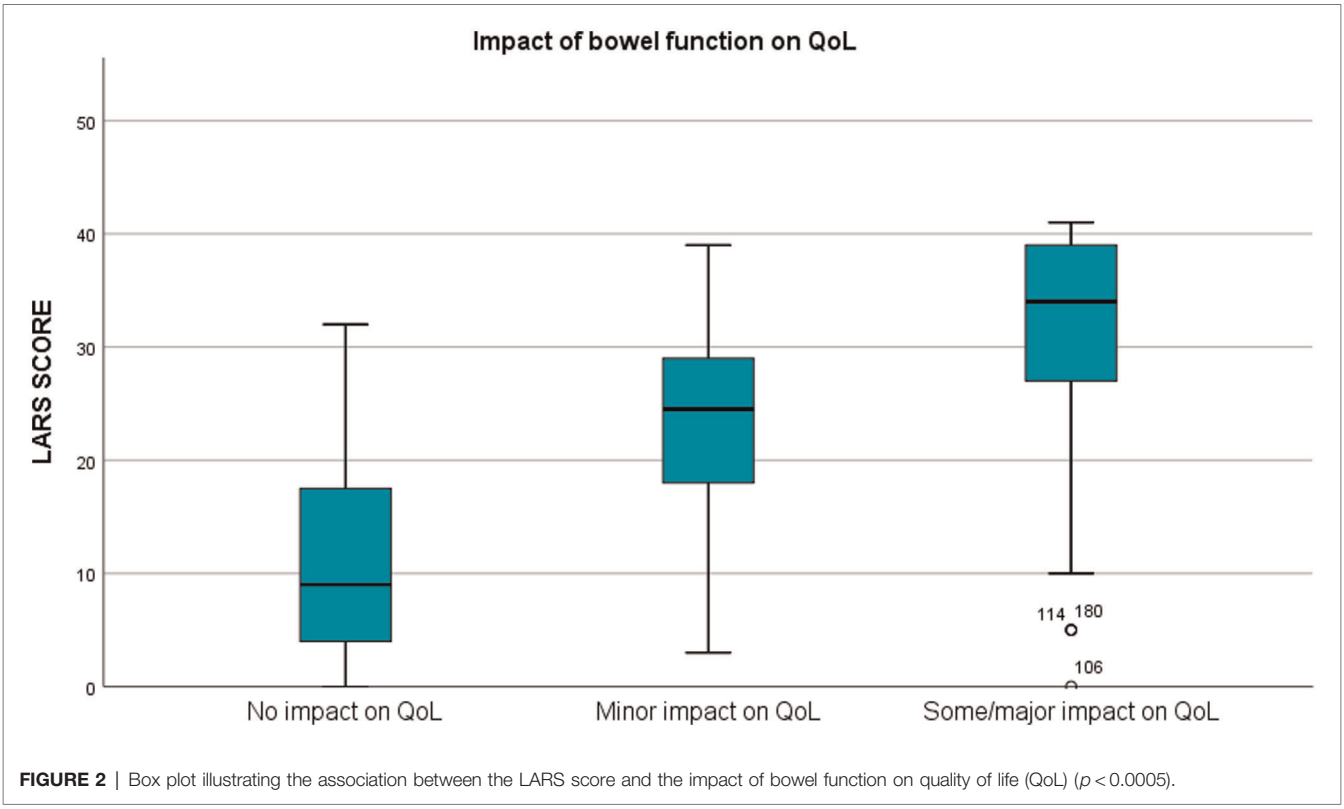

FIGURE 2 | Box plot illustrating the association between the LARS score and the impact of bowel function on quality of life (QoL) ($p < 0.0005$).

TABLE 3 | Median score, 1st and 3rd quartile of the functional scales compared between the LARS categories.

	No LARS			Minor LARS			Major LARS			*p*-value
	median	1st quartile	3rd quartile	median	1st quartile	3rd quartile	median	1st quartile	3rd quartile	
GHS	833	750	100	750	667	833	667	500	750	<0.0005
PHYS_FUNCT_SCORE	100	80	100	93	80	100	87	67	93	<0.0005
EMOT_FUNCT_SCORE	100	83	100	100	83	100	83	67	94	<0.0005
ROLE_FUNCT_SCORE	100	100	100	100	67	100	75	67	100	<0.0005
COGN_FUNCT_SCORE	100	100	100	100	83	100	83	67	100	<0.0005
SOCIAL_SCORE	100	100	100	83	67	100	67	50	100	<0.0005

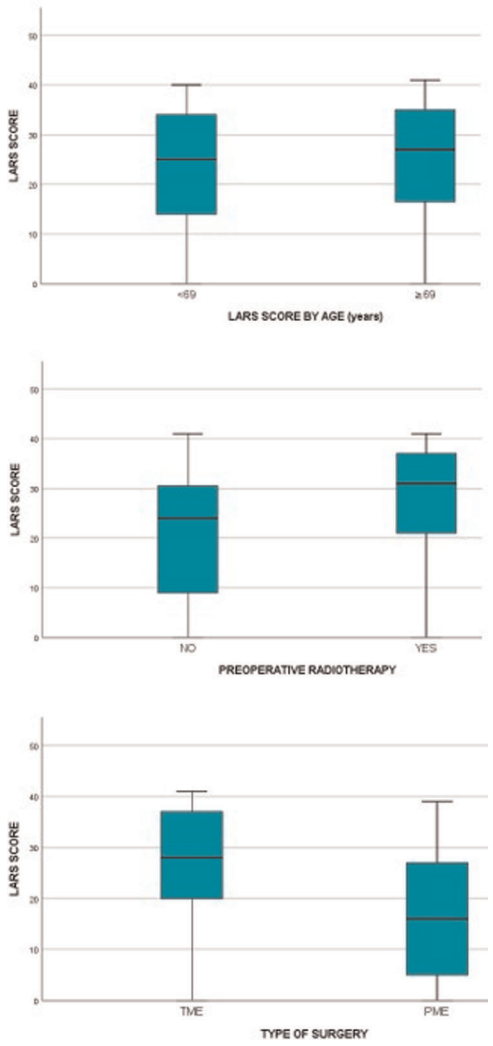

FIGURE 3 | Comparison of LARS scores in groups of patients that differ by age ($p = 0.534$), preoperative chemoradiotherapy ($p < 0.0005$) and type of surgery ($p < 0.0005$).

($p < 0.0005$). The LARS score was also able to discriminate between PME patients ($n = 46$; median = 16, IQR = 5–27.5) and TME patients ($n = 159$; median = 28, IQR = 20–37) ($p < 0.0005$). The LARS score was not able to discriminate between <69-year-old patients and ≥69-year-old patients ($p = 0.534$).

Reliability

All 205 patients were asked to complete the LARS score twice, and 204 responded to both questionnaires (response rate 99%). The median (IQR) number of days between tests was 11 (9–16). The Bland-Altman plot with 95% limits of agreement (−6.5 to 7.5) in **Figure 4** illustrates the difference between the LARS scores on the first and second tests. This difference was statistically significant ($p = 0.046$).

The degree of agreement between the initial test and the retest for each of the LARS categories (no, minor, major LARS) is presented in **Table 4**. The results showed that 88.7% of the patients remained in the same LARS category at both tests, 11.2% differed by one category and no one differed by two categories between tests. The ICC was 0.96, indicating excellent reliability.

DISCUSSION

This study demonstrated the effectiveness of the Italian translation of the LARS score in a cohort of Italian patients with rectal cancer, with a strong association between the LARS score and QoL. As regard as the validity of the score, the present version of the LARS score allowed us to discriminate between the different kinds of mesorectal resection (TME vs. PME) and patients who did and did not receive neoadjuvant CRT (19). The LARS score could not discriminate between patients younger than 69 years old and those aged 69 years and older. Moreover, the test-retest reliability was high. **Table 5** compares the data reported in the previous validation studies of the LARS score in different populations to the Italian results.

Our results were consistent with previous reports (8, 11, 12), showing a higher proportion of major LARS after TME than after PME. Indeed, in the Italian population with rectal cancer, 46% of patients complained of major LARS after TME. In earlier validation studies (8–11), 47–59% of patients reported major LARS after TME, while a higher percentage of major LARS (59.4%) was recorded in the Dutch group (12). The wide difference in the percentage of patients who had neoadjuvant CRT could explain the variable distribution of major LARS among different countries (in the Dutch population, 90% of patients received neoadjuvant CRT; in Italy, 42% did). In accordance with other validation results (8–12), patients treated with preoperative CRT had a significantly higher LARS score, confirming the negative impact of CRT on patient-reported QoL (19, 20).

In contrast to the Dutch and international validation (11, 12), no differences were found between age groups, as previously reported by Chinese and Lithuanian authors (9, 10). However, a larger sample size could have improved the discriminatory ability. As in previous validations (8, 11, 12), a single QoL category question was used to test convergent validity. The Italian results of perfect (64.3%), moderate (29.8%) and no fit (5.9%) were similar to those reported in the international validation (11).

To further investigate convergent validity, the EORTC QLQ-C30 functional and global scales were compared to the LARS score categories. There was a significant correlation between a higher LARS score and a worse QoL. As reported in the English validation (8), there was an association between the LARS scores and all the EORTC QLQ-C30 subscales, including the cognitive functioning subscale. When compared with English and other international validation studies (8, 11), the reliability of the LARS score was excellent. There was remarkable patient compliance with completion of the LARS

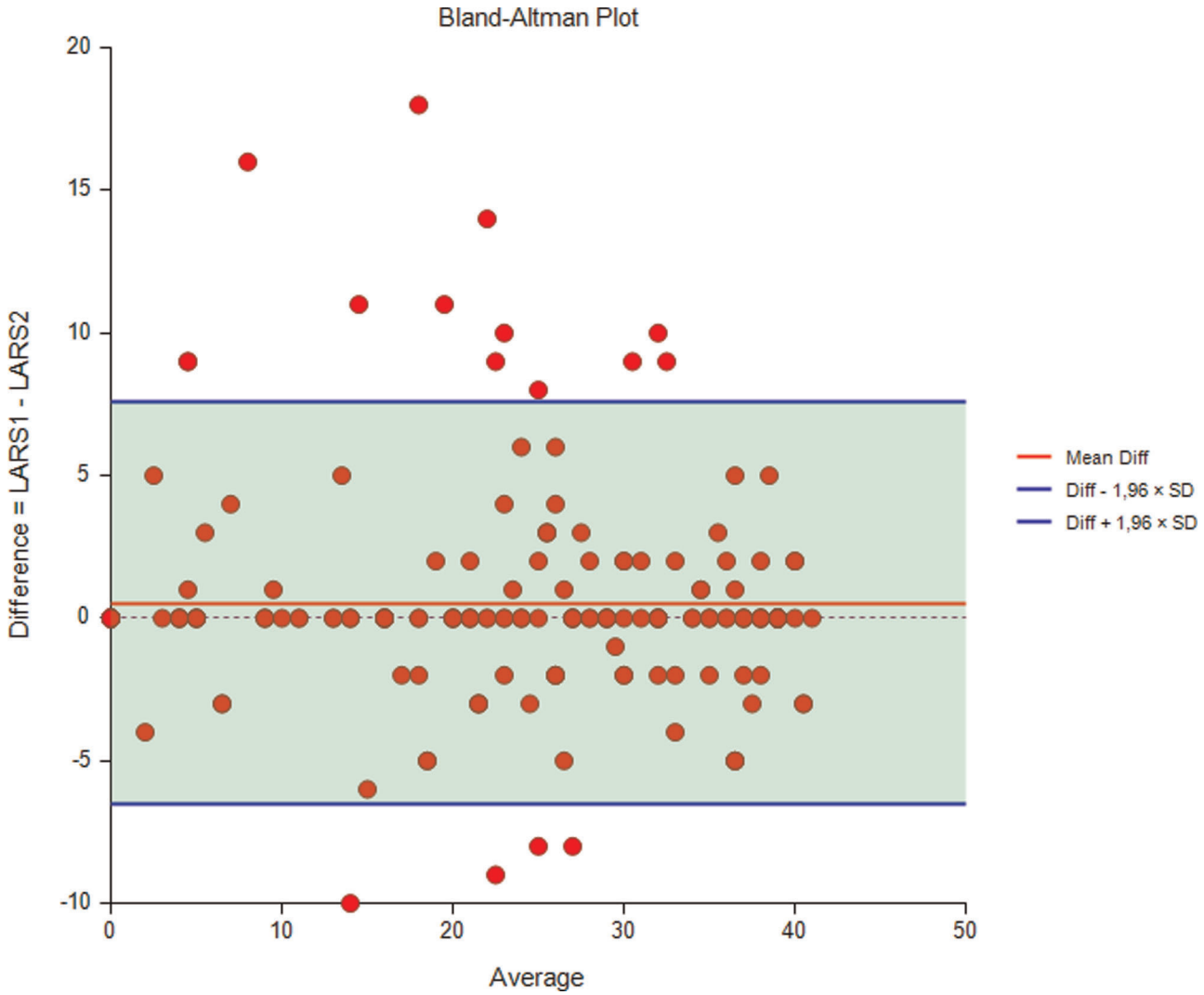

FIGURE 4 | Bland-Altman plot with 95% limits of agreement illustrating the difference between LARS scores at the first and second tests.

TABLE 4 | Agreement between first and second LARS score category.

		LARS 2 CATEGORY		
		No impact	Minor impact	Major impact
LARS 1 CATEGORY	No impact	34.3%	2.9%	0.0%
	Minor impact	2.9%	21.1%	2.9%
	Major impact	0.0%	2.5%	33.3%

Perfect fit: 88.7%.
Moderate fit: 11.2%.
No fit: 0.0%.

score questionnaire, thus demonstrating that the LARS score is easy to understand and complete.

Recently, Resendiz and colleagues (21) published a case series of 147 patients from 3 referral centers, across a 4-year period, with the aim of validating the Italian version of the LARS score. In this context, the major strenght of our study was to consider a higher volume of patients coming from the same center allowing a homogeneity of the data. Moreover, considering a period of almost 20 years, in which there has been a clear technological evolution involving rectal cancer surgery, we believe we have given the idea of a greater applicability of the LARS score whatever the chosen approach (open, laparoscopic, robotic, transanal). Lastly, we compared and critically analyzed the Italian version with other validated scores.

This study has some limitations. It was performed at a single institution that is an Italian referral centre for rectal cancer, and the expertise of the surgeons involved and the high volume of patients treated can explain the favourable distribution of LARS score categories, including a lower percentage of major LARS, compared to similar validation studies. Moreover, since the primary objective of this study was to validate the Italian version of the LARS score, anorectal function was not

TABLE 5 | Comparison between different studies aimed to validate the LARS score (values expressed in %).

	Lars categories			Convergent validity			Discriminative validity			TME/ PME	RT/ no RT	Reliability ICC
	No LARS	Minor LARS	Major LARS	Perfect fit	Moderate fit	No fit	Age groups	TME/ PME	RT/no RT			
DANISH	35.4	24.9	39.7	62.2	31.9	5.9	–	yes	yes	60/40	21/79	0.46 to 0.95[a]
ENGLISH	29.7	22.8	47.5	51.5	44.1	4.5	yes	yes	yes	81/19	31/69	0.83
INTERNATIONAL[b]	28.1	19.5	52.4	60.7	34.2	5.1	yes	yes	yes	75/25	55/45	0.91
CHINESE	23.5	21.6	54.9	78.0	18.0	4.0	no	–	yes	–	28/74	0.86[c]
DUTCH	21.8	18.8	59.4	41.8	49.7	8.5	yes	yes	yes	82/18	90/10	0.79
LITHUANIAN	56.0	24.0	25.0	54.5	38.0	7.5	no	–	no	–	49/51	0.92
ITALIAN	37.1	26.3	36.1	64.3	29.8	5.9	no	yes	yes	77/23	42/58	0.96

Abbreviations: TME, total mesorectal excision; PME, partial mesorectal excision; RT, radiotherapy; ICC, intraclass correlation coefficient.
[a]*Kappa values.*
[b]*median value of the four Countries included.*
[c]*Spearman correlation coefficient.*

homogeneously assessed before surgery. As reported in the previous validations the type of anastomosis performed (stapled or hand-sewn) was not considered as discriminatory outcome. The epidemiology of LARS in the rectal cancer population and the investigation of risk factors were not aims of this study. In the test-retest analysis, there was a short interval between tests because it was assumed that over a longer period, a change in bowel function could occur. However, a potential disadvantage of a short interval is an increased risk of patients copying their first questionnaire responses when answering the second questionnaire.

CONCLUSION

The Italian translation of the LARS score is a valid tool for the assessment of bowel dysfunction after rectal cancer surgery in the Italian population. It has demonstrated a strong association with QoL and high convergent and discriminative validity and reliability comparable to earlier validations. The Italian version of the questionnaire is reliable, easy to understand and complete, and its routine use should be included in clinical practice.

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 Comitato Etico Fondazione Policlinico Gemelli. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VDS: Substantial contributions to the conception or design of the work; acquisition, analysis and interpretation of data for the work. Drafting the work or revising it critically for important intellectual content. Final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. FL, RP, GR, LS, RM, FS, CR contributed equally to this work: Substantial contributions to the conception and design of the work; acquisition, analysis and interpretation of data for the work. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved. AB, CC, FS, FL ,MAEH contributed equally to this work: substantial contributions to the acquisition of data for the work. Final approval of the version to be published. RM: Substantial contributions to the design of the work acquisition, analysis and interpretation of data for the work; final approval of the version to be published. All authors contributed to the article and approved the submitted version.

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The clinical data analysed in this study are contained within patients' medical records. The submitted questionnaires are stored at the Proctology Unit of the Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Largo Agostino Gemelli 8, 00168, Rome, Italy.

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CASE REPORT
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Harry Potter's Occlusion: Report of a Case of Pumpkin Seed Bezoar Rectal Impact

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Bezoar is a term from Arabic "bāzahr" or ultimately from Middle Persian "p'tzhl" (pādzahr, "bezoar antidote" or less commonaly ægagropile or egagropile (2–4). It was believed to have the power of a universal antidote that works against any poison, and a glass containing a bezoar could neutralize any poison poured into it. In science, it is a mass of hair or undigested vegetable matter found in a human or animal intestines, similar to a hairball. Otherwise, the name could derive from a kind of Turkish goat whose name is just bezoar. Usually, it is found trapped in every part of the gastrointestinal system and must be distinguished by pseudobezoar, which is an nondigestible object voluntarily introduced into the digestive tract. The most common causes are a previous gastric surgery such as a gastric band (for weight loss) or gastric bypass, a reduced stomach acid (hypochlorhydria) or decreased stomach size, and a delayed gastric emptying, typically due to diabetes, autoimmune disorders, or mixed connective tissue disease. Seed bezoars are usually found in the rectum of patients without predisposing factors, causing constipation and pain. Rectal impaction is common after ingestion of seeds, while a true occlusion is rare. Although several cases of phytobezoars composed of various types of seeds are reported in the literature, bezoars of pumpkin seeds have rarely been reported. The authors report a case of fecal impaction by pumpkin seed bezoars with abdominal pain: a difficulty to void with subsequent rectal inflammation and hemorrhoid enlargement was observed. The patient underwent a successful manual disimpaction.

Keywords: pumpkin seeds, bezoar, occlusion, haematochezia, digital impaction, depression

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INTRODUCTION

In J.K. Rowling's Book of Harry Potter, the apprentice scientist is quizzed on bezoar during the very first Potions Class (1). Bezoar is a term from Arabic "bāzahr" or ultimately from Middle Persian "p'tzhl" (pādzahr, "bezoar antidote") or less commonly ægagropile or egagropile (2–4). It was believed to have the power of a universal antidote and would work against any poison

and that a drinking glass that contained a bezoar could neutralize any poison poured into it. In science, it is a mass of hair or undigested vegetable matter found in a human or animal intestines, similar to a hairball. Otherwise, the name could derive from a kind of Turkish goat whose name is just bezoar.

Usually, it is found trapped in every part of the gastrointestinal system and must be distinguished by pseudobezoar that is an nondigestible object voluntarily introduced into the digestive tract (5, 6).

Bezoars take the name from the core substance so that we can distinguish them: phytobezoars are composed of vegetable fibers and seeds, trichobezoars are formed from hair, lactobezoars are from inspissated milk, and diospyrobezoars are from unripe persimmon fruits (7).

The overall incidence of bezoars is felt to be low and is extremely rare in healthy individuals occurring in far less than 1% of patients in retrospective endoscopic series (7). Kadian et al. (8) reported that they found six cases of gastric bezoars in a 4-year period, during which time 1,400 gastroscopies were done (0.43% of gastroscopies). Ahn et al. (9) reported a similar incidence of 0.43% (14/3,247 esophagogastroduodenoscopy examinations) over a 7-year period. More recently, Mihai et al. (10) noted that there were 49 cases of gastric bezoars over a period of 20 years (0.068% of all endoscopies). Yakan et al. (9) reviewed 432 cases of small bowel obstruction treated within 10 years; of these, 14 (3.2%) cases were caused by phytobezoars. Multiple cases of persimmon phytobezoar (diospyrobezoar) have been reported in regions where the residents frequently consume fresh persimmon fruits and dried persimmons, such as South Korea, Japan, Israel, Spain, Turkey, and the southeastern United States. In a meta-analysis by Ghosheh et al. (11) reviewing 19 reported studies published from 1994 to 2005, laparoscopy was attempted in 1,061 patients presenting with acute small bowel obstruction, and bezoars represented the fifth most common cause, accounting for 0.8% (12).

FIGURE 1 | Pumpkin's seeds.

Certain at-risk groups have been identified and include patients with altered upper GI anatomy after surgery and psychiatric illness or cognitive impairment. The most common causes are a previous gastric surgery such as a gastric band (for weight loss) or gastric bypass, a reduced stomach acid (hypochlorhydria) or decreased stomach size, and a delayed gastric emptying, typically due to diabetes, autoimmune disorders, or mixed connective tissue disease. Other causes are patients who cannot or do not chew their food properly, usually because they have no teeth or poorly fitting dentures and because of an excessive intake of fibers. Edentulous patients with poor mastication of food particles may also be at greater risk for bezoar development, especially if coexisting risk factors, as described above, are also present. In addition, patients with psychiatric illnesses are at an increased risk of bezoar formation due to the possible ingestion of hair and medications (8, 9).

Many cases of bezoars have also been reported in children or adults having psychosocial problems; nevertheless, the condition can occur in normal children with no apparent psychosocial issues (8).

Seed bezoars are usually found in the rectum of patients without predisposing factors, causing constipation and pain. Although the literature has reported several cases of phytobezoars composed of various types of seeds, bezoars formed from pumpkin seeds have rarely been reported (10). The diagnosis may be suggested by the radiologic study and is confirmed by endoscopy. History and digital rectal examination are the mainstays of diagnosis, with manual extraction under local anesthesia being the procedure of choice (13). CT scanning is useful for detecting both gastric and small intestinal bezoars. Phytobezoars are visualized by CT scanning as a round occupational mass in the gastrointestinal tract. Some cases of bezoars can be coincidentally found in asymptomatic patients by esophagogastroduodenoscopy or computed tomography (CT) scanning performed during a health check-up or follow-up of other diseases.

We report a case of a man aged 50 years with a rectal bezoar composed of pumpkin seeds ingested with their shell, necessitating extensive treatment, including manual disimpaction and rectoscopy.

METHODOLOGY

The description of the case follows the 2013 CARE Checklist Guidelines (13).

CASE REPORT

Patient Information

A 50-year-old man with no significant medical history was observed in our outpatient room with a 3-day abdominal pain and difficulty passing anything rectally except some sprays of liquid stool. He also complained of hematochezia at defecation. A physical exam revealed a painful tenderness of the abdomen but the presence of normal bowel sounds.

The abdominal wall was mainly painful on the left.

He seemed scared and confused in reporting events and was accompanied by his mother. He reported having spent the Sunday afternoon alone watching TV and eating two bags of pumpkin seeds (about 400 g) with their shell. He was unemployed and showed a depressed attitude. He reported never having had problems of this nature before but having problems of constipation in the last months.

Diagnostic Findings

The plain x-ray of the abdomen showed dilatation of the left and bowel. A proctological inspection revealed a hard bolus in the rectum (**Figure 1**) with blood loss and a rectoscope examination showed a pumpkin bezoar impacted into the rectum (**Figure 2**). Starting from the history and results of the proctological inspection, the diagnosis of impaction from seeds was quite clear.

Therapeutic Intervention

Under sedation with propofol, a disimpaction of the bezoar was accomplished with a colon washing. The patient was discharged on the same evening with a prescription of intestinal antibiotics and a large bowel toilet with polyethylene glycol and enemas.

Outcomes

Two days after the first admission, the patient returned to the outpatient department complaining of a persistent difficulty to void with a burning sensation and blood loss. A residual hard bolus, smaller than the first, was detected in the rectum, and another disimpaction under local anesthesia was performed. A proctoscopy showed small diffuse ulcerations of the rectal mucosa and enlargement of hemorrhoids (**Figure 3**). The colon was empty at the end of the procedure. A daily topical application of sucralfate enemas, stool softeners, and fiber diet was prescribed, and the patient passed normal stools without pain the following day. A suggestion of psychological help was made.

Follow-up

Three weeks after this episode, the rectal mucosa reverted to normal, and the patient declared to move regularly without a burning sensation.

FIGURE 2 | Bezoar in the rectum.

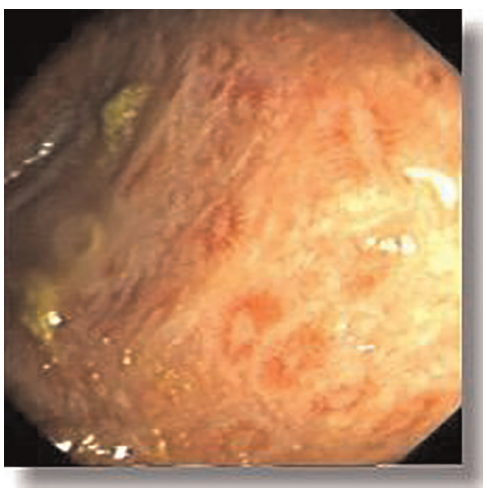

FIGURE 3 | Rectal wall after disimpaction.

DISCUSSION

Rectal seed bezoar is an uncommon cause of fecal impaction, more frequent in eastern than western countries and particularly in Middle Eastern and South Asian countries where roasted seeds are very popular (14). The composition of a bezoar is essentially mechanical due to its insoluble and indigestible content. The growth is increased by continuous ingestion of the nondegradable content. The most frequent site is the stomach, and rarely can it be observed in the colon and rectum. Clinical symptoms include nausea, vomiting, anorexia, constipation, and obstipation. Rectal ulcerations are not frequent even if the first report of a stercoral ulceration

was described by Berry in 1894: an isolated ulcer produced by pressure necrosis of a fecal mass in the rectum (15).

Seed bezoar is a subcategory of phytobezoar caused by the accumulation of indigestible vegetable or fruit seeds in the intestine lumen. They usually pass the stomach and the ileocecal valve and deposit in the colon up to the rectum, where the compound is dehydrated and forms a hard bolus impossible to evacuate (16). Seed bezoars seem to arise mostly in patients without predisposing factors, as a review from the Manatakis report: 12% of cases of previous gastric surgery, neuropsychiatric illness, and endocrinopathies were reported, contrary to fiber bezoar where rates of risk factors exceed 85% (17).

Seed bezoar occurs most frequently in the rectum both in children and adults, and symptoms are mainly constipation followed by abdominal pain and rectal burning. A true intestinal obstruction is rare, and perforation is reported only in one case (18, 19). Fiber bezoar, due to its location in the stomach, causes specific symptoms such as nausea, vomiting, and abdominal bloating. Manual evacuation under general anesthesia for rectal bezoar is the treatment of choice to avoid discomfort to the patients, while surgery is mandatory in the case of intestinal obstruction from small seeds. Manual disimpaction is the most commonly used procedure both in children and adults, while surgery is more frequent in adults than in children (30% vs. 14.5%). Chemical dissolution of the mass works better with fiber bezoars than with seed bezoars; however, Coca Cola Zero is reported to be effective in breaking a phytobezoar into small pieces (20). Finally, endoscopy is ineffective because, in most cases, the endoscope cannot transit beyond the mass (21). In case of true occlusion, surgery is mandatory even if rare

From 1980 to 2018, 52 studies were reported by Manatakis (16) responding to eligibility criteria over a total of 102 papers published. From 2018 to today, another eight papers with a full text available were published. In four out of the eight, bezoar formation was from seeds (granadilla, mango, and sunflowers in two cases), but none of the patients ate pumpkin seeds (22). According to Manatakis, the major complaint was constipation followed by atypical abdominal or rectal pain. One elderly patient was diagnosed with acute abdomen due to rectal perforation, and one intraoperative incident finding was reported.

Preventive therapy to avoid recurrence must be implemented when the bezoar is removed. The patient should be advised to increase the amount of water intake. Dietary habits must be investigated since inadequate chewing, swallowing whole seeds, or eating seeds with their shell may impact as bezoar (11, 23, 24).

Finally, gastric bezoars are common in cystic fibrosis patients after lung transplantation. The etiology is likely multifactorial, related to gastric motility, respiratory secretions, and medications. Of the 215 patients who received lung transplantation, 17 (7.9%) developed gastric bezoars confirmed by upper endoscopy and 94% of patients with bezoars (16 of 17) had cystic fibrosis ($P = 0.02$), Further investigation is needed to understand the pathogenesis of bezoar formation in this selected population (25).

CONCLUSION

Seed bezoar is an uncommon cause of fecal impaction, more frequent in eastern than western countries and particularly in Middle Eastern and South Asian countries. Seed bezoar is a subcategory of phytobezoar caused by the accumulation of indigestible vegetable or fruit seeds in the intestinal lumen: it occurs most frequently in the rectum both in children and adults, and symptoms are constipation followed by abdominal pain and rectal burning. Intestinal obstruction is rare, and perforation is reported only in one case. Manual disimpaction is the commonly used procedure both in children and adults, while surgery is more frequent in adults than in children. Preventive therapy to avoid recurrence must be implemented when the bezoar is removed. An increase in the amount of water intake should be advised. Psychiatric support is mandatory in patients with recurrent episodes of seed ingestion.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MG, general organization, clinical approach, and manuscript. LV, bibliographic research. VS, bibliographic research. GC, review of the manuscript. LS, endoscopic records.

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The evaluation of different types fecal bacteria products for the treatment of recurrent *Clostridium difficile* associated diarrhea: A systematic review and network meta-analysis

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Purpose: To determine the efficacy of different types of fecal microbiota transplantation for the treatment of recurrent clostridium difficile associated diarrhea (RCDAD).

Methods: We searched PubMed, Embase, The Cochrane Library, Web of Science, China Biomedical Medicine (CBM), China National Knowledge Infrastructure (CNKI) and WanFang database. We also tracked the references found in systematic reviews of RCDAD treated with fecal microbiota transplantation. We included randomized controlled trials (RCTs) comparing different types of fecal microbiota transplantation with other methods for the treatment of RCDAD. The search period was from the date of inception of this treatment method to January 16, 2022. Two reviewers independently screened the published literature, extracted the data and assessed the risk of bias. Systematic review and network meta-analysis were conducted using RevMan 5.4, Stata 16.0 and R 4.1.2 software.

Results: Ten RCTs involving 765 patients were included in this network meta-analysis. The results showed that treatment with fresh fecal bacteria and frozen fecal bacteria were better than vancomycin, fresh vs. vancomycin [odds ratio, (OR) = 8.98, 95% confidence interval (95% CI) (1.84, 43.92)], frozen vs. vancomycin [OR = 7.44, 95% CI (1.39, 39.75)]. However, there were no statistically significant differences in cure rate [fresh vs. frozen: OR = 1.21, 95% CI (0.22, 6.77); fresh vs. lyophilized, OR = 1.95, 95% CI (0.20, 19.44); frozen vs. lyophilized, OR = 1.62, 95% CI (0.30, 8.85)]. The Surface Under the Cumulative Ranking (SUCRA) indicated that fresh fecal bacteria were the best treatment for RCDAD.

Conclusions: Fresh fecal bacteria are the best treatment of RCDAD, frozen fecal bacteria and lyophilized fecal bacteria can achieve the same effect. Fecal microbiota transplantation is worthy of clinical and commercial application.

KEYWORDS

Fecal microbiota transplantation, clostridium difficile infection, efficacy, safety, network meta-analysis

Introduction

Clostridium difficile (CD) is gram-positive anaerobic bacteria that was originally reported by Hall and O'Toole in 1935 as a component of the fecal flora of healthy newborn infants (1). It is widely distributed in the natural environment, animal and human feces, and belongs to the normal intestinal flora. CD infection (CDI) is the main cause of diarrhea in hospitals, accounting for 20% to 30% of all antibiotic-related cases (2). Age, comorbidities and the use of antibiotics are the main risk factors (3). The incidence of CDI in hospitals and communities is increasing, posing a serious challenge for public health (4–7). The latest data showed that nearly 20% of patients were diagnosed with CDI after receiving standard antibiotic therapy, and the recurrence rate was as high as 50% to 60% (8, 9). Due to its resistance to antibiotics, recurrent CDI (rCDI) is more likely to produce serious clinical manifestations, such as inflammatory lesions and the formation of pseudo-membranes, which increase the risk of life-threatening complications (toxic megacolon, sepsis) and death (10). Fecal microbiota transplantation (FMT) is an effective method for treating recurrent or refractory CDI (11), since FMT can restore the diversity and function of the intestinal flora, allowing it to resist CD and its toxins (12, 13). In recent years, the FMT has been commonly used in clinical practice and recommended for treating multiple recurrences of CDI in international guidelines (14). However, there is a lack of evidence of evidence-based medicine comparing the efficacy of fresh fecal bacteria, frozen fecal bacteria, lyophilized fecal bacteria and the autologous fecal bacteria for the treatment of rCDI. Hence, the advantages and disadvantages of different forms of FMT remain questionable. Therefore, it is necessary to evaluate the efficacy of different forms of FMT for treating rCDI.

With improvements in theoretical systems and methods, new meta-analyses are constantly being conducted (15). Based on the traditional meta-analysis, network meta-analysis (NMA) was developed, making it possible to simultaneously compare multiple interventions. The main purpose of NMA is to comprehensively evaluate and rank all interventions at the same time (16). Towards this goal, we performed a systematic review and NMA comparing the effectiveness of FMTs and provide scientifically reliable evidence of the effectiveness of FMT in clinical practice.

Methods

Study design

This systematic review and network meta-analysis were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for Network Meta-Analyses (PRISMA-NMA) reporting standard (17), and were registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020150064) (18).

Selection criteria

We included studies based on the following criteria: (1) Study participants ≥18 years with rCDI; (2) Interventions: comparison between FMT and FMT or antibiotics. FMT mainly included: fresh fecal bacteria, frozen fecal bacteria, lyophilized fecal bacteria, and autologous fecal bacteria; (3) Study design: randomized controlled trial (RCT); (4) Outcomes: cure rate (clinical cure was defined as lack of CDI recurrence with maintenance of resolution (that is, <3 unformed stools per day) for 8 weeks without requirement for further antibiotics (metronidazole, vancomycin, or fidaxomicin).

We excluded studies based on the following criteria: (1) Non-Chinese and non-English language studies; (2) Republished studies; (3) Studies of FMT combining a variety of treatments; (4) Retrospective and historical comparison studies.

Search strategy

We systematically searched PubMed, Cochrane Library, Web of Science, Embase, China Biomedical Medicine (CBM), China National Knowledge Infrastructure (CNKI), and WanFang databases. The search period was from the date of inception to January 16, 2022. The search strategy involved multiple pre-retrievals, and the language was unlimited. We also tracked relevant reviews and systematic reviews/meta-analyses. In addition, search engines such as Google were used to retrieve relevant studies and grey literature on the Internet. We also tracked referenced studies as a supplementary search. We conducted the search using a combination of subject and free words. The main search terms used in English language databases were the following: "fecal", "faecal", "microbiota", "feces", "faeces", "stool", "fecal flora", "faecal flora", "transplant", "transfusion", "implantation", "implant", "instillation", "microbiota", "donor", "enema", "reconstitution", "infusion", "therapy", "bacteriotherapy", "clostridium difficile", "infection", "CDI", "randomized controlled trial", "RCT". Two reviewers independently conducted the search.

Literature selection and data extraction

Search records were imported into EndNote X9 literature management software. Two reviewers independently reviewed the titles and abstracts of the studies based on the inclusion and exclusion criteria. Next, the full texts of the selected studies were read and the data extracted. Dissenting points of view were discussed to reach a consensus. Two reviewers

independently extracted data using a pre-designed Excel sheet which reviewers had been previously trained to use. The items extracted included (title, author, year of publication, country), participants' characteristics (sample size, average age, gender, fecal type, infusion pathway and volume, details of the intervention, outcomes, and measured results).

Risk of bias in individual studies

After training, two authors independently assessed the risk of bias of the included RCTs based on the Cochrane Handbook Version 5.1.0 (19), and the following items were reported: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. These items were evaluated as showing high, low or unclear risk of bias. Any disagreements were resolved through discussion and by reaching a consensus with a third reviewer.

Statistical analysis

We drew a network diagram using the "network plot" command of the Stata (V.16.0) program to ensure that the included studies form a connected network for each outcome. Standardized Meta-analysis were conducted using RevMan 5.4 software. Bayesian NMA was performed using the Markov Chain Monte Carlo (MCMC) method in the R (V.4.1.2) software package. The probability of each intervention becoming the best was analyzed based on the Surface Under the Cumulative Ranking (SUCRA) probabilities. Meanwhile, we calculated the ranking results for each intervention and assessed the possibility of publication bias by funnel plot analysis (**Supplementary Appendix 1**).

Results

Study selection

We identified 598 studies according to the pre-designed search strategy, including 34 studies in Chinese, 564 articles in English, and 2 studies obtained through other pathways. With the help of EndNote X9 software, we removed 88 duplicate studies, excluded 454 studies based on the title and abstract, and then screened the full texts of 58 studies. Finally, 10 RCTs were included in the study. The flow diagram (**Figure 1**) shows the search results and selection details.

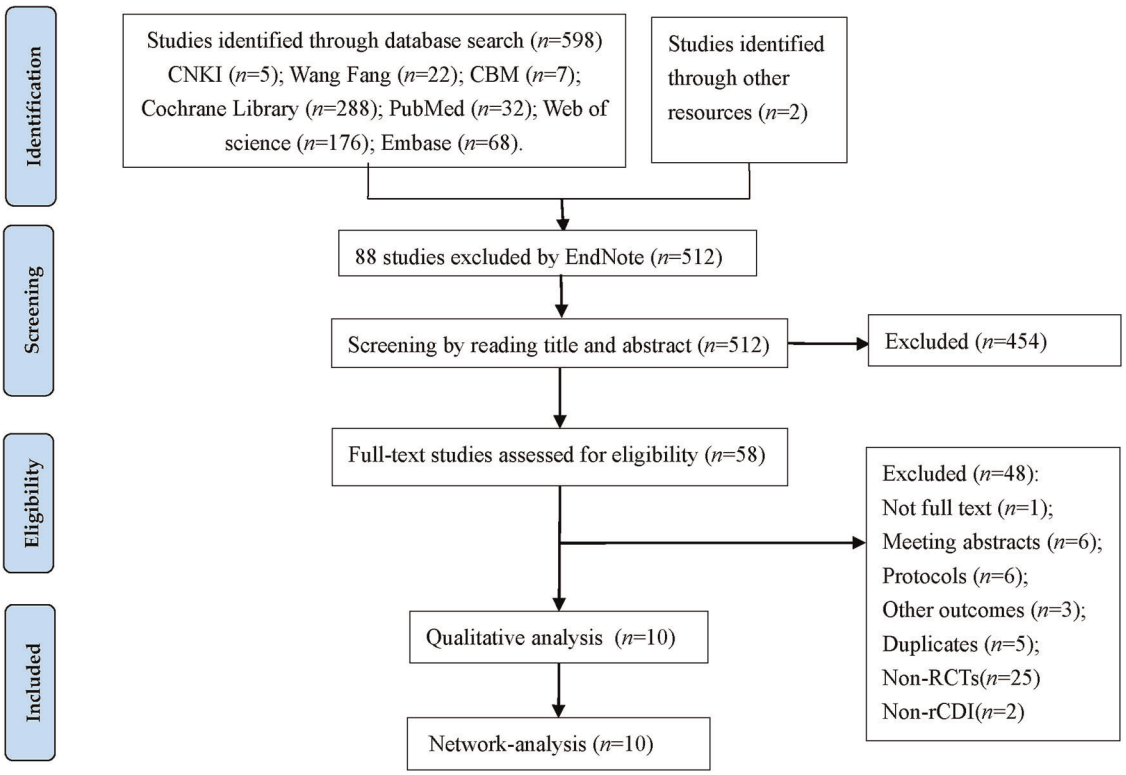

FIGURE 1
The flow chart of literature searching and screening process.

TABLE 1 Characteristics of the included studies.

Study	Disease	Country	Sample	Sample		Age (years)		Gender(male-female)		Intervention		Fecal type	FMT infusion pathway	Infusion volume	Outcomes
				T	C	T	C	T	C	T	C				
Hvas 2019 (1) (20)	rCDI	Denmark	48	24	24	22–90	24–87	4–20	11–13	B	F	B	Nasal intestinal tube or colonoscopy	50 g	①
Hvas2019(2) (20)	rCDI	Denmark	40	24	16	22–90	21–92	4–20	5–11	B	E	B	Nasal intestinal tube or colonoscopy	50 g	①
Kelly 2016 (21)	rCDI	France, America	46	22	24	48 ± 16	55 ± 14	4–18	5–19	B	D	B,D	Colonoscopy	100 g	①
Lee 2016 (22)	rCDI	Canada	219	111	108	72.5 ± 16.2	73.0 ± 16.4	37–74	36–72	A	B	A,B	Enema	64 g	①
kao 2017 (23)	rCDI	Canada	105	52	53	57.4 ± 19.1	58.7 ± 18.5	39%–61%	24.6%–75.4%	B	C	B,C	Colonoscopy, oral	360 ml, 40capsules	①
Jiang 2017 (1) (24)	rCDI	America	49	25	24	19–97	33–88	4–21	6–18	A	B	A,B	Colonoscopy	50 g	①
Jiang 2017 (2) (24)	rCDI	America	48	25	23	19–97	20–87	4–21	10–13	A	C	A,C	Colonoscopy	50 g	①
Jiang 2017 (3) (24)	rCDI	America	47	24	23	33–88	20–87	6–18	10–13	B	C	B,C	Colonoscopy	50 g	①
Jiang 2018 (25)	rCDI	America	65	34	31	63	67	9–25	10–21	B	C	B,C	Enema, oral	100–200 g/ 100 g	①
Hota 2017 (26)	rCDI	Canada	28	16	12	75.7 ± 14.5	69.6 ± 14.2	5–11	4–8	A	E	A	Enema	50 g	①
Cammarota 2015 (27)	rCDI	Roman	39	20	19	71 ± 15	75 ± 11	8–12	8–11	A	E	A	Colonoscopy	152 ± 32 g	①
van Nood 2013 (28)	rCDI	Netherlands	29	16	13	73 ± 13	66 ± 14	8–8	5–7	A	E	A	Nasal-duodenum tube	141 ± 71 g	①
Rode AA 2021 (1)(29)	rCDI	Denmark	65	34	31	75(66–81)	76(65–84)	14–20	17–14	B	E	B	Enema	50 g	①
Rode AA 2021 (2) (29)	rCDI	Denmark	67	34	33	75(66–81	67(60–79)	14–20	14–19	B	G	B	Enema	50 g	①

RCDI, Recurrent clostridium difficile infection; T, Treatment group; C, Control group; ① Cure rate.
(A) fresh fecal bacteria; (B) frozen fecal bacteria; (C) lyophilized fecal bacteria; (D) autologous fecal bacteria; (E) vancomycin; (F) fidaxomicin; (G) rectal bacteriotherapy.

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Characteristics of the included studies

Ten RCTs involving 765 patients were included in the study (20–29). All patients were diagnosed with rCDI and were from Denmark, France, the United States, Canada, Roman, and Netherlands, age ≥18 years old. Seven types of interventions were assessed in the treatment of recurrent clostridium difficile associated diarrhea (RCDAD). The included RCTs focused on 2013–2021 and were all published in the English language. FMT infusion routes include nasal intestinal tube, colonoscopy, enema, oral and nasal duodenum tube. The volume of infusion ranged from 50 g to 200 g. Nine studies (90%) (20, 22–29) compared fresh fecal bacteria, frozen fecal bacteria, lyophilized fecal bacteria, vancomycin, fidaxomicin and rectal bacteriotherapy. Only 1 study (10%) (21) compared frozen fecal bacteria with autologous fecal bacteria. In three of ten studies (30%), participants were randomly assigned to 3 groups. The basic characteristics of the 10 RCTs and clinical characteristics of patients are shown in **Table 1**.

Methodological quality of the included studies

Of the 10 RCTs, two studies (20%) (24, 25) were A-level, and the rest (20–23, 26–29) were B-level. Five studies (50%) (22–25, 27) used a computer-generated random number list for random sequence generation, and four studies (24, 25, 27, 29) used allocation concealment. Six studies (60%) (21, 22, 24, 25, 28, 29) reported the use of blinding methods for investigators and patients. We evaluated the "loss to follow-up" from the number of grouped cases and the number of results reports. Ten RCTs (100%) had no missing data. The quality evaluation showed that potential bias was caused by inadequate random sequence generation and allocation concealment, as well as by a lack of blinding of participants and personnel (**Figure 2**).

Standardized meta-analysis

The 10 studies (20–29) reported the cure of RCDAD. The results of the heterogeneity test ($I^2 > 50\%$, $p < 0.05$), the random effect model was used for meta-analysis. The results of subgroup analysis showed that the FMT was significantly better than antibiotic treatment in the cure rate of RCDAD (OR = 9.36, 95% CI: 2.43–36.03, $p = 0.001$) (82.1% vs. 37.4%), but the comparison between frozen fecal bacteria and lyophilized fecal bacteria (OR = 1.31, 95% CI: 0.53–3.25, $p = 0.95$) (90.1% vs. 88.8%), fresh fecal bacteria and frozen fecal bacteria (OR = 1.98, 95% CI: 0.16–24.54, $p = 0.08$) (75.7% vs. 76.5%) did not reach a significant difference ($p > 0.05$) (**Figure 3**).

Results of the network meta-analysis

The network plots of different FMT

Figure 4 shows the network structure of the comparisons among different interventions for the outcomes. Nodes represent different interventions and the lines between the intervention nodes indicate the direct comparisons made within RCTs. The thickness of the edge reflects the number of included trials, and is proportional to the number of trials comparing each pair of interventions. The size of the node reflects the sample size of the intervention, and it is proportional to the number of randomly assigned participants

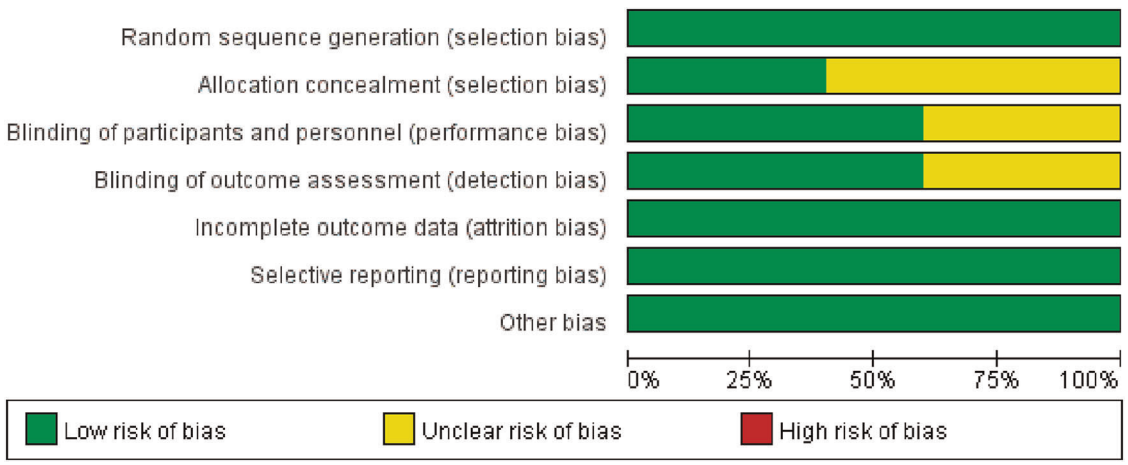

FIGURE 2
Risk of bias in included studies.

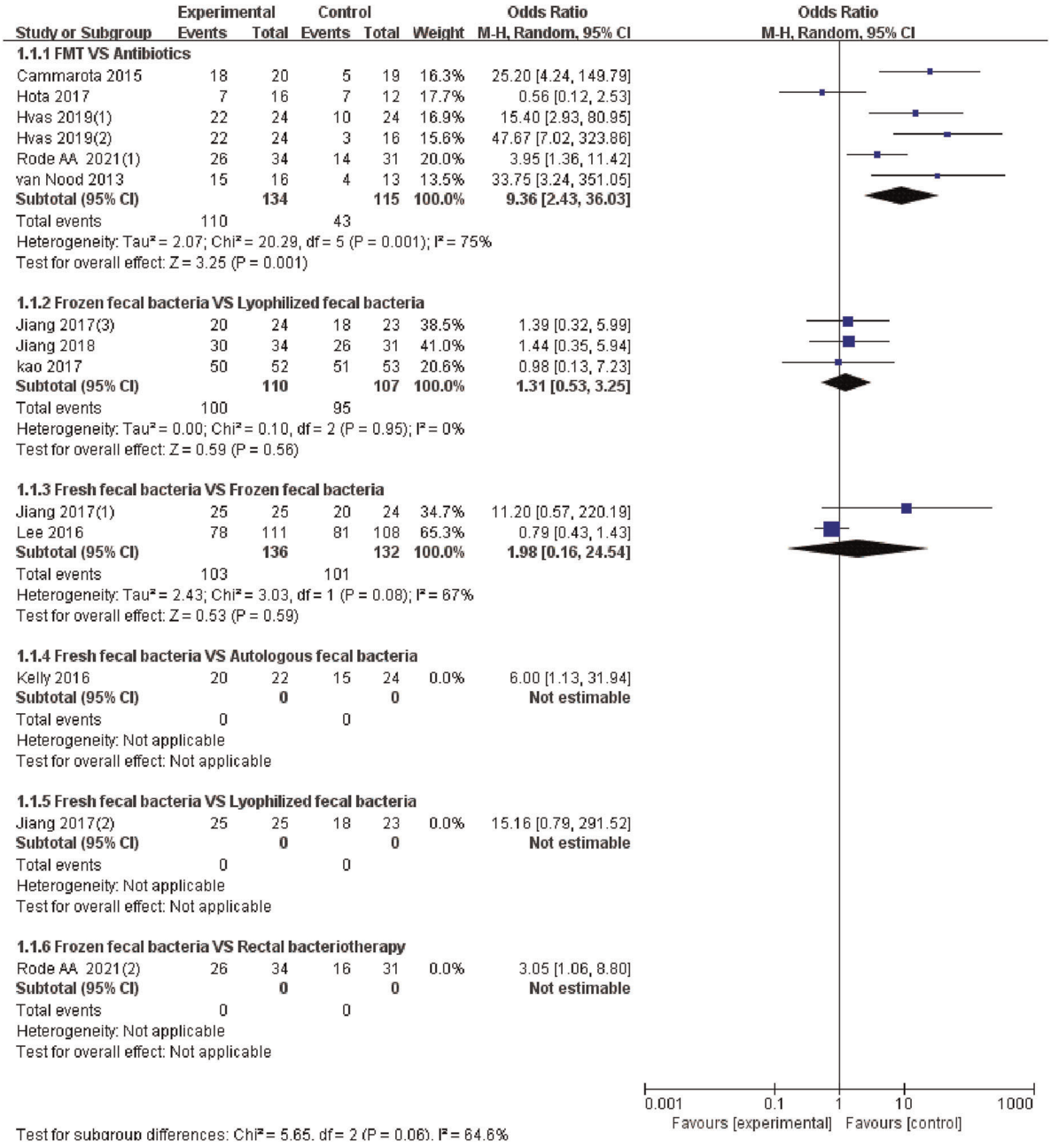

FIGURE 3
Forest of cure rate of different FMT for rCDI associated diarrhea.

(e.g., the sample size). The closed loop shows that there are both direct and indirect comparisons, and missing links between interventions reflect the lack of direct comparisons.

Network analysis

The NMA showed that fresh fecal bacteria and frozen fecal bacteria were superior to vancomycin to treat RCDAD, and the difference was statistically significant [fresh fecal bacteria vs. vancomycin (OR = 8.98, 95% CI 1.84–43.92), frozen fecal bacteria vs. vancomycin (OR = 7.44, 95% CI 1.39–39.75)]. However, differences between FMT modalities (fresh, frozen, lyophilized or autologous fecal bacteria were not statistically significant. The NMA results are shown in Table 2.

Rank probabilities

The SUCRA metric was used to rank the effectiveness of each treatment and identify the best treatment. The SUCRA line shows the percent of effectiveness of each treatment accounting for all

possible rankings and uncertainties in treatment effects. SUCRA values range from 1, being the best without uncertainty, to 0, being the worst without uncertainty. The results of the SUCRA show probability ranking in descending order is identified as fresh fecal bacteria, frozen fecal bacteria, lyophilized fecal bacteria, rectal bacteriotherapy, autologous fecal bacteria fidaxomicin and vancomycin (Figure 5).

Publication bias

Comparison-adjusted funnel plots were created for all outcomes (Figure 6). Different colors refer to different comparisons. All studies were symmetrically distributed around the $X = 0$ vertical line, so it can be assumed that included studies were less likely to show publication bias.

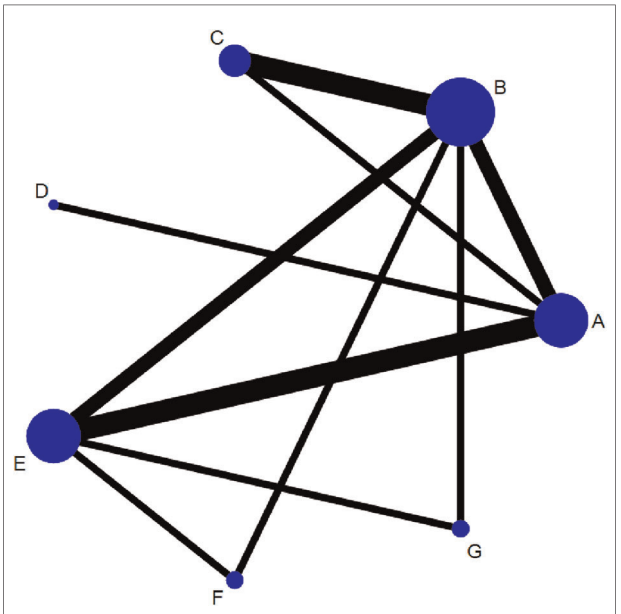

FIGURE 4
Networks for multiple treatment comparisons of cure rate. Lines between points indicate evidence of direct comparisons between two interventions. The thickness of lines indicates the number of studies using the two treatments, whereas the size of the dots indicates the total sample size of the intervention. (A) fresh fecal bacteria; (B) frozen fecal bacteria; (C) lyophilized fecal bacteria; (D) autologous fecal bacteria; (E) vancomycin; (F) fidaxomicin; (G) rectal bacteriotherapy.

Discussion

FMT, in which the fecal microbiome of a healthy donor is transplanted into a patient, aims to restore the normal gut microbiome and is already a successful therapy for rCDI (30). However, the underlying mechanisms remain unclear. Bacilli and thick-walled bacteria are key components of FMT (31). Mullish et al. (32) reported that FMT accelerated the hydrolysis of taurocholic acid by restoring the activity of bile salt hydrolase in the gut microbiome (33). Although there are still many challenges in FMT, this method has shown therapeutic potential to treat refractory or rCDI (34). We conducted the first network meta-analysis to date on the treatment of recurrence of CDI compared different types of FMT with standard-of-care treatment with antibiotics, and compared with rectal bacterial therapy.

The 10 studies included in this NMA met quality evaluation standards: 2 studies were assessed as being A-level, and 8 studies were B-level. The risk of bias depended mainly on the blinding methods and other biases. The cure rate is an objective outcome. Therefore, the use of blinding methods in these studies brought less bias. Other biases stemmed mainly from unreported information about funding and conflicts of interest. Therefore, the methodological quality of the studies included in this NMA was high and it is hoped that follow-up research will further improve random sequence generation, allocation concealment, blinding methods and data integrity.

The risk of recurrence after antibiotic treatment of CDI has attracted the attention of medical experts, and a high mortality has been reported (35–37). Therefore, CDI remains a significant medical challenge. The meta-analyses (38–40) confirmed that FMT was an effective, safe and economical method to treat rCDI. Unfortunately, there was no indirect comparison of different FMT modalities. Hui's study (41) suggested that fresh fecal bacteria worked better than antibiotics and placebo for rCDI, but the effect of an infusion of fresh fecal bacteria

TABLE 2 Head-to-head comparisons of efficacy of FMT.

A	0.83(0.15,4.64)	0.51(0.05,5.09)	0.17 (0.01,3.51)	0.11(0.02,0.5)	0.14(0.01,2.64)	0.20 (0.01,3.15)
1.21 (0.22,6.77)	B	0.62 (0.11,3.38)	0.20 (0.01,6.67)	0.13(0.03,0.72)	0.17 (0.01,2.53)	0.24 (0.02,2.97)
1.95 (0.20,19.44)	1.62 (0.30,8.85)	C	0.33 (0.01,14.79)	0.22 (0.02,2.19)	0.28 (0.01,6.49)	0.38 (0.02,7.83)
6.00 (0.28,126.34)	4.97(0.15,164.69)	3.07 (0.07,139.57)	D	0.67(0.02,20.74)	0.86(0.01,58.13)	1.18 (0.02,72.65)
8.98 (1.84,43.92)	7.44(1.39,39.75)	4.60 (0.46,46.37)	1.50 (0.05,46.49)	E	1.28(0.09,18.32)	1.77(0.14,21.87)
7.01 (0.38,129.38)	5.80(0.40,85.13)	3.59 (0.15,83.50)	1.17 (0.02,79.25)	0.78(0.05,11.14)	F	1.38 (0.04,44.62)
5.08 (0.32,81.14)	4.21(0.34,52.48)	2.60 (0.13,52.91)	0.85 (0.01,52.04)	0.57 (0.05,6.99)	0.72(0.02,23.45)	G

(A) fresh fecal bacteria; (B) frozen fecal bacteria; (C) lyophilized fecal bacteria; (D) autologous fecal bacteria; (E) vancomycin; (F) fidaxomicin; (G) rectal bacteriotherapy.

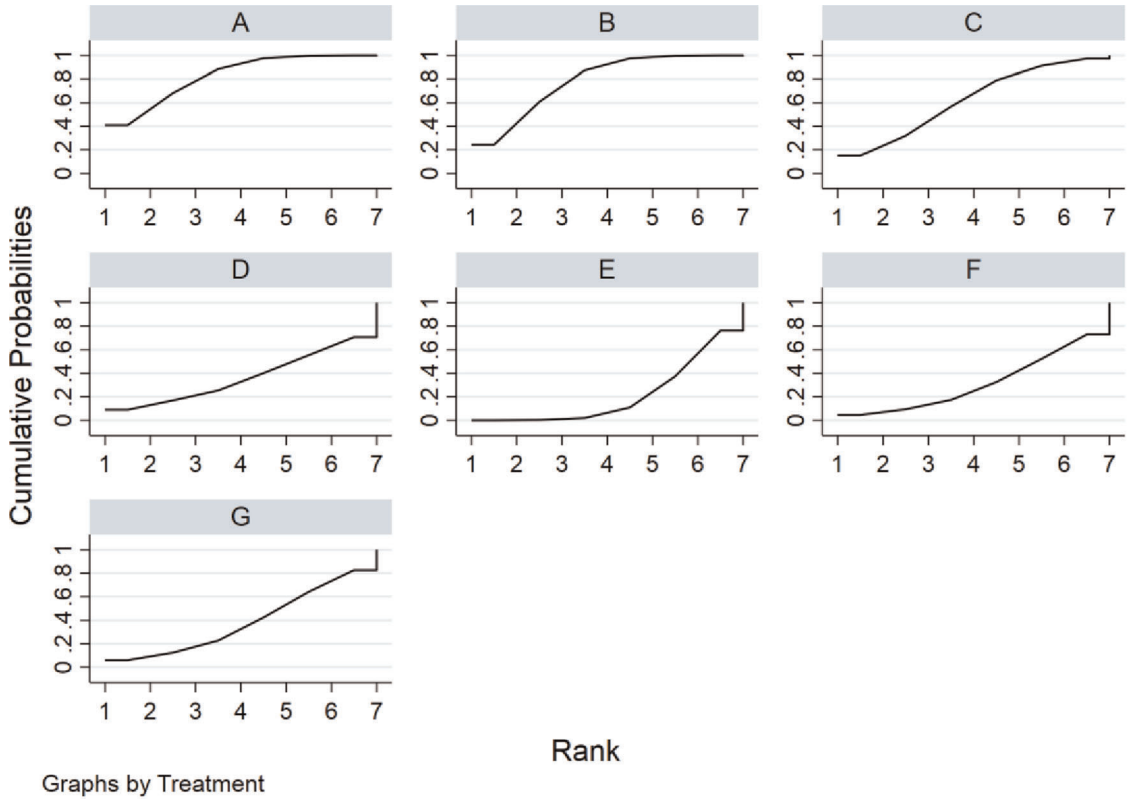

FIGURE 5
Rank probabilities for cure rate. (A) fresh fecal bacteria; (B) frozen fecal bacteria; (C) lyophilized fecal bacteria; (D) autologous fecal bacteria; (E) vancomycin; (F) fidaxomicin; (G) rectal bacteriotherapy.

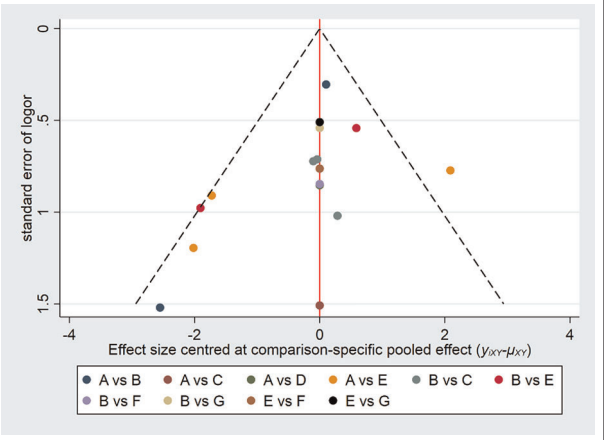

FIGURE 6
Funnel plot of the cure rate with different forms of FMT for rCDI-associated diarrhea. (A) fresh fecal bacteria; (B) frozen fecal bacteria; (C) lyophilized fecal bacteria; (D) autologous fecal bacteria; (E) vancomycin; (F) fidaxomicin; (G) rectal bacteriotherapy.

by colonoscopy or enema was not significantly different from that of frozen fecal bacteria or lyophilized fecal bacteria administered through oral capsules. This was consistent with the results of this study.

This NMA confirmed that there were no statistically significant differences between fresh fecal bacteria, frozen fecal bacteria or lyophilized fecal bacteria for the treatment of RCDAD. The reason may be that the number and type of fecal bacteria found in fresh, frozen or lyophilized fecal bacteria preparations are similar (42), so there were no significant differences in terms of therapeutic effects. Since it is difficult to collect fresh fecal bacteria, they can be replaced with frozen fecal bacteria or lyophilized fecal bacteria to treat rCDI in the future. Lyophilized fecal bacteria are easy to store and very useful for patients and doctors, it can be used at any time and have commercial value (43, 44). Lyophilized fecal bacteria not only improve the effectiveness of rCDI treatment, but also provide alternative treatments for rCDI patients. Furthermore, lyophilized fecal bacteria has the potential of

large- scale production with a larger capacity than fresh fecal bacteria and frozen fecal bacteria, even when donor stool banks are established.

During the course of FMT treatment, different degrees of bloating, abdominal pain, diarrhea and other manifestations may appear, which are caused by changes in the composition of the gut microbiome, gene expression by mucosal cells, immunologic function of the intestinal mucosa, intestinal ecological environment and differences in body metabolism (45–47). Tang's (48) meta-analysis indicated that FMT was safe for rCDI. Although some serious adverse reactions related to FMT have been reported, these are not serious and do not cause harm to patients. Ten studies described the adverse events, but did not elaborate on the preventive measures. It is hoped that the adverse events produced by FMT for the treatment of rCDI can be studied in detail in the future. Moreover, the finding of a potential reduction in all causes mortality after FMT were reported in two study included in our NMA.

Our study has several limitations. First, current studies have used FMT for the treatment of RCDAD as an example to validate the NMA method, based on the OR value and 95% CI in Stata 16.0 and R 4.1.2 software. However, this method has some limitations and can't comprehensively reflect all the therapeutic effects. To determine the OR value at different time points, NMAs based on the cure rate should be adopted. SUCRA provides an opportunity to determine the best available treatment, one must interpret with caution as high values may only provide supportively, but not conclusive, evidence for treatment options. In addition, this study only focused on the cure rate. The total effective rate, and adverse events rate after FMT for rCDI need to be further analyzed to strengthen the evidence.

Conclusions

Fresh fecal bacteria and frozen fecal bacteria were superior to vancomycin for the treatment of RCDAD, but there were no significant differences in cure rate between fresh fecal bacteria, frozen fecal bacteria or lyophilized fecal bacteria. Based on the SUCRA analysis, fresh fecal bacteria were the best treatment for RCDAD diarrhea, frozen fecal bacteria and lyophilized fecal bacteria may also achieve the same effect.

Data availability statement

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

Author contributions

LY and WL are co-first authors, they have contributed equally to this manuscript. LY and WM conceived and designed this systematic review and network meta-analysis. XM, LH, WL and JT were involved in the data acquisition and data analysis. LY and HW interpreted the results. LY, WL and X Z drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Supplementary material

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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.

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Incision pressing, a simple and effective intervention to reduce colorectal surgical site infection: A propensity score-matched study

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Background: Colorectal surgery is associated with a high risk of surgical site infection (SSI). In March 2017, we developed an intervention, called "PRESS", with the aim of reducing colorectal superficial SSI. This study assessed the effect of the new intervention in reducing the rates of superficial SSI in colorectal surgery.

Methods: This study was a retrospective review of 312 PRESS+ patients compared to 171 historical control PRESS– patients who were 18 years of age or older and underwent elective colorectal surgery with clean-contaminated wounds from January 2015 to June 2020. In the PRESS+ groups, we pressed the incision downward hard with clean gauze after the interrupted suturing of the skin. Propensity score matching with 15 variables was performed in a 1:1 ratio to reduce selection bias. Univariate analysis and multivariate analysis were performed to identify risk factors associated with SSI.

Results: The characteristics of the PRESS+ ($n = 160$) and PRESS– ($n = 160$) groups were well balanced after propensity score matching. The PRESS+ group had a lower superficial SSI rate (1.9% vs. 6.9%, $P = 0.029$) and a lower overall SSI rate (2.5% vs. 10.0%, $P = 0.006$) than the PRESS– group. Furthermore, multivariate analysis showed that the incisional press was an effective protective factor for superficial SSI (adjusted odds ratio = 0.215, 95% confidence interval = 0.057–0.818, $P = 0.024$). In addition, female sex ($P = 0.048$) and blood transfusion ($P = 0.011$) were demonstrated to be independent risk factors for superficial SSI.

Conclusion: The incisional press after suturing is a simple, costless, and effective intervention in reducing superficial incisional SSI.

KEYWORDS

surgical site infection (SSI), colorectal surgery, risk factor, prevention bundle, propensity score (PS) matching (PSM)

Introduction

Surgical site infection (SSI) is a common postoperative complication after surgery (1). SSI leads to increased postoperative pain, longer hospital stays, increased healthcare costs and worse long-term survival outcomes (2, 3). Due to the high bacterial load in the colorectal lumen, colorectal surgery is associated with a high risk of SSI with incidence rates up to 34.7% (4–6).

To lower the incidence of SSI following colorectal surgery, many interventions have been studied as follows: mechanical bowel preparation; prophylactic oral and intravenous antibiotics; and appropriate skin preparation to reduce endogenous bacteria in the colorectal lumen and skin; wound protection; and subcutaneous wound irrigation to directly prevent wound contamination (5–10). Additionally, subcutaneous drainage is implemented to obliterate the dead space between the sutured skin and facia (11, 12). The presence of dead space has been believed to be a risk factor for superficial incisional SSI since the 1880s (13–15). However, the efficiency of subcutaneous drainage in reducing the rate of incisional SSI is controversial (12, 16–18).

In March 2017, we developed a simple and costless intervention, called "PRESS", which could theoretically obliterate the incisional dead space. Here, we assessed the effect of this new intervention in reducing rates of superficial incisional infection in patients undergoing colorectal surgery. We also performed analyses to identify risk factors associated with SSI in our study population.

Methods

Description of intervention

Suture often leads to the formation of dead space. Following continuous closure of the linea alba fascia with PDS Plus (**Figure 1A**), the skin is closed with interrupted 2-0 nonabsorbable sutures without suturing subcutaneous tissue. As the stitches are tied, the skin and part of the subcutaneous tissue are usually gathered, creating a ridge in the middle of the incision, which causes the formation of dead space between the subcutaneous tissue and sutured linea alba fascia (**Figure 1B**). The dead space accumulates tissue fluid and blood clots, facilitating the occurrence of SSI. To reduce the rate of superficial SSI, a unique intervention was developed in March 2017, which was performed on all the incisions in the subsequent colorectal surgeries performed at our institution. After completing the interrupted sutures of the skin, we pressed the incision downward hard with clean gauze using our hands (**Figure 1C**, and **Supplemental Video**), which resulted in a sensation of friction between the incisional tissues and stitches. The process of pressing took about half a minute to one minute, and was stopped until we could not feel any frictions. The subcutaneous fat tissue was redistributed, and the dead space under the incision was theoretically obliterated. In general, tissue fluid seeped out from the dead space (**Figure 1D**).

To verify the assumed effect of incisional pressing on obliterating the dead space, we examined the dead space under the incision before and after incisional pressing by ultrasonography. As shown in **Figure 2**, there was an obvious dead space (**Figure 2A**) before incisional pressing. Then the dead space was obliterated following incisional pressing in **Figure 2B**.

Before the introduction of the incisional press intervention, an SSI prevention bundle had been applied to patients who underwent colorectal surgery in our institution since January 2015, which included the following interventions: mechanical bowel preparation; prophylactic intravenous antibiotics; appropriate method of hair removal and skin preparation; application of wound edge protector; and wound irrigation.

In brief, oral polyethylene glycol electrolyte powder was administered on the day before surgery. Oral antibiotic bowel preparation was not performed. Second-generation cephalosporin and metronidazole were administered to all patients 30–60 min before surgery, repeated every 3 h during surgery or when 800 ml of estimated blood loss occurred and continued for 24 h after surgery. Hair removal was performed with clippers just before the surgery, and the skin was scrubbed with povidone–iodine three times and 75% alcohol one time. The midline surgical wound was protected by a plastic wound edge protector during laparotomy. After closure of the linea alba, the incision was routinely irrigated with 500 milliliter 0.9% saline. No subcutaneous suture was performed, and no subcutaneous drain was placed. Interrupted sutures with 2-0 Mersilk (Ethicon) were placed for skin closure. Finally, the incision was covered with sterile dressings in both groups. The incision was monitored every two days. A 30-day short-term follow-up was performed in the outpatient department by M.K. and Y.J.

Study design and participants

The present study was a retrospective review of prospectively collected data from January 2015 to June 2020 in Shandong Provincial Hospital, China. Consecutive patients who were 18 years of age or older and underwent elective colorectal surgery with clean-contaminated wounds were included. Patients who underwent emergency laparotomy, abdominoperineal resection, Hartmann's procedure, colostomy and closure of stoma were excluded. We also excluded patients who were treated with steroids and who had bowel obstruction, perforation, any preoperative intraperitoneal

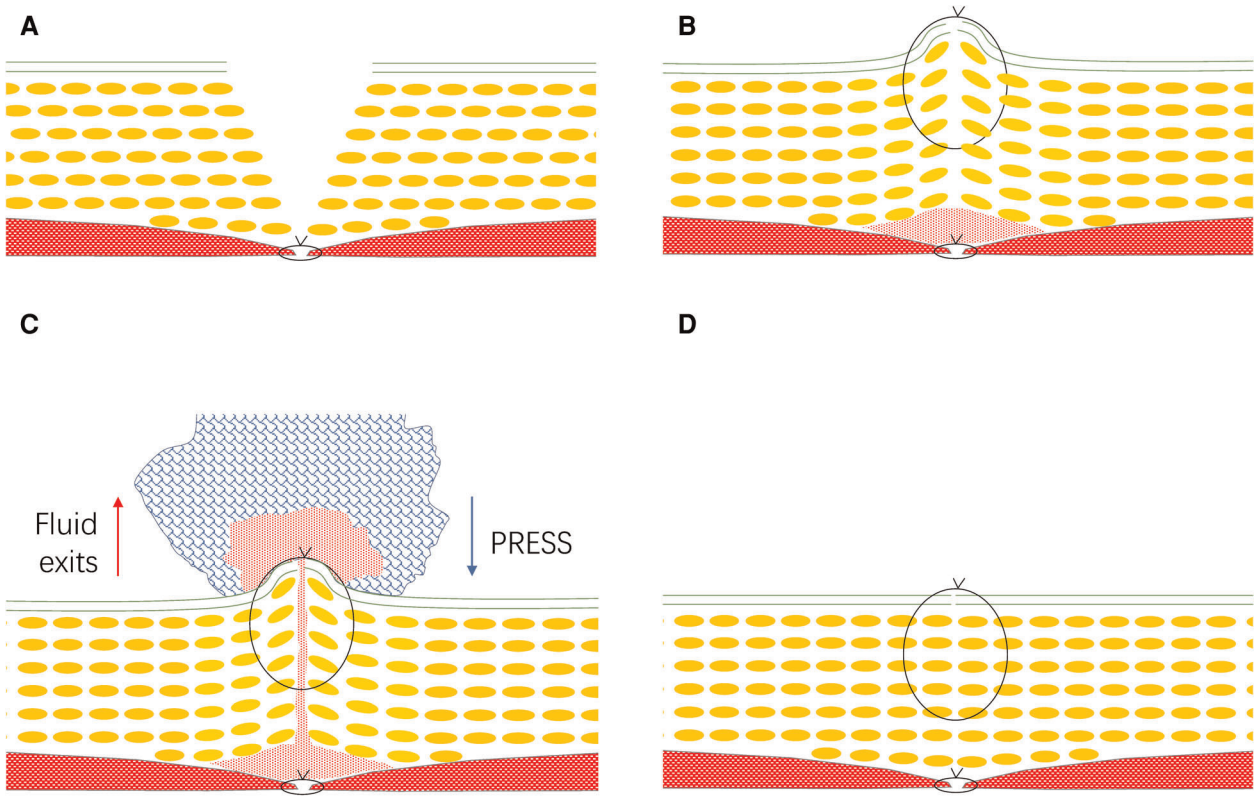

FIGURE 1
Illustration of suturing wound. Following closure of the linea alba fascia (A), the skin is closed with interrupted 2-0 nonabsorbable sutures without suturing subcutaneous tissue. As the stitches are tied, the skin and part of the subcutaneous tissue are usually gathered, creating a ridge in the middle of the incision, which causes the formation of dead space (B). The dead space accumulates tissue fluid and blood clots. To minimize dead space, we pressed the incision downward with clean gauze (C). The subcutaneous fat tissue was redistributed, and the dead space under the incision was obliterated. In general, tissue fluid seeped out from the dead space (D).

infection and reoperation within 30 days due to nonwound complications. All the rectal cancer patients with neoadjuvant chemoradiotherapy were also excluded because of the existence of defunctioning stoma. This study was performed in line with the principles of the Declaration of Helsinki. The Ethical Committee of Shandong Provincial Hospital approved this study. Patient consent was waived because this was a retrospective review.

We divided the participants into the following two groups: (1) participants who received incisional press intervention from March 2017 to June 2020 (PRESS+ group); and (2) historical controls who did not receive incisional press intervention from January 2015 to February 2017 (PRESS− group).

Variables and definitions of outcomes

Variables were collected directly from electronic patient records. Patient parameters, including sex, age, indication for surgery, body mass index (BMI), American Society of Anesthesiologists (ASA) score, smoking history, diabetes mellitus, cardiovascular diseases, hypertension, chronic obstructive pulmonary disease (COPD), preoperative hemoglobin (HGB), preoperative albumin (ALB), surgical approach (open or laparoscopic), surgical procedure (right hemicolectomy, left hemicolectomy, anterior resection or others), intraoperative estimated blood loss and perioperative blood transfusion, were analyzed. In the present study, the conversion from laparoscopic to open surgery was classified into open surgery, and sigmoid resection was classified into left hemicolectomy.

The primary outcome for our analysis was the incidence of superficial incisional SSI. SSIs were diagnosed by one of the experienced surgeons from our surgical team (M.K., C.H., Y.J. or H.S.) according to the Centers for Disease Control (CDC) guidelines (19). Superficial incisional SSI was considered as an infection that occurred within 30 days after the operation and involved only skin and subcutaneous tissue. The overall SSI, deep incisional SSI (involving only deep soft tissue) and organ/space SSI (involving only the intra-abdominal space) were analyzed separately. Anastomotic leakage (AL) was diagnosed according to the definition of the International Study Group of Rectal Cancer (20).

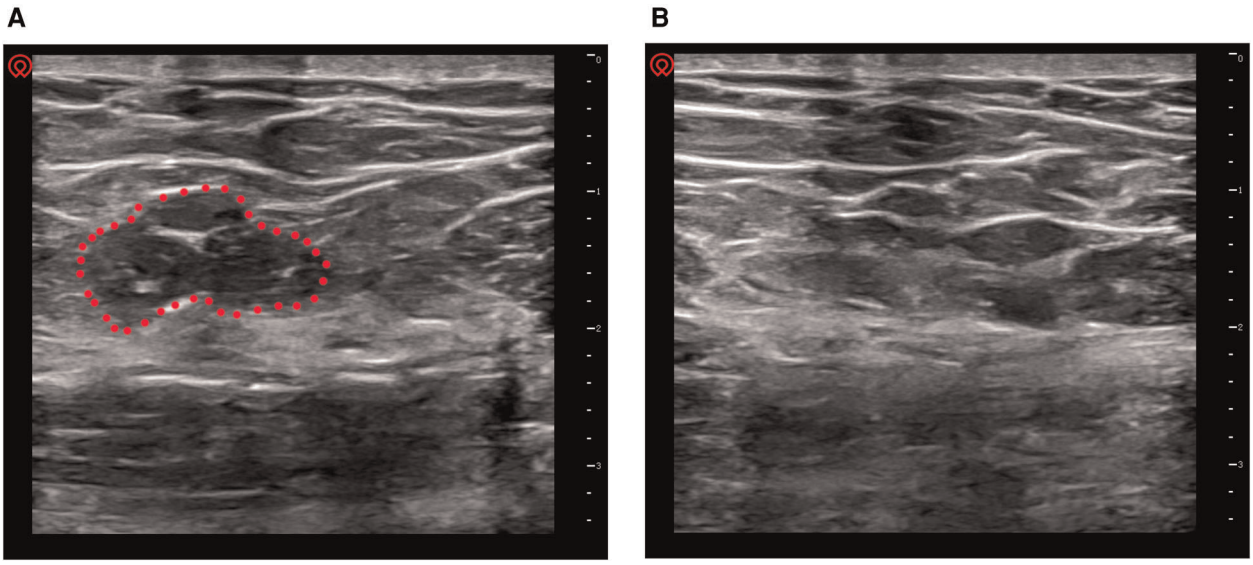

FIGURE 2
Verifying dead space by ultrasonography. (A) before incisional pressing. there was an obvious dead space under the incision (the area in the red dotted circle); (B) after incisional pressing, the dead space disappeared.

Statistical analysis

Continuous variables are presented as the mean (standard deviation [SD]) or median (interquartile range [IQR]) depending on distribution type. To compare characteristics between groups, Student's t-test or Wilcoxon rank sum test was used for continuous variables, and Pearson's Chi-square test or Fisher's exact test was used for categorical variables.

To estimate the impact of the incisional press on SSI with minimized selection bias between the PRESS+ group and the PRESS− group, propensity score matching was performed. Fifteen variables, including preoperative characteristics (age, sex, indication for surgery, BMI, smoking history, diabetes mellitus, cardiovascular diseases, hypertension, COPD, ASA score, preoperative CRT, preoperative ALB level and preoperative HGB level) and surgical characteristics (surgical approach and surgical procedure), were selected for matching. Optimal matching was performed in a 1:1 ratio without replacement and with a caliper distance of 0.03. A matched cohort was generated with well-balanced background characteristics.

Furthermore, in both the unmatched cohort and matched cohort, univariate analysis and multivariate analysis were performed sequentially to identify independent factors associated with superficial incisional SSI and overall SSI. Continuous variables were transformed into categorical variables for the logistic regression model. In particular, age greater than 65 years, BMI greater than or equal to 28, ASA score higher than or equal to 3, preoperative HGB level less than or equal to 110 and preoperative ALB level less than or equal to 35 were used as variables for the analysis. Variables with P-values <0.10 in the univariate analysis were then subjected to a multivariate stepwise backward logistic regression analysis. Values of the univariate and multivariate analyses were expressed as odds ratios (ORs) and 95% confidence intervals (CIs).

We used SPSS 24.0 (IBM Corp, Armonk, NY) for data analysis. R software 4.0.3 (R Project for Statistical Computing) was used to generate forest plots for the multivariate analysis results. All P-values were two-sided, and a value of $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

We identified 638 patients who underwent elective colorectal surgery by our surgical team at the Shandong Provincial Hospital from January 2015 to June 2020. A total of 155 patients were excluded according to the exclusion criteria (**Figure 3**). A total of 483 patients were included in the analysis as follows: 312 patients received the incisional press procedure (PRESS+ group); and 171 patients who underwent surgery before March 2017 were assigned to the control group (PRESS− group). All the patients were available for a 30-day follow-up. **Table 1** compares the preoperative and surgical characteristics between the PRESS+ and PRESS− groups. There were more patients with colorectal cancer (95.5% vs. 90.1%, $P = 0.019$) and laparoscopic surgery (67.0% vs. 36.8%, $P < 0.001$) in the PRESS+ group than in the PRESS− group. Other baseline characteristics were similar ($P > 0.05$)

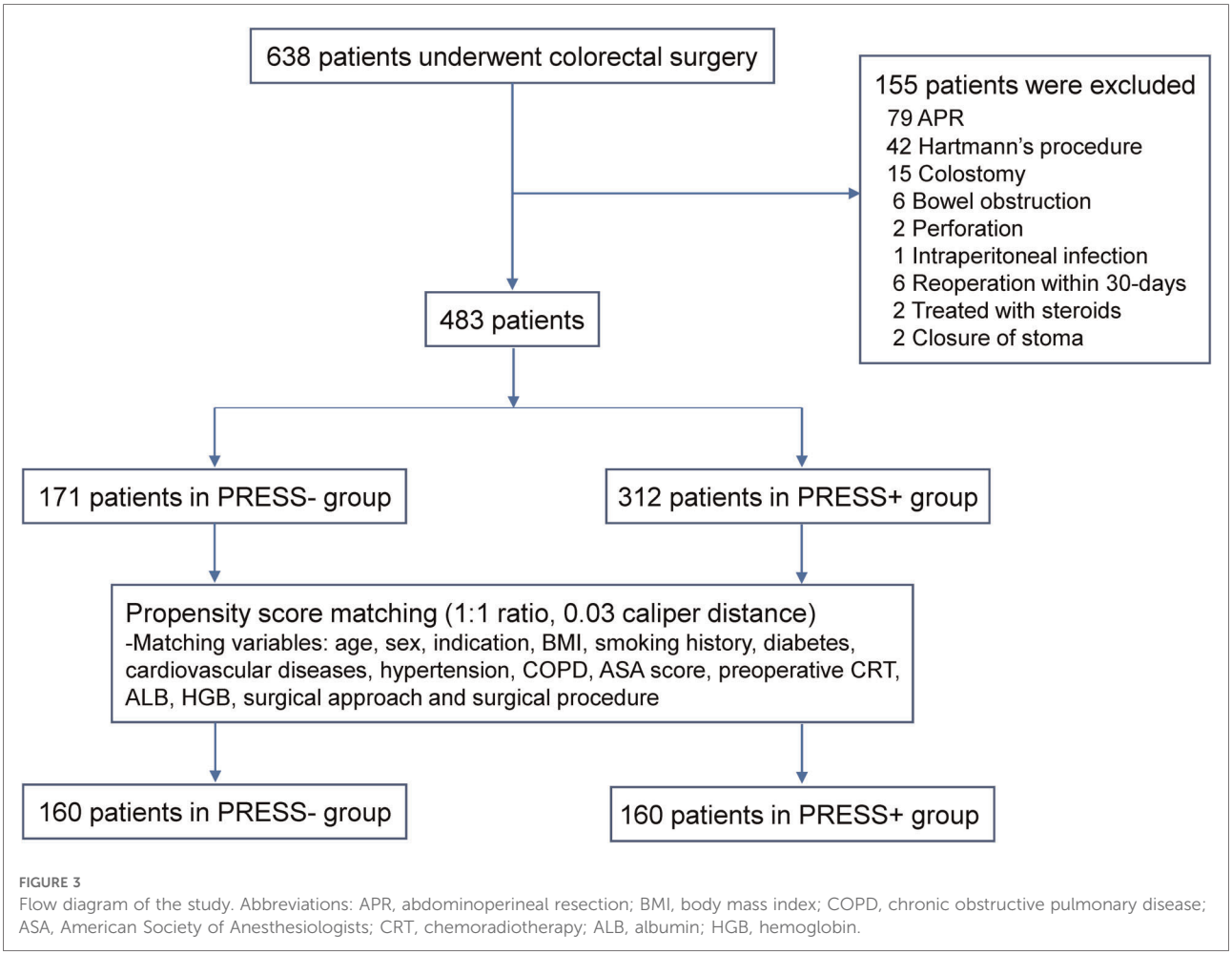

FIGURE 3
Flow diagram of the study. Abbreviations: APR, abdominoperineal resection; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists; CRT, chemoradiotherapy; ALB, albumin; HGB, hemoglobin.

between groups before matching. After matching, 160 patients in each group remained for the final analysis. All preoperative and surgical characteristics, including indications for surgery ($P = 0.671$) and surgical approaches ($P = 0.909$), were well balanced between the groups.

Outcomes

The outcome parameters in the unmatched cohort and matched cohort are shown in **Table 2**. After matching, the PRESS+ group had a significantly lower overall SSI rate (2.5% vs. 10.0%, $P = 0.006$) and a significantly lower superficial incisional SSI rate (1.9% vs. 6.9%, $P = 0.029$) than the PRESS− group. However, the rates of other types of SSIs were not different between the two groups, including deep SSIs (0.0% vs. 0.6%, $P = 1.000$) and organ/space SSIs (0.6% vs. 2.5%, $P = 0.371$). Furthermore, wound disruption, anastomotic leakage and hospital stay did not significantly differ between the PRESS+ and PRESS− groups ($P = 1.000$, $P = 0.556$ and $P = 0.136$, respectively).

Factors associated with SSI

Univariate analysis and multivariate analysis were performed successively to identify factors associated with overall SSI and superficial incisional SSI in our study. The results are presented in **Figure 4**, **Supplementary Table S1, S2**. Female sex and blood transfusion were significant independent risk factors for overall SSI and superficial SSI in both unmatched and matched cohorts. In contrast, incisional press was a significantly effective protective factor for overall and superficial SSI. In particular, the adjusted OR of superficial SSI was 3.393 for female sex (95% CI = 1.013–11.362, $P = 0.048$), 4.450 for blood transfusion (CI = 1.411–14.028, $P = 0.011$) and 0.215 for incisional press (95% CI = 0.057–0.818, $P = 0.024$) in the matched cohort.

Discussion

SSI following colorectal surgery is a major cause of morbidity. To reduce the rate of SSI, we implemented a

TABLE 1 Comparison of baseline characteristics and surgical characteristics in the overall population, before and after propensity score matching.

Variables	All patients	Before matching			After matching		
	n = 483	PRESS −group *n* = 171	PRESS + group *n* = 312	*P*-value	PRESS −group *n* = 160	PRESS+ group *n* = 160	*P*-value
Patient characteristics							
Age, mean (SD), y	59.59 (12.14)	58.82 (11.98)	60.00 (12.22)	0.308	59.39 (11.57)	59.48 (12.68)	0.952
Sex							
Female	171 (43.3)	74 (43.3)	135 (43.3)	>0.99	69 (43.1)	70 (43.8)	0.910
Male	312 (56.7)	97 (56.7)	177 (56.7)		91 (56.9)	90 (56.3)	
Indication							
Colorectal cancer	452 (93.6)	154 (90.1)	298 (95.5)	**0.019**	147 (91.9)	149 (93.1)	0.671
Other	31 (6.4)	17 (9.9)	14 (4.5)		13 (8.1)	11 (6.9)	
BMI, mean (SD), kg/m^2	24.37 (3.43)	24.65 (3.53)	24.23 (3.37)	0.225	24.62 (3.45)	24.44 (3.76)	0.679
Smoking history							
No	323 (66.9)	120 (70.2)	203 (65.1)	0.254	110 (68.8)	109 (68.1)	0.904
Yes	160 (33.1)	51 (29.8)	109(34.9)		50 (31.3)	51 (31.9)	
Diabetes mellitus							
No	412 (85.3)	147 (86.0)	265 (84.9)	0.760	138 (86.3)	138 (86.3)	>0.99
Yes	71 (14.7)	24 (14.0)	47 (15.1)		22 (13.8)	22 (13.8)	
Cardiovascular diseases							
No	445 (92.1)	157 (91.8)	288 (92.3)	0.847	148 (92.5)	148 (92.5)	>0.99
Yes	38 (7.9)	14 (8.2)	24 (7.7)		12 (7.5)	12 (7.5)	
Hypertension							
No	343 (71.0)	119 (69.6)	224 (71.8)	0.610	114 (71.3)	118 (73.8)	0.617
Yes	140 (29.0)	52 (30.4)	88 (28.2)		46 (28.8)	42 (26.3)	
COPD							
No	458 (94.8)	165 (96.5)	293 (93.9)	0.221	154 (96.3)	150 (93.8)	0.305
Yes	25 (5.2)	6 (3.5)	19 (6.1)		6 (3.8)	10 (6.3)	
ASA score							
I-II	348 (72.0)	123 (71.9)	225 (72.1)	0.965	115 (71.9)	110 (68.8)	0.541
III-IV	135 (28.0)	48 (28.1)	87 (27.9)		45 (28.1)	50 (31.3)	
Preoperative CRT							
No	418 (86.5)	147 (86.0)	271 (86.9)	0.783	137 (85.6)	142 (88.8)	0.403
Yes	65 (13.5)	24 (14.0)	41 (13.1)		23 (14.4)	18 (11.3)	
Preoperative HGB, mean (SD), g/L	125.49 (24.17)	125.89 (24.02)	125.27 (24.29)	0.787	125.50 (24.35)	123.76 (24.81)	0.526
Preoperative ALB, mean (SD), g/L	39.14 (4.16)	39.31 (4.04)	39.04 (4.24)	0.493	39.09 (3.95)	38.82 (4.46)	0.571
Surgical characteristics							
Surgical approach							
Open[a]	211 (43.7)	108 (63.2)	103 (33.0)	**<0.001**	97 (60.6)	98 (61.3)	0.909
Laparoscopic	272 (56.3)	63 (36.8)	209 (67.0)		63 (39.4)	62 (38.8)	
Surgical Procedure							
Right hemicolectomy	134 (27.7)	47 (27.5)	87 (27.9)	0.500	45 (28.1)	48 (30.0)	0.956
Left hemicolectomy	88 (18.2)	33 (19.3)	55 (17.6)		30 (18.8)	32 (20.0)	
Anterior resection	248 (51.3)	84 (49.1)	164 (52.6)		80 (50.0)	75 (46.9)	
Others	13 (2.7)	7 (4.1)	6 (1.9)		5 (3.1)	5 (3.1)	
Blood Loss							
<200 ml	416 (86.1)	142 (83.0)	274 (87.8)	0.146	134 (83.8)	135 (84.4)	0.879
≥200 ml	67 (13.9)	29 (17.0)	38 (12.2)		26 (16.3)	25 (15.6)	

(*continued*)

TABLE 1 Continued

Variables	All patients	Before matching			After matching		
	n = 483	PRESS −group *n* = 171	PRESS + group *n* = 312	*P*-value	PRESS −group *n* = 160	PRESS+ group *n* = 160	*P*-value
Blood transfusion							
No	413 (85.5)	146 (85.4)	267 (85.6)	0.953	136 (85.0)	131 (81.9)	0.452
Yes	70 (14.5)	25 (14.6)	45 (14.4)		24 (15.0)	29 (18.1)	

Abbreviations: SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists; CRT, chemoradiotherapy; HGB, hemoglobin; ALB, albumin.
Values in parentheses are percentages, unless identified otherwise.
Bold P-values indicate that differences between the groups were statistically significant.
[a]Includes the procedures that are converted from laparoscopic to open surgery.

TABLE 2 Comparison of outcome parameters in the overall population, before and after propensity score matching.

Variables	All patients	Before matching			After matching		
	n = 483	PRESS− group *n* = 171	PRESS+ group *n* = 312	*P*-value	PRESS− group *n* = 160	PRESS+ group *n* = 160	*P*-value
Overall SSI							
No	458 (94.8)	154 (90.1)	304 (97.4)	**<0.001**	144 (90.0)	156 (97.5)	**0.006**
Yes	25 (5.2)	17 (9.9)	8 (2.6)		16 (10.0)	4 (2.5)	
Superficial SSI							
No	466 (96.5)	159 (93.0)	307 (98.4)	**0.002**	149 (93.1)	157 (98.1)	**0.029**
Yes	17 (3.5)	12 (7.0)	5 (1.6)		11 (6.9)	3 (1.9)	
Deep SSI							
No	482 (99.8)	170 (99.4)	312 (100.0)	0.354	159 (99.4)	160 (100.0)	>0.99
Yes	1 (0.2)	1 (0.6)	0 (0.0)		1 (0.6)	0 (0.0)	
Organ/space SSI							
No	476 (98.6)	167 (97.7)	309 (99.0)	0.251	156 (97.5)	159 (99.4)	0.371
Yes	7 (1.4)	4 (2.3)	3 (1.0)		4 (2.5)	1 (0.6)	
Wound disruption							
No	482 (99.8)	171 (100.0)	311 (99.7)	>0.99	160 (100.0)	159 (99.4)	>0.99
Yes	1 (0.2)	0 (0.0)	1 (0.3)		0 (0.0)	1 (0.6)	
AL							
No	466 (96.5)	164 (95.9)	302 (96.8)	0.612	153 (95.6)	155 (96.9)	0.556
Yes	17 (3.5)	7 (4.1)	10 (3.2)		7 (4.4)	5 (3.1)	
Hospital stay[a], median (IQR), d	10 (8–11)	10 (8–13)	10 (8–11)	**0.019**	10 (8–13)	10 (9–11)	0.136

Abbreviations: SSI, surgical site infections; AL, anastomotic leakage; IQR, interquartile range.
Values in parentheses are percentages, unless identified otherwise.
Bold P-values indicate that differences between the groups were statistically significant.

simple and costless intervention beyond the previously existing SSI prevention bundle in our institute. The propensity score-matched analysis indicated that implementation of an incisional press after suturing in elective colorectal surgery led to a significant reduction in superficial SSI and overall SSI. In addition, we demonstrated that incisional press intervention was a significantly effective protective factor, and female sex and blood transfusion were independent risk factors for superficial SSI and overall SSI.

Before the introduction of the incisional press procedure, an SSI prevention bundle was implemented in our institution, and the rate of superficial SSI was 6.9% in colorectal surgery, which

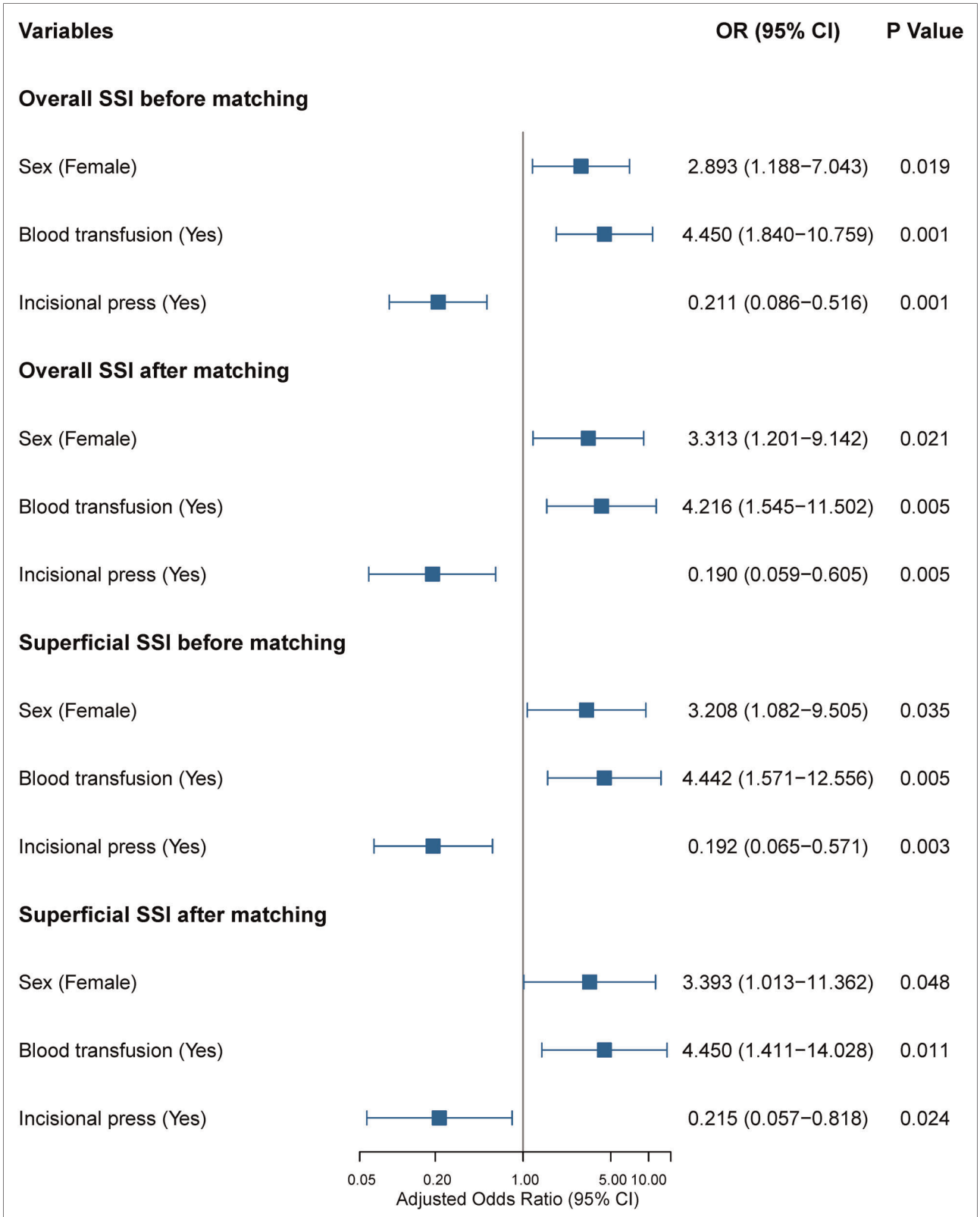

FIGURE 4
Adjusted odds ratios of overall SSI and superficial SSI before and after matching. Abbreviations: SSI, surgical site infection; OR, odds ratio.

was at a normal level compared with that in several previous studies (10, 21, 22). However, the SSI prevention bundle in our institution did not include interventions.

Dead space in the sutured wound may accumulate tissue fluid and blood clots, which are excellent culture media for possible bacteria from the colorectal lumen in the wound (14). Three strategies have been studied to obliterate the dead space as follows: suturing subcutaneous tissue and placing subcutaneous drains, and topical negative-pressure wound therapy. However, most of these studies did not find any benefits of suturing subcutaneous tissue on reducing SSI (23, 24). Holl et al. found that suture closure of the dead space increases the incidence of SSI (14), and they suggested that sutures may cause subcutaneous tissue necrosis, which may induce subcutaneous tissue loss and enlarge the dead space, eventually leading to wound infection. Moreover, the presence of stitches as foreign bodies may also increase the risk of bacterial infection.

Additionally, prophylactic subcutaneous drainage is used to decrease wound infection in many medical centers (11, 12). The placement of a subcutaneous drain could avoid wound fluid accumulation and eliminate the growth environment of bacteria in the dead space. However, the efficiency of subcutaneous drainage in reducing the rate of incisional SSI in clean-contaminated wounds is still controversial (16–18). Furthermore, placement of subcutaneous drains has several disadvantages in the enhanced recovery after surgery (ERAS) era as drains can cause pain and hinder early mobilization.

Moreover, as another method which could reduce fluid accumulation within the dead space (25, 26), topical negative-pressure wound therapy has been shown to be associated with reduced SSI rates of colorectal surgery in several studies (27, 28). However, the intervention is costly, and may cause skin-related complications, such as contact dermatitis (28).

In our present study, the incision pressing was first reported as an intervention with a theoretical effect on reducing the dead space. The incision pressing can not only force the tissue fluid out of the incision at the first time, but also avoid wound fluid accumulation in the incision in next few days. This intervention is easy to perform and requires one minute at most, and it does not cause postoperative pain or any inconvenience. A 5% reduction (6.9% to 1.9%) in the rate of superficial incisional SSI by this intervention was observed in our study. Furthermore, multivariate analysis also confirmed the protective role of the incisional press in superficial SSI with an odds ratio of 0.215. In summary, the incisional press after suturing is a simple, costless and effective intervention, suggesting that it should be used in colorectal surgery. However, given the study design, the effect of incisional press on obliterating dead space could not be precisely accessed and was more like a hypothetic mechanism. Further studies are needed to explore the specific mechanisms underlying the effect of incision pressing on reducing SSI.

Consistent with previous studies (29, 30), we identified female sex as an independent risk factor for superficial SSI. Due to estrogens, females have higher levels of subcutaneous adipose tissue than males (31). The thickness of subcutaneous fat tissue has been demonstrated to be positively associated with the incidence of SSI in colorectal surgery (32, 33), suggesting that females with thicker subcutaneous fat tissue may have higher risks of SSI. The multivariate analysis in the present study also demonstrated that perioperative blood transfusion increased the risks of superficial SSI and overall SSI, which agreed with previous findings on SSI in colorectal surgery (34–36). In the present study, patients with perioperative blood had a 4.216-fold higher risk of superficial incisional SSI than those without blood transfusion. Allogeneic blood transfusion may affect immunosuppression and increase the risk of infection following colorectal surgery (37, 38). Furthermore, the present findings that blood transfusion with no preoperative anemia was a risk factor highlighted the importance of minimizing blood loss in surgery.

There were several limitations to our study. First, this was a single-center retrospective study. Although 15 variables were included in the propensity score matching to reduce the effects of selective bias, other latent confounders that may have a role in the development of SSI may still exist. Therefore, further randomized trials are required to confirm the protective role of the incisional press in superficial SSI. Second, because more than 90% of patients in this study had colorectal cancer, this study did not represent patients with benign diseases, including inflammatory bowel disease and diverticular disease. Third, the skin was closed with interrupted sutures and without subcutaneous sutures in our study. Intervention with an incisional press may be only suitable for interrupted sutures rather than continuous subcuticular sutures or subcutaneous sutures. Fourth, midline incision was used for all the colorectal surgeries in this study. Therefore, whether incision pressing can be applied to other types of incisions needs further exploration. Finally, because the entire operative time did not reflect the time of incisional exposure in laparoscopic surgery and we lacked data about the time of surgical incision to skin closure, we did not include the operative time in the analysis.

Conclusions

In conclusion, this study showed that incisional pressing after suturing is a simple, costless and effective intervention in reducing superficial incisional SSI. Thus, this intervention is suggested for colorectal surgery.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee of Shandong Shandong Provincial Hospital . Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

MK and YJ contributed to conception and design of the study. YJ, HC and HS collected data. YJ, GL and ML performed the statistical analysis. MK wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.917559/full#supplementary-material.

SUPPLEMENTARY VIDEO S1
How to press the incision.

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Sclerotherapy for III- and IV-degree hemorrhoids: Results of a prospective study

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Background: In the last 2 years, anorectal surgery has been strongly affected and even surgery for urgent cases cannot be scheduled; also, patients with III- and IV-degree bleeding hemorrhoids should be treated conservatively. The aim was to evaluate the effectiveness of sclerotherapy in patients who had to postpone surgery.

Methods: We included all patients with III- and IV-degree bleeding hemorrhoids who underwent outpatient sclerotherapy. The visual analog scale and the hemorrhoid severity score were used at the baseline and at 4 weeks after the procedure with a telephone interview, and all patients were outpatient-evaluated 1 week, 1 month, and 1 year after the treatment. All pre- and postoperative data were recorded.

Results: From October 2020 to November 2021, 19 patients with III- (12 patients; 63%) and IV-degree (7 patients; 37%) bleeding hemorrhoids were enrolled. The mean operative time was 4.5 min, and no intraoperative complications occurred. One case of tenesmus and three failures were detected. Six months after the procedure, the overall success rate was 84%, although all of the patients enrolled reported persistent bleeding at the end of the study period. Of these, 5 patients (26%) were scheduled for surgery and 11 patients (58%) refused surgery and asked to undergo a re-do sclerotherapy.

Conclusion: Sclerotherapy with 3% polidocanol foam is a safe and effective procedure also in III- and IV-degree bleeding hemorrhoids. The long-term data on the length of the foam remain to be evaluated in additional studies.

KEYWORDS

sclerotherapy, proctology, polidocanol 3%, bridge treatment, hemorrhoid

Introduction

Hemorrhoids (HDs) are one of the most frequent anorectal disorders; nevertheless, the incidence of the disease is still unclear and probably underestimated (1–5). A therapeutic strategy may vary from medical treatment to outpatient treatment and to a more invasive procedure such as hemorrhoidectomy or hemorrhoidopexy (6, 7). According to the literature, sclerotherapy (ST) and rubber band ligation (RBL) are the most common outpatient procedures for the treatment of I- and II-degree HDs

among patients with failed conservative treatment; despite little is known about sclerotherapy in the III- and IV-degree hemorrhoids, few studies are published in the literature, even if still very heterogeneous, that reported the results of sclerotherapy in the treatment of I-, II- and III-degree hemorrhoids (8–10).

During the COVID-19 pandemic, 28 million procedures for benign diseases have been cancelled or rescheduled, with an estimated overall 12-week cancellation rate of 72% (11–13). All outpatient visits and operations of nononcological patients were suspended, except for highly urgent cases (14, 15). Non-COVID hospitals have been allowed outpatient proctological visits, although surgery cannot also be scheduled as a day case procedure, and even patients with several bleeding hemorrhoids should be treated conservatively. Because of this critical scenario, we recently proposed sclerotherapy for III- and IV-degree bleeding hemorrhoids as "bridge treatment" awaiting the surgical procedure proposed.

Sclerotherapy with 3% polidocanol foam induces an inflammatory reaction with sclerosis of the submucosal tissue; moreover, the obliteration of the vascular support may lead to a reduction in the hemorrhoidal volume (9, 16). Unfortunately, even if this is a reproducible and minimally invasive treatment, several life-threatening complications with liquid polidocanol have occurred (17, 18). However, from what we know, an episode of mild prostate inflammation has been detected (19).

The aim of our report was to evaluate the safety, effectiveness, and length of 3% polidocanol foam for the treatment of Sclerotherapy for III- and IV-degree hemorrhoids degree bleeding hemorrhoids in a cohort of consecutive patients during and after 1-year follow-up.

Materials and methods

All patients above 18 and below 80 years old affected by III- and IV-degree bleeding hemorrhoids (20) with indication to surgery but postponed due to the pandemic were eligible for inclusion in this prospective study. Informed consent was submitted by all patients. Inclusion in the study was permitted only if III- and IV-degree bleeding hemorrhoidal disease could be verified by a physical examination and anoscopy. All patients were evaluated by the same surgeon (GL). Exclusion criteria are as follows: pregnancy, allergy to polidocanol, acute thrombosis, fecal incontinence, perianal fistula, anal fissure, proctitis, perianal abscess, and known hereditary thrombophilia. Pre- and postoperative data were recorded in our prospective database.

The number of bleeds per day was identified as the parameter for assessing bleeding, and it was defined as persistent in cases of more than one episode after two sclerotherapy sessions. Success was assessed as the absence of persistent bleeding. Recurrences were defined as the presence of persistent bleeding. After two ST sessions, all the patients were instructed to evaluate their postoperative pain and satisfaction with the visual analog scale (VAS) score. The hemorrhoid severity score (HSS) was used to evaluate symptoms at the baseline and 4 weeks after the treatment with a telephone interview, and all patients were examined 2 weeks, 6 months, and 1 year after the treatment (9).

All patients were submitted to clinical examination, the digital rectalexploration, and proctoscopy during the follow-up.

As "bridge treatment," the main target of our treatment was to solve the main hemorrhoid-related symptom of bleeding, in those patients who had to postpone surgery due to the pandemic, evaluating the short-term effectiveness of sclerotherapy and after 1-year follow-up.

Technique

Our procedure includes two sclerotherapy sessions 2 weeks apart to avoid discomfort due to the treatment of the three piles in a single session. We used an intravenous needle (20-G green, 0.9 mm, and 10 cc silicone syringes) of greater caliber, which made it possible to inject thicker and "creamy" foam that was obtained following the technique previously described by Tessari and subsequently by Moser and Lobascio (9, 19, 21), and the amount of foam injected for every single pile was 2 ml of 3% polidocanol (**Figures 1A,B**). Before each injection, the foam already obtained was re-emulsified for 45 s. All patients were treated in the Sims position (lateral decubitus position) in our outpatient clinic, injecting the foam in the two piles at 3 and 7 in the first session, then after 2 weeks at 11 o'clock, and the others if a second injection was still required. No local anesthetic nor antibiotics were used. We agree with Gallo et al. (10) on the need to use the foam in the mucosa and not in the submucosa nor the muscular layer. Furthermore, by injecting at the base of each hemorrhoidal pile above the dentate line to reduce postoperative pain, we ensured the maximum efficacy of the technique; it is necessary to inject the foam above the dentate line to avoid pain during the procedure to ensur greater effectiveness of the treatment; as emerged from recent phlebological studies, polidocanol allows tissue shrinkage and endothelium synthesis while maintaining the safety of the treatment.

Results

A total of 19 patients with III- ($n = 12$, 63%) and IV-degree ($n = 7$, 37%) bleeding hemorrhoids with a mean age of 47 years (range 21–73 years) were consecutively enrolled and treated with 3% polidocanol foam injection. Of these, 12 (63%) patients were male and 7 were female (37%). The mean

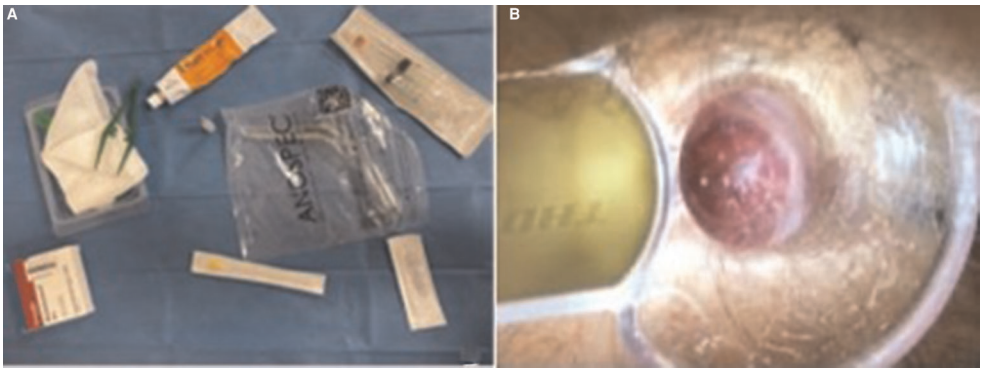

FIGURE 1
(A) Kit for the ST procedure: self-lighting anoscope, 20 g needle, 2 ml 3% polidocanol foam, and two 10 ml syringes. (B) Site of 3% polidocanol foam injection after 2 weeks.

operative time was 4.5 min. No intraoperative complications or drug-related side effects were detected. All patients were discharged 10 min after the treatment. Three days after the procedure, one case of bleeding was detected. This patient was the first case with IV-degree hemorrhoids enrolled, and the bleeding was outpatient-treated with a hemostatic absorbable sponge in the anal canal removed the day after. This patient was one of the three cases where the procedure failed due to persistent bleeding after two sclerotherapy sessions (two patients with IV-degree and one patient with III-degree hemorrhoids). Finally, one case of tenesmus (III-degree) 2 days after the second ST session was detected and resolved spontaneously 2 weeks later, confirmed by the telephone interview. All patients completed the 12-month follow-up. The mean VAS after the second sclerotherapy session was 1 (range 0–1). No difference in terms of HSS comparing preoperative and postoperative symptoms at the end of the follow-up was reported (**Figure 1**).

Six months after the procedure, the overall success rate was 84%, although all the patients enrolled reported persistent bleeding at the end of the study period. Of these, 5 patients (26%) were scheduled for Milligan–Morgan hemorrhoidectomy because of failed treatment, but the procedure was postponed due to the pandemic, and 11 patients (58%) refused surgery and asked to undergo a re-do sclerotherapy. Finally, three patients chose to leave this study and rely on another center (**Table 1**). Patients with failed sclerotherapy underwent Milligan–Morgan hemorrhoidectomy as a private practice procedure.

Discussion

As highlighted by Gallo and co-authors in their recent national report, proctology was one of the most penalized surgical specialties during the outbreak, and benign anorectal disorders have been dramatically postponed. Indeed, according to a recent study including 1,050 colorectal surgeons, it emerged that proctology, surgery for benign disorders, and inpatient practice were reduced or postponed with an increased liability of malignant disease (22).

HD affects almost 5% of the western population and is a very frequent motive for attending a surgical outpatient clinic, especially in III- and IV-degree hemorrhoids (23–25). Besides causing discomfort and bleeding, these symptoms often cause restlessness, fear of cancer, and social embarrassment; Usually, this disease is not recognized as a priority today and is therefore underestimated. Due to these reasons and the need to respond to patients suffering from III- and IV-degree bleeding hemorrhoids and achieve a resolution of the bleeding, we have decided to use sclerotherapy as we cannot offer surgical therapy due to the outbreak.

TABLE 1 Pre- and postoperative data.

	N (%)
Hemorrhoid degree[a]	
III	12 (63)
IV	7 (37)
Gender	
Male	12 (63)
Female	7 (37)
Failure	3 (16)
Success rate	
After 6 months	17 (84)
After 12 months	0
End—study treatment	
Re-do—ST	11 (58)
Hemorrhoidectomy	5 (26)
Exit from the study	3 (16)

ST, sclerotherapy.
[a]Hemorrhoid degree according to Goligher (20).

The use of sclerotherapy for the treatment of hemorrhoids has risen in recent years; in fact, the strong points are cost-effectiveness, reproducibility, and the almost painless procedure, although there is a lack of homogeneous reports regarding its availability for III- and IV-degree hemorrhoids (26).

Recently, Ronconi and Colleagues (27), in their first Italian study using polidocanol foam, reported 1,427 procedures on 615 patients with a mean of 2.32 sclerotherapy sittings for each patient and a mean follow-up of 12 months. Most of the sample had II-degree HDs (317; 51.4%), and 17 (2.8%), 253 (41.1%), and 28 (4.7%) had, respectively, I-, III-, and IV-degree hemorrhoids. Furthermore, 97 patients previously underwent either excisional or nonexcisional surgery. Seventeen patients (2.7%) reported postoperative pain, which was conservatively solved.

These results were in line with another Italian retrospective report (9) concerning the use of 3% polidocanol foam in 66 patients with II- and III-degree hemorrhoids, in which the overall success rate after a single session was 78.8%; furthermore, the effectiveness reached 86% after a second sclerotherapy session. Despite these promising results, the heterogeneous sample size and absence of a control group and data on long-term effectiveness have reduced the strength of their outcomes.

Despite the small sample size, in our case series, we treated only III- and IV-degree bleeding hemorrhoids; we have chosen these patients because this was the main symptom for which they went to the hospital and asked for surgical treatment. After 6-month follow-up, compared to Gallo et al. (9), our overall success rate (84%) after two sclerotherapy sessions was lower than that reported by Moser et al. in their first experience with sclerotherapy for HD (19). However, after 1 year, all of our patients have recurrent bleeding, but we cannot compare our data at all because they treated I-degree hemorrhoids without using validated scores; moreover, according to our experience, III- and IV-degree HDs may require two sclerotherapy sessions than I-degree HDs. Moreover, the design of their report was completely different from the previous paper, which was a randomized, controlled, single-blind, and multicenter trial.

Another case series that considered sclerotherapy for I- to III-degree HDs was recently published by Salguerio et al. (28). The authors randomized 120 patients and compared rubber band ligation (RBL) and sclerotherapy, achieving an overall success rate of 88.3% with polidocanol foam and a recurrence rate of 16.1% after 1 year; despite these results were not significantly different between the groups (ST vs. RBL), the heterogeneous sample size may reduce the strength of the study.

Recently, Figueiredo et al. (29) proposed sclerotherapy with 2% polidocanol foam in 243 patients with different grades of HDs. Despite several limitations as the average follow-up, there was no information about the sample size and the number of sessions used; certainly, it cannot be considered a reliable study, although it would be interesting to compare the results with 2% and 3% polidocanol foam in terms of bleeding recurrence, effectiveness, and postprocedure complications (30).

In our case series, no life-threatening complications were reported in the perianal and prostatic areas; moreover, one case of tenesmus was spontaneously resolved. Besides, the low incidence of postoperative pain detected could be due to injection above the dentate line, which strengthens the transanal procedure compared to the endoscopic one.

Despite the small sample size, we are convinced that the strength of our study was the homogeneity of the case series and the follow-up completed by all patients. According to our experience, some considerations can be made. First, sclerotherapy with 3% polidocanol foam may be safe and effective also in III- and IV-degree HDs in terms of resolving bleeding, although we cannot be sure of the length of effectiveness; in fact, after 6 months, 84% of success rate was detected; unfortunately, all patients reported bleeding recurrence after 1 year. We believe that several studies are needed to define after how long a further session should be recommended.

Interestingly, 11 patients (58%) refused surgery and asked to undergo re-do sclerotherapy; this procedure could change the way of dealing with HDs in several patients, focusing on the main symptom reported and not on the anatomical changes due to the disease.

Conclusion

Sclerotherapy with 3% polidocanol foam is a safe procedure in III- and IV-degree bleeding hemorrhoids also; surely, its long-term effectiveness is debated. It can be proposed in patients with or without comorbidities who could not undergo surgical treatment; however, further randomized trials are needed to confirm its use in these patients, and the long-term data on the length of the foam remain to be evaluated in additional studies.

Data availability statement

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

Ethics statement

Written informed consent was obtained from the individual (s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LG and MC designed and wrote the paper; UP and SO collected data; DS carried out the drawing study, and PG

drafted 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

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Comparison of botulinum toxin (BoNT) injection and lateral internal sphincterotomy (redo-LIS) for recurrent anal fissure treatment

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Objective: Today's gold standard for treating chronic anal fissure is the Lateral Internal Sphincterotomy (LIS). Botulinum Toxin (BoNT) injection is, on the other hand, an alternative treatment for patients who do not want to have surgical treatment, patients undergoing chemotherapy, patients of high risk for surgery, and those who have the risk of anal incontinence (e.g., elderly, past anorectal surgery, vaginal multiple births, etc.). The aim of this study is to compare the effectiveness of BoNT and redo-LIS for treatment of post-LIS recurrent chronic anal fissure, and reveal differences if any.This study aims to compare redo-LIS and BoNT injection for treating post-LIS recurrent anal fissure.

Material and method: Nineteen patients who received LIS treatment and then redo-LIS or BoNT injection due to recurrence in the follow-up were included in this study. Group I (redo-LIS group) include 11 patients and group 2 (BoNT group) includes 8 patients. Their data on age, sex, anal incontinence scores and pain (VAS score) score as well.

Results: During the 3-month post-surgery follow-up period, there was statistically significant difference ($p < 0.01$) between groups by pain. No deterioration in the incontinence scores of patients in the group during the 6-month post-surgery period.

Conclusion: This study demonstrates that redo lateral internal sphincterotomy (LIS) is a reliable method for patients who received LIS but developed recurrent chronic anal fissure, and achieves successful results in terms of recurrence and relief of pain.

KEYWORDS

anal fissure, sphincterotomy, botulinum toxin, recurrent fissure, redo sphincterotomy

Introduction

Anal fissure is a frequent disease in the society with a lifetime incidence of 11% (1). For treatment of acute anal fissure, healing is possible by exercising high-fibre diet, taking warm-sitz bath, and applying cremes that reduce internal sphincter pressure (2). Today's gold standard for treating chronic anal fissure is the Lateral Internal Sphincterotomy (LIS) (3). Botulinum Toxin (BoNT) injection is, on the other hand, an

alternative treatment for **patients who do not want to have surgical treatment**, patients undergoing chemotherapy, patients of high risk for surgery, and those who have the risk of anal incontinence (e.g., elderly, past anorectal surgery, vaginal multiple births, etc.) (4, 5).

Anal fissure is one of the most frequent benign anorectal diseases (1). The most frequent complaint at clinical visits includes painful defecation accompanied by rectal bleeding (6). Pain particularly may reduce the quality of life of patients (7, 8). Chronic anal fissure is accompanied by hypertrophic papilla along whose edge internal sphincter muscle fibres become visible (9). Physical and chemical agents are used basically to reduce sphincter pressure for treating acute anal fissure. The guidelines of American Society of Colon and Rectal Surgeons (ASCRS) recommend using faeces softeners, high-fibre diet and warm-sitz bath (6). Such treatment methods are currently under discussion (10). Lateral Internal Sphincterotomy (LIS) is indicated as the gold standard for anal fissure treatment (6, 11, 12). The LIS treatment executed by surgeons experienced in proctology proved to achieve better results in terms of removing symptoms and shorter healing time (13).

Recurrence is rare after treatment of chronic anal fissure by LIS. The reason for recurrency, if it ever occurs, is generally the inadequately performed LIS which does not ensure compete healing and causes patients to develop non-healing fissure or early recurrence. The patient continues to experience, though may be at lower intensity, such pre-LIS symptoms as pain, bleeding, avoidance of defecation, anal spasm and pain for 1 to 2 h following defecation.

In case of anal fissure that recurs or continues following an inadequate/inappropriate LIS, surgeons or patients mostly avoid redo-LIS. The reason is that a redo-LIS will likely exacerbate the damage to anal sphincter which in turn creates a heightened risk of anal incontinence. **Some patients avoid surgical treatment because sphincterotomy is influenced by the complication of incontinence. This has called for the application of alternative treatments such as Botulinum Toxin (BoNT) injection for recurrent fissures.**

BoNT inhibits the secretion of acetylcholine at the presynaptic terminal of neuromuscular combination. The injection works by inducing temporary paralysis in the muscle (14, 15). The effect of BoNT depends on localization, concentration and volume of the injected solution. The volume and concentration varies proportionally to the size of the muscle being treated (16). The literature includes no report that demonstrates an evidence-based result of effect of BoNT on fibrous tissue. Immunological properties of BoNT may stimulate creation of antibodies, which may in turn increase the likelihood of failure in subsequent treatments. No minimum dosage is yet established that will start creation of antibodies (17).

A meta-analysis on 489 patients by Chen et al. revealed that LIS obtained higher healing rates, and a higher rate of incontinence as well; but found no statistically significant difference between LIS and BoNT for other complications. BoNT cases had higher recurrence than LIS. The results of the meta-analysis indicted that LIS was superior in terms of recurrence and healing rates (18, 19). Another study found 93.1% for post-LIS healing rate and 62.6% for BoNT injection (1). The risk of permanent damage to anal sphincter has called for the application of alternative treatments such as BoNT injection. The aim of this study is to compare the effectiveness of BoNT which is a less invasive procedure and redo-LIS for treatment of post-LIS recurrent anal fissure.

Methods

The study involves 19 patients who received LIS treatment and then redo-LIS or BoNT injection due to recurrence in the follow-up. Observing the criteria of Helsinki Declaration, approval was obtained from the ethics board. Files of 118 patients who had received LIS and BoNT injection for chronic anal fissure were reviewed. Patients who had inflammatory bowel disease, prior anorectal surgery for non-fissure reasons, underlying hemorrhoidal condition and/or fistula, presence or suspicion of malignity were excluded from the study. The 19 patients who were included in the study in accordance with the methodology had developed post-LIS recurrent anal fissure and received redo-LIS or BoNT injection. These patients were assessed through standardized clinical forms, their medical history and files were reviewed in detail, and anorectal examinations were conducted.

Using standardized forms, patients' age, sex and complaints (pain, bleeding, continence and recurrence) were recorded. **Study groups had patients who chose redo-LIS or BoNT**. Two groups were formed as Group I including patients who received redo-LIS, and Group II including those who received BoNT application.

The redo-LIS group (Group I) included patients who had received LIS for chronic anal fissure, then were given redo-LIS due to pain or recurrence the 3-month post-surgery follow-up period.

Redo-LIS was performed as internal sphincterotomy by incision through LIS scar contra-lateral through fissure apex under sedation and local anaesthesia, in the prone jack-knife position.

The BoNT group (Group II) included patients who had received LIS for chronic anal fissure, then developed recurrence or failed to heal, but did not want repeat surgical treatment and had incontinence anxiety. BoNT was applied, under sedation, by injection into the internal sphincter from two laterals in the form of two insulin injectors each containing 0.5 ml of solution containing 100 IU Botulinum Toxin type A diluted with 1 ml of physiological saline solution.

After the procedure, patients were instructed, for 2 weeks, to have high-fibre diet and warm sitz-bath three times a day.

Both groups were called in for control in the 1st week, 1st month and 3rd month, and examination findings, pain and continence scores were recorded through standardized forms. The criteria for fissure healing were adopted as fissure epithelization and complete disappearance of pain during and after defecation. The status of continence was assessed using the Cleveland Clinical Incontinence Score (CCIS) system (20). The data were statistically analysed using Statistical Package for Social Sciences (SPSS 22). **The results were accepted statistically significant with $p < 0.01$ within the confidence interval of 95%.**

Results

The 19 patients included in the study had previously received LIS for anal fissure. Of the 19 patients, 11 were male (57.89%) and 8 were female (42.10%) with average age of 42.37 ± 5.96. Table 1 presents the sex and average age of patients in Group I and Group II. There was no statistically significant difference by age or sex between groups ($p = 0.89$, $p = 0.13$ respectively). Of the patients, 11 (57.89%) were performed redo-LIS, with 8 being male (73%), and 3 being female (27%). Of the 8 patients who were applied BoNT, 3 were male (38%) and 5 were female (62%).

Pain was present in all patients prior to intervention. Following the intervention there was statistically significant difference **($p = 0.008$)** between groups by pain (Table 2).

Of redo-LIS recipients, one had minor bleeding at the incision location that did not require intervention in the post-surgery period. Of BoNT recipients, one had ecchymosis at the injection area, later receded spontaneously.

For incontinence, one of the patients in Group I had mild gas incontinence (CCSI = 3), and no patient in Group II had incontinence. The 3rd-month follow-up of patients resulted in complete disappearance of incontinence complaint in Group I as well. There was no statistically significant difference between groups by pre- or post-surgery incontinence (by CCIS) of both groups ($p = 0.87$; $p = 0.83$ respectively). Table 2 presents the status of patients by incontinence and pain**. In group I healing rate was 100%, while in group 2 (BoNT group) two of eight patients recurrence were assessed.**

TABLE 1 Study group status by age and sex.

	Group I (Redo-LIS)	Group II (BoNT)	*P* value
Male	8 (avg. age 46, 5)	3 (avg. age 33.6)	0.13[a] 0.89[b]
Female	3 (avg. age 51.3)	5 (avg. age 43, 2)	0.13[a] 0.89[b]

[a]Age.
[b]Sex.

TABLE 2 Study group status by pain and incontinence.

	Group I (redo-LIS)	Group II (BoNT)	*P* value
Preop CCIS	0, 36	0, 25	0.87
Postop 3rd month CCIS	0, 12	0, 13	0.83
Preop VAS	7, 64	7, 62	0.13
Postop 3rd month VAS	0.09	7.25	0.008*

CCIS, cleveland clinic incontinence score; VAS, visual analogue score.
Comparisons were peformed by the Mann Whitney *U*-test.
*$p < 0.01$ compared with the pre-operative VAS score.

Discussion

Anal fissure has a vicious cycle characterised by internal sphincter spasm, pain and bleeding during defecation (21). The fundamental objective of treating anal fissure is to reduce internal sphincter pressure to normal levels. To treat acute anal fissure, warm-sitz baths and cremes that reduce internal sphincter pressure are used (3).

When the condition becomes chronic, LIS or BoNT injection may be applied. LIS is the gold standard for treating chronic anal fissure**. BoNT injection into internal sphincter is used due to the risk of incontinence though low, for cases** where the patient has some clinical risks for surgery (undergoing chemotherapy, high cardiac risk, requirement to use blood diluents etc.) or **the patient avoids surgical treatment** (1, 6, 11, 12).

Studies reported recurrence rates following LIS treatment of chronic anal fissure as 1.3% to 25% (21, 22). Post-LIS recurrence could go down to 0.3% if applied in clinics experienced in proctology (23). This may be associated with the more effective and complete performance of the LIS procedure.

Based on our clinical experience, one of the reasons for failed surgical treatments of chronic anal fissure is the selected method of anaesthesia. Muscle relaxing drugs administered to the patient for the LIS under general anaesthesia or the spinal anaesthesia affect internal sphincter causing relaxation and consequently difficulty in surgical dissection. For such patients, any difficulty in dissecting internal sphincter may result in inadequate sphincterotomy.

Our clinical experience also leads us to think that the performance of LIS procedure under sedation and local anaesthesia improves the visibility of internal sphincter, thus allow better dissection, resulting in a more successful LIS or avoiding an unsuccessful one. LIS patients that receive LIS by this method do not have stay in the hospital following LIS.

For cases where recurrence have developed, treatment approaches are still discussed. The top reason for recurrence is inadequate sphincterotomy.

In case of anal fissure that recurs or continues following an inadequate/inappropriate LIS, surgeons or patients mostly avoid redo-LIS. The reason is that a redo-LIS will likely exacerbate the

damage to anal sphincter which in turn creates a heightened risk of anal incontinence. This may lead to preferring BoNT injection for recurrent fissures (1).

We compared the success rates of treatment of patients by redo-LIS or BoNT injection due to developing recurrence after having received LIS for chronic anal fissure. Our study demonstrates that, at the clinics experienced in proctology, the most dreaded risk of incontinence following redo-LIS is at acceptable levels at the early phase and returns to normal at the end of 3rd month. Its rates were reported in the literature as 0.4% to 35% (23, 24).

As for the assessment of pain following redo-LIS and BoNT procedures, the BoNT group was observed to have continued pain following defecation which was statistically significant ($p = 0.008$). There is no study in the literature comparing BoNT and redo-LIS for treating recurrent anal fissures. One sole study reports 4% for the recurrence rate following redo-LIS for treating recurrent anal fissure (21).

In our study, BoNT application was found to be less successful for the patient group who had previously received surgery. We conjecture that the reason is the internal sphincter fibrosis related to the previous LIS which reduces the effectiveness of BoNT. BoNT application for treating chronic anal fissure may be less successful for those who previously had anorectal surgery than those not.

Redo-LIS is a reliable, successful method for patients who developed recurrence or did not heal following LIS. The performance of the redo-LIS by incision through previous scar's contra-lateral may facilitate dissection and contribute to adequate performance of sphincterotomy.

Conclusion

This study demonstrates that redo lateral internal sphincterotomy (LIS) is a reliable method for patients who received LIS but developed recurrent chronic anal fissure, and achieves successful results in terms of recurrence and relief of pain. BoNT application is less successful for patients group who previously received surgery and developed recurrence than patients who did not receive surgical treatment. The likely reason is the internal sphincter fibrosis related to the previous LIS which reduces the effectiveness of BoNT.

Study limitations

This study was limited because it was a single-armed, retrospective analysis of prospectively designed data.

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 Yuksek Ihtisas University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualisation: AA, MG; Data collection and/or processing: AA, MG; Analysis and/or interpretation: AA, BE; Writing the article: AA; Critical review and supervision: BE. 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.

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A predictive model of bowel resection for incarcerated inguinal hernia based on the systemic immune-inflammation index

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Background and Purpose: An inguinal hernia is a common surgical disease. Once incarcerated or strangulated, it may endanger the life of the patient. Therefore, it is essential to study the risk factors of incarcerated inguinal hernia (IIH) and strangulated inguinal hernia (SIH). One of the serious complications of IIH and SIH is intestinal necrosis, which occurs owing to blood supply disorder. The study explores the risk factors of intestinal resection and establishes a simple model to assess the incidence of intestinal resection to provide significant assistance and limited guidance for clinical work.

Patients and Methods: Our research team collected and retrospectively analysed the clinical data of 338 patients with IIH who were hospitalized in the First Affiliated Hospital of Wenzhou Medical University between September 2008 and December 2016. According to the surgical plan, we divided the included cases into two groups, non-intestinal and intestinal resection groups, and the clinical case characteristics of these groups were statistically analysed.

Results: Based on multivariable logistic regression analysis, we found that increased risk of bowel resection was highly correlated among the elderly (≥70 years), and for people with high temperature (≥37.3°C), high systemic immune-inflammation index(SII) values (≥1230.13), presence of bowel obstruction, and signs of peritonitis. Further, we processed the five independent risk factors using special software to obtain a simple model called a nomogram. To verify the nomogram's accuracy and predictive ability, we calculate the C-index: 0.806 and use the calibration curve to evaluate its stability and predictive performance. We constructed the ROC curve nomogram and other sub-variables, and calculated the area under the curve (AUC) corresponding to the nomogram (AUC = 0.808, 95% CI = 0.762 to 0.848), SII (AUC = 0.752, 95% CI = 0.703 to 0.797), age (AUC = 0.641, 95% CI = 0.587 to 0.692), temperature (AUC = 0.579, 95% CI = 0.524 to 0.632), bowel obstruction (AUC = 0.685, 95% CI = 0.633 to 0.734), and signs of peritonitis (AUC = 0.580, 95% CI = 0.525 to 0.633).

Conclusion: It can be said that we found for the first time that clinical variables such as SII are independent risk factors for enterectomy for IIH. The nomogram based on SII and other variables can accurately and easily predict the probability of IIH requiring bowel resection.

KEYWORDS

systemic immune-inflammation index(SII), incarcerated inguinal hernia, nomogram, bowel resection, strangulated inguinal hernia

Introduction

External abdominal hernias occurring in the groin area are collectively referred to as inguinal hernias, which are the most common type of hernia, causing bulging in the groin area (1, 2). Further, they can also lead to pain and bowel obstruction (1, 2). Incarcerated inguinal hernia (IIH) is a common acute abdominal disease, and most patients with IIH require emergency surgery (3). Failing to reset IIH effectively can rapidly make the necrotic hernia content due to severe blood supply disorder. This condition is called strangulated inguinal hernia (SIH). The most effective treatment for IIHs is timely surgical intervention, especially in the case of SIHs (3). Due to prolonged incarceration and avascular necrosis of hernia content, approximately 15% of the patients with SIH require bowel resection (4). Therefore, it is essential to assess the risk of bowel resection prior to the surgery of patients with IIH. Based on our knowledge, apart from obvious peritonitis, there are no clear clinical criteria to distinguish among different strangulations. The study explores the risk factors of intestinal resection and establishes a simple model to assess the incidence of intestinal resection to provide significant assistance and limited guidance for clinical work.

Patients and methods

Study population

Our research team collected and retrospectively analysed the clinical data of 410 patients with IIH who were hospitalized in the First Affiliated Hospital of Wenzhou Medical University between September 2008 and December 2016. Our inclusion criteria were as follows: (1). Attainment of complete clinical case information; (2). All the cases should be that of IIH; (3). All should have successfully undergone surgery; (4). During the operation, the hernia content should be present in the intestinal tract; (5). No other severe concomitant disease should exist in the patient. The following were excluded based on the inclusion criteria: 31 cases of incomplete information, 24 cases of non-intestinal incarceration patients (the content of the incarceration was omentum), and 17 patients with severe concomitant diseases, such as patients with respiratory infections. All laboratory tests were performed after admission and before antibiotics. Finally, we successfully screened 338 cases, including 265 (78.4%) non-intestinal and 73 (21.6%) intestinal resection cases, respectively. Our research was supported by the ethics committee and Institutional Review Board of our hospital, and all the patients signed informed consent before participating in the research.

Data collection and analysis

According to the surgical plan, we divided the included cases into two groups, non-intestinal and intestinal resection groups, and the clinical case characteristics of these groups were statistically analysed. The observed clinical variables were as follows: gender, age (years), body temperature (°C), height, weight, duration of incarceration (hours), presence or absence of bowel obstruction, presence, or absence of peritonitis signs, and presence or absence of chronic disease. The laboratory data included the following: neutrophil count, lymphocyte count, platelet count, fibrinogen, prothrombin time (PT), and activated partial thromboplastin time (APTT). Based on the height and weight, the body mass index was calculated using the formula: weight/height (2) (kg/m^2). The systemic immune-inflammation index (SII) was calculated with laboratory variables using the formula: platelet count × neutrophil count/lymphocyte count.

Statistical analysis

Continuous variables were divided into two groups depending on the cut-off value obtained according to a receiver operating characteristic (ROC) curve and maximum Youden's index. Numbers (%) were used to identify categorical variables. The Mann-Whitney U and Chi-square tests were used to distinguish between the variables in these groups. The multivariable logistic regression analysis was used to screen the independent risk factors of intestinal resection for IIH patients, and the odds ratio (OR) and 95% confidence interval were calculated. Based on the obtained independent risk factors, scientific, accurate, and simple nomogram was constructed. The concordance index (C-index) and the

calibration curve were used to verify the model's prediction accuracy and expressiveness. The ROC curve was used to compare the difference between the model and other risk factors. Statistical analyses and drawing were implemented using IBM SPSS 21.0 (SPSS Inc, Armonk, NY) and R software (a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). $P < 0.05$ was considered to be statistically significant.

TABLE 1 Univariate analysis of clinical/laboratory parameters and incarcerated groin hernia patients with or without bowel resection.

Variables	No bowel resection $n = 265$ (78.4)	Bowel resection $n = 73$ (21.6)	*P* value
Gender			0.021*
Male	206 (77.7)	47 (64.4)	
Female	59 (22.3)	26 (35.6)	
Age (years)			0.002*
<70	127 (47.9)	20 (27.4)	
≥70	138 (52.1)	53 (72.6)	
Temperature (°C)			0.017*
<37.3	222 (83.8)	52 (71.2)	
≥37.3	43 (16.2)	21 (28.8)	
BMI (kg/m^2)			0.115
<21.94	162 (61.1)	52 (71.2)	
≥21.94	103 (38.9)	21 (28.8)	
PT (S)			0.061
<13.5	131 (49.4)	27 (37)	
≥13.5	134 (50.6)	46 (63)	
Fibrinogen (g/l)			0.030*
<3.94	140 (52.8)	28 (38.4)	
≥3.94	125 (47.2)	45 (61.6)	
APTT (S)			0.769
<36.1	114 (43)	30 (41.1)	
≥36.1	151 (57)	43 (58.9)	
SII			0.000*
<1230.13	155 (58.5)	14 (19.2)	
≥1230.13	110 (41.5)	59 (80.8)	
Duration of incarceration (hours)			0.007*
<24	116 (43.8)	19 (26)	
≥24	149 (56.2)	54 (74)	
Bowel obstruction			0.000*
Presence	138 (52.1)	11 (15.1)	
Absence	127 (47.9)	62 (84.9)	
Signs of peritonitis			0.000*
Absence	253 (95.5)	58 (79.5)	
Presence	12 (4.5)	15 (20.5)	
With chronic disease			0.516
Absence	160 (60.4)	41 (56.2)	
Presence	105 (39.6)	32 (43.8)	

Abbreviation: BMI, body mass index; PT, prothrombin time; APTT, activated partial thromboplastin time; PLR, platelets -to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index.
Notes: *$P < 0.05$.

Results

Patients' characteristics

Among the 338 cases of IIH, 206 (77.7%) and 47 (21.6%) patients were male in the non-intestinal and intestinal resection groups. The median age of the patients was 70 years. A total of 73 patients were in the bowel resection group, accounting for 21.6% of the total cases. Further, the non-intestinal resection group accounted for 78.4% of the patients. The results of the univariate analysis of clinicopathological characteristics in our research group are listed in Table 1.

Risk factors associated with bowel resection of IIH patients

Based on multivariable logistic regression analysis, we obtained five independent risk factors for bowel resection after surgery for IIH, which were age, temperature, SII, bowel obstruction, and signs of peritonitis. We found that increased risk of bowel resection was highly correlated among the elderly (≥70 years), and for people with high temperature (≥37.3°C), high SII values (≥1230.13), presence of bowel obstruction, and signs of peritonitis (Table 2).

Nomogram for bowel resection of IIH

Further, we processed the five independent risk factors using special software to obtain a simple model called a nomogram (Figure 1). Each sub-variable was observed to

TABLE 2 Multivariable analysis of clinical/laboratory parameters and incarcerated groin hernia patients with or without bowel resection.

Variables	*P* value	OR	95%CI
Age (<70, ≥70 years)	0.038*	2.039	1.039–4.002
Temperature (<37.3, ≥37.3°C)	0.041*	2.153	1.033–4.487
SII (<1230.13, ≥1230.13)	0.000*	4.387	2.183–8.816
Bowel obstruction (absence, presence)	0.001*	3.498	1.627–7.518
Signs of peritonitis (absence, presence)	0.005*	3.727	1.492–9.312

Abbreviation: SII, systemic immune-inflammation index; OR, odds ratio; CI, confidence interval.
Notes: *$P < 0.05$.

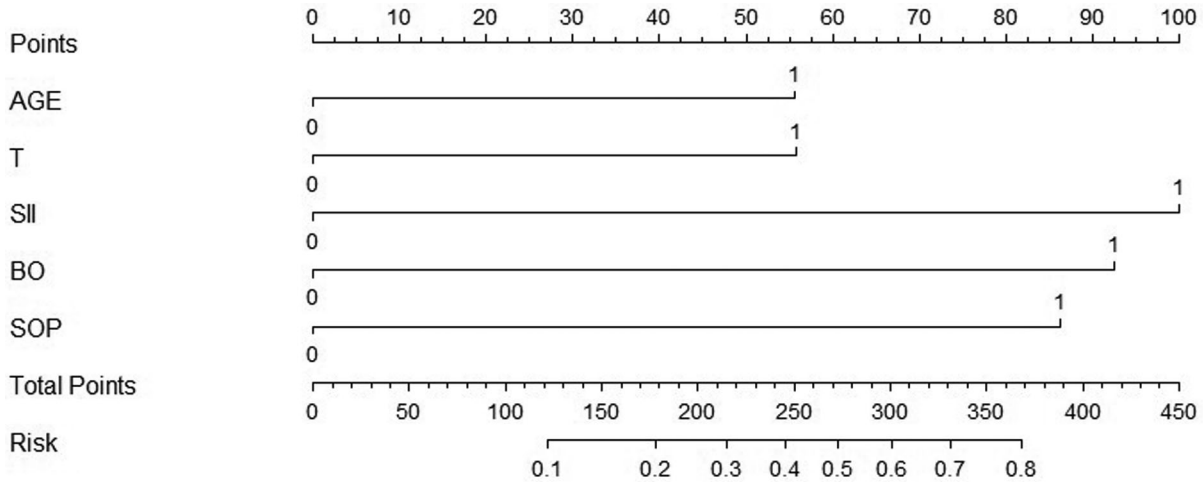

FIGURE 1
Nomogram for predicting the risk of enterectomy for incarcerated groin hernia.
Abbreviation: AGE, age (0 means <70, 1 means ≥70 years); T, temperature (0 means <37.3, 1 means ≥37.3°C); SII, systemic immune-inflammation index (0 means <1230.13, 1 means ≥1230.13); BO- Bowel obstruction (0 means absence, 1 means presence); SOP- Signs of peritonitis (0 means absence, 1 means presence).

have been assigned a certain score. These scores were added to obtain the total score and determine the corresponding point on the total score scale. A vertical line was drawn in the downward direction from this point, which enabled an easy estimation of bowel resection risk probability. To verify the model's accuracy, we calculated the C-index: 0.806, wherein a larger value indicated higher reliability of the model. The calibration curve was used to verify the performance of the model (**Figure 2**). Further, to confirm the predictive power of the model, we constructed the ROC curve nomogram and other sub-variables, and calculated the area under the curve (AUC) corresponding to the nomogram (AUC = 0.808, 95% CI = 0.762 to 0.848), SII (AUC = 0.752, 95% CI = 0.703 to 0.797), age (AUC = 0.641, 95% CI = 0.587 to 0.692), temperature (AUC = 0.579, 95% CI = 0.524 to 0.632), bowel obstruction (AUC = 0.685, 95% CI = 0.633 to 0.734), and signs of peritonitis (AUC = 0.580, 95% CI = 0.525 to 0.633) (**Figure 3**). **Table 3** lists each variable's exact boundary values in the nomogram and exact probability values of bowel resection.

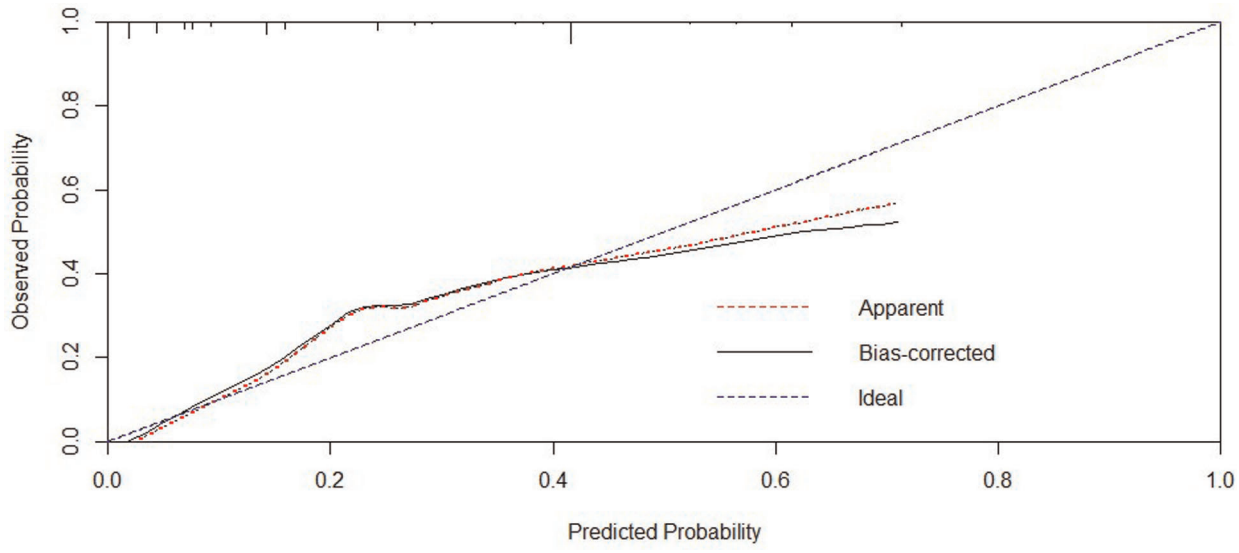

FIGURE 2
Calibration curve of the nomogram.

Discussion

An inguinal hernia is a common surgical disease. Once incarcerated or strangulated, it may endanger the life of the patient. Therefore, it is essential to study the risk factors of IIH and SIH. One of the serious complications of IIH and SIH is intestinal necrosis, which occurs owing to blood supply disorder.

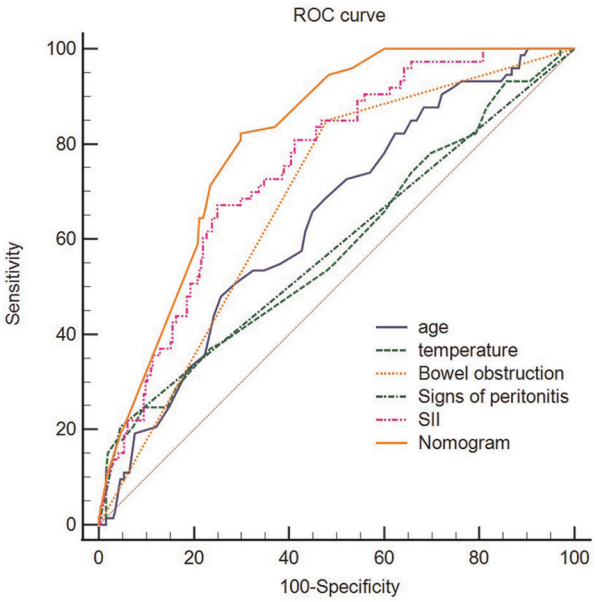

FIGURE 3
ROC curve of the nomogram, SII,temperature, bowel obstruction, signs of peritonitis.
Abbreviation: SII, systemic immune-inflammation index; ROC, receiver operating characteristic.

In recent years, studies on the risk factors of IIH requiring bowel resection have been reported successively. Alvarez et al. reported that approximately 12.9% of 70 patients with inguinal hernia require bowel resection (5). Xie et al. found that the neutrophil-to-lymphocyte ratio (NLR) has clinical significance in predicting the severity of IIHs (6). Similarly, Zhou et al. believed that NLR is significant in diagnosing adult SIH (3). Compared to the previous method of judging whether an IIH has strangulation based on clinical manifestations and signs, NLR is an objective biological indicator calculated using laboratory data. Based on this, we concluded that the SII index is also an infectious index enabling us to understand if SII is inevitable based on the severity of IIH. Our team retrospectively analysed the clinicopathological data of 338 patients with IIH undergoing emergency surgery at our hospital-based on this conjecture. As expected, SII and other clinical indicators are closely related to the intestinal resection rate of IIH. Based on the literature, we found that SII has not been studied and reported by scholars as a new biological indicator for judging the severity of IIH. Although SII is closely related to IIH resection, wherein the probability of intestinal resection in patients with high levels of SII increases, the specific mechanism is still unclear. Based on previous reports, it is noted that scholars found SII to be closely related to the prognosis of tongue cancer (7), non-small cell lung cancer (8), colorectal cancer (9), intrahepatic cholangiocarcinoma (10), esophageal squamous cell carcinoma (11), and anal cancer (12). SII is calculated from the ratio of neutrophils, platelets, and lymphocytes. Nathan et al. confirmed that neutrophils are human immune cells, and as an indicator of inflammation, they can promote the formation and development of tumors. Further, an increase in neutrophils can inhibit lymphocyte production, which is a form of inflammation (13). Jenne et al. believed that

TABLE 3 Nomogram scoring system.

Age (years)	Points	Temperature (°C)	Points	SII	Points	Bowel obstruction	Points	Signs of peritonitis	Points
<70	0	<37.3	0	<1230.13	0	without	0	no	0
≥70	56	≥37.3	56	≥1230.13	100	with	92	yes	86

Total points	Risk
122	0.1
178	0.2
215	0.3
245	0.4
273	0.5
301	0.6
331	0.7
368	0.8

Abbreviation: SII, systemic immune-inflammation index.

platelets are effective immune modulators and effectors in the human body, which can identify, isolate, and kill pathogens and can enhance phagocytosis and the destroying ability of white blood cells (14). When IIH causes peritonitis, an inflammatory response is triggered in the body. This could be the reason why the higher the SII value calculated from the inflammation index is, the severe the inflammatory response in the body is, followed by a greater risk of bowel resection. The relevant mechanism is yet to be further studied by scholars.

The risk of bowel resection after strangulation of an incarcerated hernia is not just significantly related to SII but also closely related to the patient's age, body temperature, intestinal obstruction, and signs of peritonitis. The risk of intestinal resection in patients over 70 years with an incarcerated hernia is significantly higher than that in patients who are less than 70 years old, which could be related to the decline in older patients' immunity and physical functionality. Our study also found that intestinal obstruction is one of the independent risk factors for IIH undergoing enterectomy, consistent with previous studies. However, the specific mechanism is still not clear and may be related to intestinal necrosis caused by incarceration for an extended time. In addition, the presence of peritonitis significantly increases the risk of bowel resection. In addition, the presence of peritonitis also greatly increases the risk of bowel resection, which may be related to the inflammation caused by intestinal necrosis or intestinal perforation that stimulates the peritoneum (15).

After analysing the risk factors of enterectomy for IIH, we further developed a simple model called the nomogram to predict the intestinal resection rate intuitively and accurately. In recent years, nomograms have been widely used to predict prognosis or complications of various diseases, such as liver cancer (16), stomach cancer (17), rectal cancer (18), and small cell lung cancer (19). The nomogram graphically represents each predictor variable's influence on the outcome, which enables the readers to have a specific explanation for the variable's influence (20). To the best of our knowledge, our research team is the first to construct a nomogram to predict the rate of bowel resection for IIHs based on five clinicopathological variables, including SII. To verify the nomogram's accuracy and predictive ability, we calculate the C-index: 0.806 and use the calibration curve to evaluate its stability and predictive performance. Both the C-index and the calibration curve indicate that our nomogram is accurate and stable.

Our research still has a few drawbacks, which are as follows: (1). Our research data includes only one institution and one region, and, hence, lacks universality; (2). Owing to strict inclusion criteria, this study is only applicable to incarcerated groin hernia, and the content of the hernia is intestinal tubes; (3). Our sample size is small, and a large sample is needed to confirm our research results further.

In conclusion, it can be said that we found for the first time that clinical variables such as SII are independent risk factors for enterectomy for IIH. The nomogram based on SII and other variables can accurately and easily predict the probability of IIH requiring bowel resection.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by The First Affiliated Hospital of Wenzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LC and LC are contributed this work equally. X-gX and L-xZ are co-corresponding authors. 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.

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Intestinal neuronal dysplasia presenting as psoas abscess: A case report

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Background: Intestinal neuronal dysplasia (IND) is a rare condition mainly affecting the children. Constipation and abdominal distension have been reported as common manifestations. In addition, the reports about adult cases are scarce.
Case report: A 31-year-old man presented with pain in his left hip and intermittent fever for 1 month. The whole abdomen CT and pelvic contrast-enhanced MRI revealed a left psoas abscess (PA). The patient has been given anti-infective treatment and underwent CT-guided drainage of left PA with a temporary drain. But the patient's condition did not improve significantly. Then, the colonoscopy revealed that it may be the PA secondary to inflammatory bowel disease. But the pathology was not in line with inflammatory bowel disease. We finally performed an ileostomy surgery and took the whole layer of intestinal wall for biopsy. The pathological result revealed that a large number of proliferative ganglion cells and circuitous hyperplastic nerve fibers were found in the submucosa and muscular layer of the intestinal wall. Given pathological results and clinical manifestations, the patient was diagnosed with IND-B.
Conclusion: In this case, we first report an extremely rare case of adult IND manifesting as PA. So, this unusual case provides a new supplement to adult cases of IND.

KEYWORDS
intestinal neuronal dysplasia, psoas abscess, inflammatory bowel disease, case report, constiption

Introduction

Intestinal neuronal dysplasia (IND) is a rare anomaly of the enteric nervous system, with an estimated incidence of approximately one in 7,500 newborns (1). This disorder is a frequent cause of gut dysmotility and pseudo-obstruction which shows the clinical features similar to Hirschsprung's disease (HD). But, IND is a distinct clinical entity genetically different from HD (2). Due to IND mainly affecting children, few adult cases have been reported. Here, we report an extremely rare case of adult IND with psoas abscess (PA) as the initial symptom.

Case presentation

A 31-year-old man came to our hospital with left hip pain and intermittent fever for 1 month. For nearly a year, the patient occasionally has abdominal distention which

alleviated after defecation. The frequency of defecation was about once every two days. The mass was seen as a reddish skin color around the anterior superior iliac spine which was painful and palpated.

Diagnostic assessment

The laboratory examination revealed white blood cell 13.25×10^9/L (3.5–9.5), neutrophil percentage 85% (40–75), platelet 420×10^9/L (125–350), C-reactive protein 82.6 mg/L (0–10) and erythrocyte sedimentation rate 48 mm/h (0–20). The tumor-related biomarkers (AFP, CEA, PSA, CA19–9, ferritin), serum tuberculosis antibodies and T-cell spot test for tuberculosis infection (T-TB.Spot) were within normal limits. The whole abdomen CT and pelvic contrast-enhanced MRI were performed. The imaging revealed a left PA (**Figures 1A, B**) Colonoscopy revealed mucosal stiffness and multiple polyps on the ascending colon (**Figure 1C**). Then, the mucosal biopsy of ascending colon was performed. To sum up, we think that it may be the PA secondary to inflammatory bowel disease. But pathology was not in line with the typical manifestations of inflammatory bowel disease.

Treatment

Since admission, the patient was given piperacillin sodium plus tazobactam for anti-infective treatment, but the patient's condition did not improve significantly. Then, the patient underwent CT-guided drainage of left PA with temporary drain placement and drained 450 ml pus. The patient still had intermittent pain and fever. We finally decided to perform a laparoscopic exploration. During the operation, we found the sigmoid colon with slight expansion and severely adhering to the surrounding tissue. Later, we performed a temporary ileostomy surgery and tried to take the whole layer of intestinal wall (descending colon, sigmoid colon about 0.5 cm in diameter) for biopsy. In addition, the primary closure was done after full thickness biopsy. The patient recovered well and was discharged two weeks after the operation. Moreover, followed up for 6 months after operation, the fever and pain in his left hip was no recurrence without specific treatment. The temporary stoma was scheduled to be closed one year after surgery.

Histopathology

The result of mucosal biopsy was scattered infiltration of lymphocytes, plasma cells and eosinophils in the colonic mucosa. The Haematoxylin and Eosin staining technique has been used for hystopathological diagnosis. The pathological results revealed that a large number of proliferative ganglion cells and circuitous hyperplastic nerve fibers were found in the submucosa and muscular layer of the intestinal wall (**Figure 1D**). Given pathological results and clinical manifestations, the patient was diagnosed with IND-B.

Discussion

Swiss pathologist Meier-Rule first proposed the pathological phenomenon of colonic neuronal dysplasia in 1971 (3). It is classified into two clinical and histologically subtypes as types A or B. IND type B (IND-B), which comprises >95% of IND cases, is a pathological entity of the group of gastrointestinal neuromuscular diseases characterized by hyperplasia of the submucosal nerve plexuses (4) and presents as chronic constipation usually during childhood (5). In addition, the etiopathogenesis of IND-B is widely debated. It is mainly recognized as genetic alterations resulting in intestinal neuronal system development disorder (6, 7). However, IND-B can also be understood as a secondary phenomenon due to congenital intestinal obstructions or local inflammatory processes (8).

There had been several adult cases reported in the past few years. In addition, constipation and abdominal distension were a common manifestation in reported adult cases (9, 10). Referring to the relevant literature, the adult IND with PA as the initial symptom is reported for the first time in our case. The PA is an infectious disease with nonspecific clinical presentation which frequently leads to diagnostic difficulty. The PA is mostly secondary abscess. The most common etiologies of PA were vertebral osteomyelitis, colorectal cancer, gastrointestinal tract infection and Crohn's Disease (11, 12). Therefore, when the patient was admitted to the hospital, we first measured the tumor-related biomarkers, serum anti-tuberculosis antibodies and T-cell spot test for tuberculosis infection (T-TB.Spot). The above indexes all indicated negative results. And combining with imaging examinations, some possible diseases such as tuberculosis, tumor or vertebral osteomyelitis were excluded. In addition, we also took into account the diagnosis of Crohn's disease. In our case, both colonoscopy and barium enema revealed marked stenosis of colon, but the result of mucosal biopsy did not conform to the pathological manifestations of Crohn's disease. The above imaging and related examination results made the diagnosis more difficult, coupled with long-term anti-infective treatment did not have a good effect. Finally, we decided to explore the abdominal cavity and perform full-thickness biopsy of colon wall. Pathologic examination of the specimen showed that there were a large number of proliferated ganglion cells and nerve fibers in the submucosa and muscular layer of the colon wall, which can be considered as an important reference index in the process of diagnosis. Combining the clinical manifestations with the results of pathological and laboratory investigations, the diagnosis of IND-B was established.

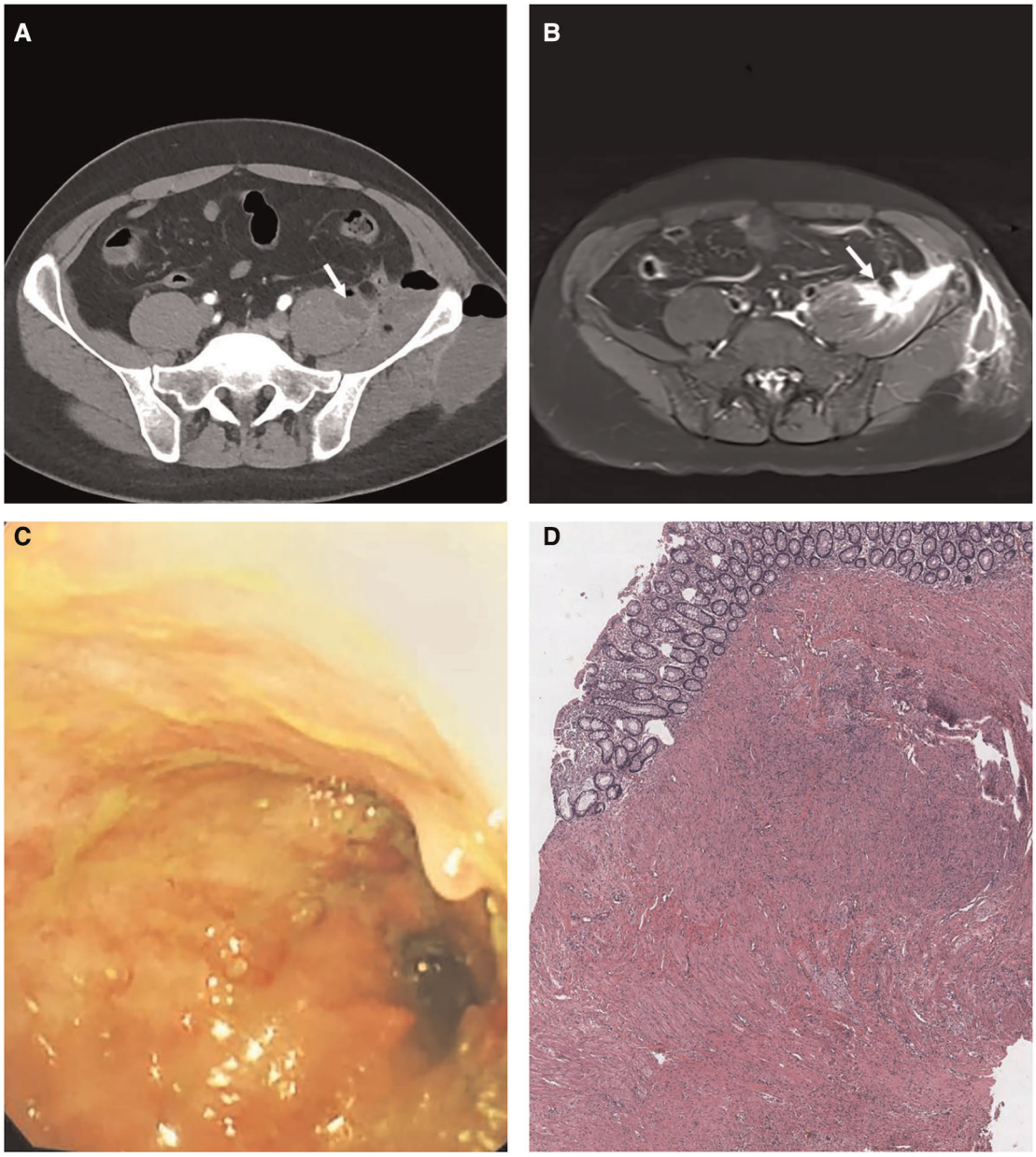

FIGURE 1
The abdominal CT showed patchy low-density shadow of the left pelvic wall soft tissue (**A**). The pelvic MRI showed that the lower part of the left psoas major muscle, the left pelvic wall and the left buttock were thickened with multiple high signal shadows (**B**). Colonoscopy showed multiple filling defects and local lumen stenosis in the terminal ileum, ileocecum and the beginning of the ascending colon (**C**). The pathological results revealed that a large number of proliferative ganglion cells and circuitous hyperplastic nerve fibers were found in the submucosa and muscular layer of the colon wall (**D**).

Due to the rarity of adult cases and the non-specificity of symptoms, the diagnosis of adult IND is more difficult than that of infants. And early diagnosis remains a great challenge for IND. The auxiliary diagnostic methods include barium enema, anorectal manometry and rectal mucosa biopsy. However, the histological examination remains the gold standard of the diagnosis. Usually, it is necessary to include a sufficient amount of submucosa in the suction biopsy specimens. In this case, it is worth noting that the rectal mucosal biopsy of the patient was negative. Thus, full-thickness biopsy of colon wall can be considered as an important reference index in the diagnosis of IND.

According to the latest report, blood Sox 10 promoter methylation can be used as a noninvasive and efficient

diagnosis method for IND (13). Recently, an endoscopic device has been developed to obtain full-thickness biopsies from the bowel wall without laparotomy and anesthesia (14). It is a promising minimally invasive procurement of intestinal full-thickness biopsies for the diagnosis of intestinal neuropathies.

Conclusion

In conclusion, for patients with PA, physicians should consider IND as a possible diagnosis after excluding other more common causes. So, this unusual case of psoas major abscess provides a new supplement to adult cases of IND. More importantly, a non-invasive diagnostic method with a high degree of accuracy needs to be developed. No matter for the diagnosis and treatment of IND in infants and adults, further exploration is needed and attention should be paid to individual treatment.

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

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

BR, BZ, and SC: collected the data and drafted the manuscript. HH and DS: reviewed and modified the manuscript. All authors contributed to the article and approved the submitted version.

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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.

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A novel knotless hand-sewn end-to-end anastomosis using V-loc barbed suture vs. stapled anastomosis in laparoscopic left colonic surgery: A propensity scoring match analysis

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Background: Laparoscopic colectomy is widely practiced for colon cancer, but many variations exist for anastomosis after laparoscopic colon cancer radical resection.

Method: We retrospectively analyzed 226 patients who underwent laparoscopic-assisted radical resection for left colon cancer with knotless hand-sewn end-to-end anastomosis (KHEA) technique with barbed V-loc™ suture material and compared perioperative outcomes, safety, and efficacy to those undergoing stapled anastomosis from 2010 to 2021.

Results: After the 1:2 propensity score matching, 123 participants with similar preoperative characteristics (age, body mass index, TNM stage, and tumor location) were enrolled in the study: 41 in the KHEA and 82 in the stapler group. Statistically significant differences were found in time to accomplish the anastomosis (mean 7.9 vs. 11.9 min, $p < 0.001$) and hospital costs (mean 46,569.71 vs. 50,915.35 CNY, $p < 0.05$) that differed between the KHEA and stapler group, respectively. No statistically significant difference was found in the mean delay to bowel function recovery (2.6 vs. 2.7 days, $p = 0.466$), duration of hospital stay (8.6 vs. 7.9 days, $p = 0.407$), or rate of postoperative complications (14.6% vs. 11.0%, $p = 0.563$). Anastomotic leakage occurred in 11 patients: 5 (12.2%) vs. 6 (7.3%) ($p > 0.05$) in the KHEA and stapler group, respectively.

Conclusion: KHEA is feasible and safe for anastomosis after laparoscopic left hemicolectomy. The KHEA technique could reduce operation time and hospital costs with complication rates comparable to stapling.

KEYWORDS

barbed suture, laparoscopic surgery, left hemicolectomy, colon cancer, left colon anastomosis, extracorporeal anastomosis, intracorporeal anastomosis

Introduction

Laparoscopic colectomy is widely performed for colon cancer (1), but many variations exist for the method of anastomosis after laparoscopic radical resection for cancer (2–4). Left hemicolectomy may sometimes be a complex procedure [mobilization of the splenic flexure, unexpected adhesions or tumor invasion, intraoperative vascular problems (5, 6). Complete laparoscopic colectomy with an intracorporeal reconstruction technique requires advanced surgical skills and may increase operation time, hospitalization costs, and/or the risk of abdominal contamination (7–9).

The recent advent of barbed sutures has made manual suturing more convenient and quicker because of good tissue adhesion and eliminated need for knot tying. At present, the barbed suture is mainly used for gastrointestinal anastomoses (10, 11) and urinary tract surgery (12), but there are very few reports on left colonic anastomosis.

In this study, we describe the details of a novel extracorporeal anastomosis (ECA) with barbed thread—a knotless hand-sewn end-to-end anastomosis (KHEA) technique—with a video and compare the perioperative outcomes of KHEA to those of stapled anastomosis.

Material and methods

Patients selection and data

This was an Institutional Review Board approved study. We retrospectively analyzed 226 patients who underwent laparoscopic-assisted left hemicolectomy (resection of the last third of the transverse colon, descending and upper sigmoid colon) from 2010 to 2021 at the General Surgery Department of Ruijin Hospital, Shanghai, China. The clinical data were recorded prospectively in the database of Ruijin Hospital, and the results were evaluated retrospectively. Patients were divided into two groups: KHEA and stapled anastomosis.

The inclusion criteria for this study included (1) age between 18 and 85 years; (2) diagnosis of colonic adenocarcinoma by colonoscopy, computed tomography (CT), and pathological examination; (3) clinical T stage I to IVa without distant metastases; and (4) laparoscopic-assisted left hemicolectomy. Exclusion criteria were (1) multiple primary tumors; (2) other previous or concurrent major abdominal surgery; (3) metastases found during surgery; (4) associated enterostomy; and (5) unavailable or incomplete clinical data.

A total of 211 patients were included in the study: 49 underwent the KHEA technique and 162 underwent stapled anastomosis. A 1:2 propensity score matching (PSM) was performed (**Figure 1**). All surgeries were performed by physicians who had crossed the learning curve of laparoscopic radical colectomy.

Preoperative demographic and clinicopathologic characteristics included age, gender, body mass index (BMI), TNM stage based on the AJCC Staging Manual 8th edition, and tumor location. Operative data included anastomosis complications, anastomotic time, days to bowel function recovery, postoperative hospital stay, and hospital costs. The postoperative complications were classified according to the Clavien–Dindo grading (13). The anastomosis leak was graded by the modified International Study Group of Rectal Cancer (ISREC) classification (14, 15).

Surgical technique

The patient was placed in the supine split-leg position. Under general anesthesia, pneumoperitoneum was established and maintained at 15 mmHg, and five trocar ports were placed (**Figure 2**). Exploration of the abdominal cavity identified any peritoneal, liver, or other distant metastasis. Surgery was performed according to the complete mesocolic excision principle, with proximal and distal margins of at least 5 cm. For tumors located at the sigmoid-descending colon junction, mobilization of the splenic flexure depends on the tension of the colon.

KHEA procedure

The technique consists of two steps: (1) left lower longitudinal incision and (2) continuous double-layer hand-sewing with knotless barbed suture (**Supplementary Video**).

(1) Abdominal incision: A longitudinal incision was made at the left lower quadrant of the abdomen (approximately 5 cm). The tumor-bearing colon segment was extracted, and the tumor completely resected. The upper and lower resection margins were both over 5 cm.
(2) Colon suspension: The mesenteric border and the opposite mesangial border of the two colon ends were identified and the two extremities were suspended with one single-strand suture each. These two threads were used to maintain tension and lift the bowel (**Figure 3A**).
(3) Inner layer suture: Barbed suture was then used to perform a continuous full-thickness suture from the mesangial to the mesenteric border. Suture bites were placed 3–5 mm apart and 2–3 mm from the cut edge of the tissue (**Figure 3B**).
(4) Outer layer suture: The serosa was sutured from the opposite mesangial to the mesenteric border in a continuous fashion. Suture bites were placed 5 mm apart and 5 mm from the line of anastomosis. The outer layer completely buried the inner suture line (**Figure 3C**). Finally, the barbed suture ends were cut as short as possible.

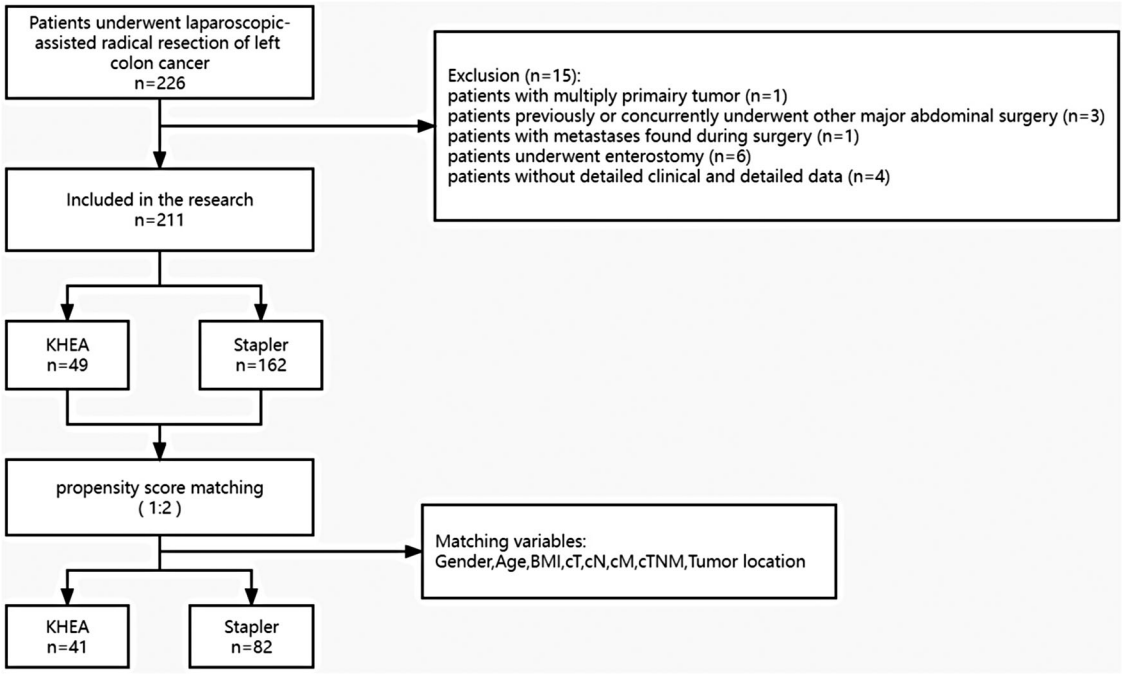

FIGURE 1
Flow chart.

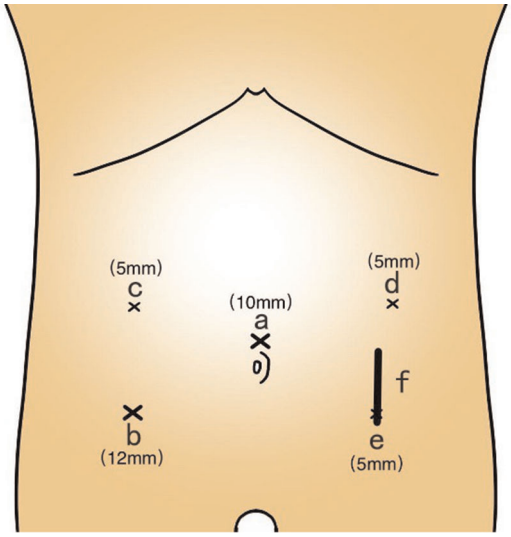

FIGURE 2
Trocar placement. (A) Camera port for laparoscope. (B) Manipulation port. (C–E) Assistant ports. (F) Abdominal incision extended for specimen resection and extraction (approximately 5 cm).

The opposite hemi-circumference of anastomosis is sutured following the same procedures outlined in (2)–(4). Duration of anastomosis was measured from resection of the tumor until completion of the anastomosis.

Procedure of stapled anastomosis

A longitudinal incision was made at the mid or left lower abdomen (approximately 5 cm). The tumor-bearing colonic segment was extracted and resected with its mesentery. The proximal and distal resection margins were both at least 5 cm. Both side-to-side linear stapler and end-to-side circular stapler anastomoses were included in this study. Duration of anastomosis was measured from resection of tumor until completion of the anastomosis.

Linear stapler anastomosis procedure: A linear stapler is inserted into both proximal and distal stump and the common opening is closed with a second linear stapler to complete the anastomosis.

Circular stapler anastomosis procedure: The anvil of a circular stapler is inserted into the distal stump and the purse-string was secured. The circular stapler is inserted into the proximal stump, and the common opening is closed with a linear stapler to complete the anastomosis.

Postoperative management

Early mobilization was encouraged. Patients were allowed fluid intake after bowel function recovery, and a liquid diet was started the next day. All patients had an abdominal drain, which was removed when the volume of drainage was less than 20 ml. Patients with a normal postoperative course were discharged on

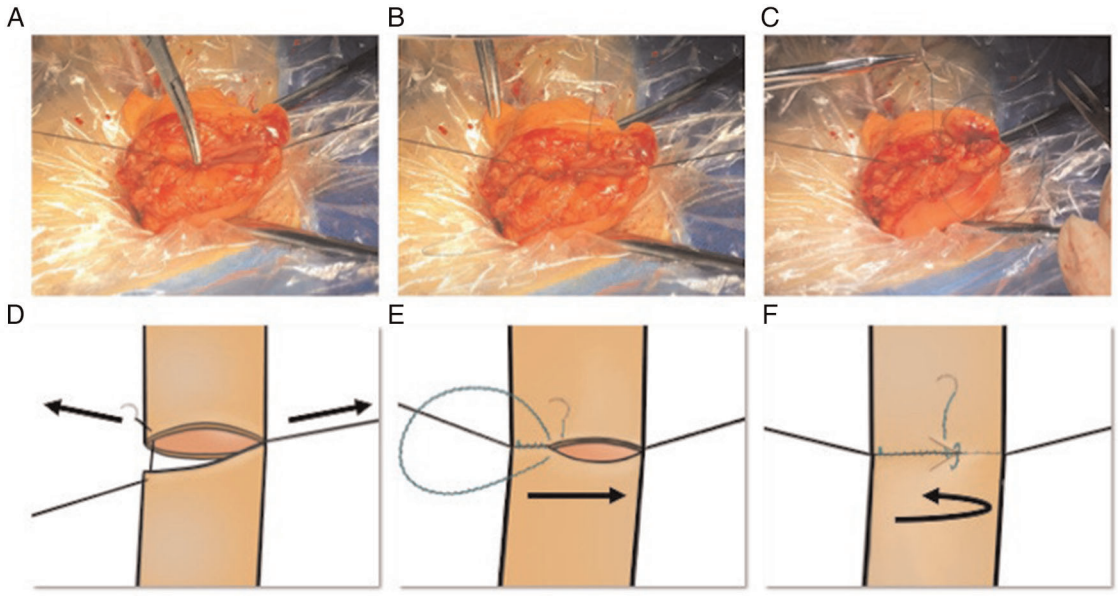

FIGURE 3
Intraoperative photograph and schematic illustration of KHEA. (A,D) Colon suspension: identification of the mesenteric and the mesangial borders of the two colonic extremities, suspended with single-strand sutures. These two threads are used to maintain tension and lift the bowel. (B,E) Inner layer suture: We use barbed suture to perform continuous full-thickness suture from the opposite mesangial to the mesenteric border. Suture bites are placed 3–5 mm apart and 2–3 mm from the cut edge of the tissue. (C,F) Outer layer reinforcement: We continuously suture the serosa from the mesangial to the mesangial border. Suture bites are placed 5 mm apart and 5 mm from the line of anastomosis. The outer layer suture completely buries the inner suture. KHEA, knotless hand-sewn end-to-end anastomosis.

postoperative day (POD) 8. Verbal and written instructions specifying warning signs were given to all patients. All patients were followed up by clinic visits or phone calls every 3 months for the first year after surgery. When complications were suspected, endoscopy or CT scan was performed.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 (IBM Corporation, Chicago, IL, United States). Continuous variables were expressed as mean ± standard deviation. Student's *t*-test was used for independent samples comparison, the chi-square test and Fisher's exact test was used to compare definite variables. A p value <0.05 was considered statistically significant. Schematic diagrams of the surgery were drawn using Sketchbook (IpadOS, Autodesk, United States).

Results

Demographic and clinicopathologic characteristics

After the 1:2 PSM, 123 participants with similar preoperative characteristics (age, BMI, TNM stage, and tumor location) were enrolled in the study: 41 in the KHEA and 82 in the stapler group (Table 1).

Short-term outcomes and costs

Table 2 shows the comparison of short-term outcomes and costs. There was no statistically significant difference in the mean bowel function recovering day (2.61 vs. 2.71, $p = 0.466$), duration of hospital stay (8.61 vs. 7.91, $p = 0.407$), or rate of postoperative complications (14.6% vs. 11.0%, $p = 0.563$). The occurrence of anastomotic leak, graded by the modified classification of International Study Group of Rectal Cancer (ISREC), was observed in 11 patients: 6 in the stapler group (7.3%) and 5 in the KHEA group (12.2%) ($p > 0.05$). Anastomotic bleeding at the colonic anastomotic site was observed in one patient in the stapler group on POD 2. This complication was treated with local adrenaline injection and endoscopic monopolar electrocautery. No anastomotic stenosis or bowel obstruction was observed in either group. One patient in the stapler group had a wound disruption while another patient in the KHEA group had a surgical site infection: all patients were discharged after local treatment. One patient in the stapler group developed a chyle fistula after operation but was discharged from the hospital after

TABLE 1 Demographic and clinicopathologic characteristics.

Characteristic		Before matching			After matching		
		KHEA $N = 49$	Stapler $N = 162$	p	KHEA $N = 41$	Stapler $N = 82$	p
Gender (%)	Male	33 (67.3)	111 (68.5)	0.877[a]	29 (70.7)	53 (64.6)	0.320[a]
	Female	16 (32.7)	51 (31.5)		12 (29.3)	29 (35.4)	
Age, years [mean (SD)]		59.1 (12.613)	63.6 (12.290)	0.026[b]	61.7 (10.900)	61.0 (12.172)	0.742[b]
BMI, kg/m^2 [mean (SD)]		23.4 (2.929)	23.4 (3.146)	0.949[b]	23.5 (2.768)	23.3 (2.914)	0.700[b]
cT (%)	cT1	13 (26.5)	31 (19.1)	0.463[a]	12 (29.3)	16 (19.5)	0.437[a]
	cT2	5 (10.2)	13 (8.0)		5 (12.2)	6 (7.3)	
	cT3	17 (34.7)	76 (46.9)		15 (36.6)	36 (43.9)	
	cT4	14 (28.6)	42 (25.9)		9 (22.0)	24 (29.3)	
cN (%)	cN0	30 (61.2)	102 (63.0)	0.892[a]	29 (70.7)	47 (57.3)	0.383[a]
	cN1	10 (20.4)	35 (21.6)		7 (17.1)	19 (23.2)	
	cN2	9 (18.4)	25 (15.4)		5 (12.2)	16 (19.5)	
cM (%)	cM0	46 (93.9)	154 (95.1)	0.491[a]	40 (97.6)	75 (91.5)	0.186[a]
	cM1	3 (6.1)	8 (4.9)		1 (2.4)	7 (8.5)	
cTNM (%)	I	17 (34.7)	38 (23.5)	0.303[a]	16 (39.0)	19 (23.2)	0.231[a]
	II	13 (26.5)	63 (38.9)		13 (31.7)	27 (32.9)	
	III	16 (32.7)	53 (32.7)		11 (26.8)	29 (35.4)	
	IV	3 (6.5)	8 (4.9)		1 (2.4)	7 (8.5)	
Tumor location	SDJ	24 (49.0)	48 (29.6)	0.004[a]	19 (46.3)	35 (42.7)	0.487[a]
	DC	22 (44.9)	75 (46.3)		20 (48.8)	37 (45.1)	
	TC	3 (6.1)	39 (24.1)		2 (4.9)	10 (12.2)	

KHEA, knotless hand-sewn end-to-end anastomosis; SD, standard deviation; BMI, body mass index; SDJ, sigmoid-descending colon junction; DC, descending colon; TC, transverse colon.
[a]Chi-square test.
[b]Student's t-test.

being placed on a fat-free diet and clear drainage fluid was noted. Completion of the anastomosis required a shorter time in the KHEA group (mean 7.8 vs. 11.9, $p < 0.001$) than in the stapler group. The surgery cost was also significantly decreased in the KHEA group (mean 46,569.71 vs. 50,915.35 CNY, $p < 0.05$) for V-Loc vs. stapled anastomosis, respectively.

Discussion

In this study, the mean duration for completion of anastomosis and operation costs were statistically significantly decreased in the KHEA group, while no statistically significant difference was found in the rate of postoperative complications, delay to bowel function recovery, or duration of hospital stay.

The minimally invasive approach for colectomy can be performed *via* either a "minimally invasive assisted" technique with ECA or a "total minimally invasive" technique with intracorporeal anastomosis (ICA), i.e., performing the anastomosis in the abdominal cavity under the direct view of a laparoscope. In recent years, ICA has received increasing focus, but its superiority over extracorporeal anastomosis is still inconclusive (16). Several studies have shown that that ICA has advantages over ECA such as shorter length of incision, less estimated blood loss, and shorter time to bowel function recovery (2, 17, 18). However, two recent high-quality randomized controlled trials (8, 19) and one study on robotic left colectomy (20) failed to show that outcomes after ICA were better than after ECA. The advantages of the KHEA technique could be a further argument in favor of the ICA technique.

For left hemicolectomy, anastomosis can be performed either manually or with staplers. As reported, no statistically significant superiority has been found between these two methods with respect to safety or anastomotic leakage (4, 21). Based on our experience, an end-to-end hand-sewn anastomosis could save approximately 3–5 cm of colon segment compared with stapled anastomosis, enabling surgeons to avoid unnecessary mobilization of the colon and the longitude tension of anastomosis. However, the traditional

TABLE 2 Comparison of short-term outcomes and costs.

	KHEA $N = 41$	Stapler $N = 82$	p
Anastomotic complications (%)			
Leakage	5 (12.2)	6 (7.3)	0.439[a]
Grade A	3 (7.3)	2 (2.4)	
Grade B	2 (4.8)	4 (4.8)	
Grade C	0	0	
Hemorrhage	0	1 (1.2)	
Stenosis	0	0	
Other complications (%)			
Bowel obstruction	0	0	
Wound-healing complications	1 (2.4)	1 (2.4)	
Chyle leakage	0	1 (2.4)	
Time to complete anastomosis, min [mean (SD)]	7.85 (1.22)	11.92 (1.28)	0.005[b]
Bowel function recovery days, days (SD)	2.61 (0.74)	2.71 (0.68)	0.466[b]
Postoperative hospital days, days (SD)	8.61 (6.05)	7.91 (3.22)	0.407[b]
Hospitalization cost[c] (SD)	46,569.71 (10,415.15)	50,915.38 (7,248.56)	0.008[b]

KHEA, knotless hand-sewn end-to-end anastomosis; SD, standard deviation.
[a]Fisher's exact test.
[b]Student's t-test.
[c]Chinese Yuan.

hand-sewing anastomosis technique requires higher technical skills from surgeons and takes a longer operation time than stapled anastomosis. In our experience, the hand-sewn technique using the new KHEA technique facilitates an easy anastomosis with comparable outcomes.

We extract the bowel specimen from a left lower quadrant incision, approximately 5 cm long. Compared with the midline incision, the left lower incision allows for extraction of the colon segment with less tension, thus avoiding unnecessary bowel dissection and incision extension and may cause less pain for patients. Also, a midline incision could lead to higher morbidity and, particularly, incisional hernia as reported in a systemic review (22).

In recent years, the use of barbed suture has proven to be safe and efficient in urinary tract surgery (23), gynecological surgery (24), and gastrointestinal anastomosis (10, 11). Although multifilament absorbable suture was generally used for gastrointestinal anastomosis, since the application of barbed sutures, more and more surgeons prefer the knotless technique because of the lower operational difficulty, especially in total minimally invasive operations. Applying barbed suture in anastomosis can reduce the number of knots and results in less operation time.

In our series, the postoperative complications were comparable between KHEA and stapled anastomosis. As tension on the anastomosis and poor vascularization of the proximal colon limb are among the risk factors for anastomotic leakage (25), we believe that the KHEA technique might decrease the leakage rate. We found that less mobilization of the bowel is required for the KHEA technique, which might potentially reduce the risk of marginal vascular injury such as injury to Riolan's arch. Moreover, manual suturing may potentially reduce the incidence of anastomotic bleeding (26) because of a better view of the bowel mucosa.

Based on our experience, special attention should be paid to the cut end of the barbed suture material. We recommend cutting the end flush against the intestinal wall to prevent adherence to surrounding tissues, which are a potential source of intestinal obstruction.

We recognize certain limitations in our study. First, this was not a randomized controlled study. We performed propensity score matching to minimize the effects of potential biases due to preoperative patient characteristics. Second, all the health economics calculations were based on the Chinese medical system and might vary in different countries with different insurance policies. Third, we did not evaluate the long-term outcomes. Late-onset postoperative complications such as incisional hernias were not evaluated.

Conclusion

The KHEA technique is a safe, economical, convenient, and feasible anastomosis method for laparoscopic left hemicolectomy. This technique could substantially reduce hospitalization cost and operational time with comparable complication rates. It may also have more potential benefits because of the less range of bowel dissection and shorter abdomen incision.

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 the Ethics Committee of the Ruijin Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

SX and XZ wrote the main manuscript and prepared the illustrations. ZH and XY collected the clinical data. JJM, FD, and LZa enrolled the patients. MZ, LZh, and AF designed the concept and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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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.

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Supplementary material

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Synchronous liver and peritoneal metastases from colorectal cancer: Is cytoreductive surgery and hyperthermic intraperitoneal chemotherapy combined with liver resection a feasible option?

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Background: Traditionally, synchronous liver resection (LR), cytoreductive surgery (CRS), and hyperthermic intraperitoneal chemotherapy for colorectal liver and peritoneal metastases have been contraindicated. Nowadays, clinical practice has promoted this aggressive treatment in selected cases. This study aimed to review surgical and survival results of an extensive surgical approach including CRS with hyperthermic intraperitoneal chemotherapy (HIPEC) and LR.
Methods: PubMed, EMBASE, and Web of Science databases were matched to find the available literature on this topic. The search period was limited to 10 years (January 2010–January 2021). A threshold of case series of 10 patients or more was applied.
Results: In the search period, out of 114 studies found about liver and peritoneal metastases from colorectal cancer, we found 18 papers matching the inclusion criteria. Higher morbidity and mortality were reported for patients who underwent such an extensive surgical approach when compared with patients who underwent only cytoreductive surgery and HIPEC. Also, survival rates seem worse in the former than in the latter.
Conclusion: The role of combined surgical strategy in patients with synchronous liver and peritoneal metastases from colorectal cancer remains controversial. Survival rates and morbidity and mortality seem not in favor of this option. A more accurate selection of patients and more restrictive surgical indications could perhaps help improve results in this subgroup of patients with limited curative options.

KEYWORDS

peritoneal metastases, cytoreductive surgery, liver resection, liver metastases, HIPEC, colorectal metastases.

Introduction

Colorectal cancer (CRC) is a major health problem and is the leading cause of death in developed countries (1).

Metastatic diseases are present in approximately 20%–25% of patients with advanced CRC (2).

In patients with metastatic diseases from colorectal cancer, the liver and peritoneum are the most frequently affected sites; liver metastases (LM) are present in up to 55% of patients, while secondary peritoneal involvement (PM) affects up to 25% of patients (3–5).

Peritoneal carcinomatosis is considered a negative prognostic factor in metastatic colorectal cancer (6). Peritoneal carcinomatosis occurs when the tumor invades the bowel serosa, allowing malignant cells to shed and circulate through the peritoneal fluid. During surgery, iatrogenic manipulation may lead to tumor cells seeding within the peritoneal cavity; these tumor cells implant in the peritoneal microenvironment with blood vessels and lymphatics. Due to gravity and physiologic peritoneal fluid circulation, anatomical sites of the peritoneum that are most frequently affected include the upper abdominal regions such as the subphrenic regions, the lesser sac, bowel surfaces, mesentery, and in the pelvis. Tumor cell implantation leads to tumor plaque formation that may then involve extending to peritoneal surfaces (7, 8). The National Comprehensive Cancer Network (NCCN) guidelines recommend, in high-volume centers and for patients with limited peritoneal metastases [i.e., peritoneal cancer index—peritoneal cancer index (PCI) not more than 16–20, depending on different experiences], cytoreductive surgery (CRS) in association with hyperthermic intraperitoneal chemotherapy (HIPEC) (9).

Metastatic spread from the primary tumor to the liver occurs through hematogenous dissemination. The production of tumor growth factors induces the secretion of vascular endothelial growth factor that stimulates the generation of new endothelial cells through angiogenesis. Malignant cell dissemination happens from microscopic vessels to the portal venous system and liver sinusoids, which represent the suitable microenvironment for tumor growth (10).

Oligometastatic diseases with combined hepatic and peritoneal metastatic spread affect approximately 8% of those with CRC (6), especially the presence of peritoneal metastases associated with shorter overall survival (OS) (11). The prognosis of patients with isolated LM or isolated peritoneal metastases (PM) has improved with the combination of systemic chemotherapy and complete resection, yielding a 5-year overall survival rate of 40%–50% (12, 13). CRS with intraperitoneal chemotherapy, including HIPEC, has been considered a potentially curative treatment for PM of CRC, reaching a median OS of 31 months and up to 41 months in highly selected patients (14–16).

The best strategy to treat advanced colorectal cancer with synchronous peritoneal and liver metastases (PMLM) is unclear; in the past, this was considered a terminal condition, and these patients were referred to palliative care with systemic chemotherapy with a median survival of 12–24 months (17).

A change in the trend started in 2008 when patients with CRC with up to three or fewer small resectable parenchymal hepatic metastases, good performance status, and no major comorbidities could be considered as candidates for complete R0 resection of all tumors with CRS, liver resection (LR), and hyperthermic intraperitoneal chemotherapy (HIPEC) (18).

In recent years, smaller pilot series have shown, in highly selected patients, excellent median survival beyond 40 months in resections of simultaneous liver and peritoneal metastases with CRS plus HIPEC (16, 19–23). However, to date, no standard management has been established.

Moreover, the resectability rate in patients with unresectable or multiple hepatic metastases can be increased by approaching these cases with advanced procedures such as portal vein embolization or two-stage hepatectomy (24).

Optimizing patient selection with good performance status or with minimal comorbidity and accurate perioperative management is crucial to maximizing patient outcomes while minimizing morbidity and mortality. Variations in outcomes depend on the severity of the disease represented by the PCI, tumor differentiation, histologic findings, liver extension, and the completeness of cytoreduction (25, 26). Currently, centers demonstrate large heterogeneity in whether combining CRS–HIPEC with liver resection can offer beneficial results.

Given the contradicting data and the lack of standardized management for patients with simultaneous peritoneal and hepatic metastases from CRC, a thorough evaluation of the current literature is warranted to guide the correct strategy for these patients.

This study aimed to review surgical and survival results of an extensive surgical approach including CRS + HIPEC combined with LR in patients affected by peritoneal and hepatic metastases from CRC.

Methods

PubMed, EMBASE, Cochrane, and Web of Science databases were matched to find the available literature on this topic. The search period was limited to 10 years (2010–2021) to consider only up-to-date experiences in this relatively recent field of integrated treatments. Search terms including synonyms and keywords such as “metastatic colorectal cancer, HIPEC, intraperitoneal chemotherapy, liver metastases, liver resection, hepatectomy, peritoneal carcinomatosis, and peritoneal metastases” were used. Case reports, case series analyzing fewer than 10 patients, and duplicate articles were excluded. Two reviewers screened all potentially relevant titles and abstracts, selecting papers that described patients treated

with CRS–HIPEC who had peritoneal and liver metastases. English-language articles were eligible for inclusion if they specified types of studies [randomized control studies (RCTs), cohort studies, case–control studies, and cross-sectional studies], types of participants (patients with colorectal cancer metastasized to the liver or peritoneum), and types of treatments (both CRS and HIPEC). The review excluded letters to the editor, case reports, reviews, and meta-analyses. Data were collected from the included studies. Patients were divided into two groups: a group of patients with PM only and a group of patients with PMLM. The primary endpoints were OS and disease-free survival (DFS) calculated from the date of CRS–HIPEC. The secondary endpoints were perioperative outcomes including morbidity and mortality. Major morbidity was defined as the presence of a complication classified as Clavien–Dindo grade 3 or higher. Data on length of stay, operative time, PCI, pre- and postoperative chemotherapy, and follow-up period were also recorded (Tables 1 and 2).

Results

Our literature search identified 859 studies. After removing duplicates, 361 of the 475 remaining studies were excluded based on title and abstract assessment. Exclusion criteria are as follows: studies describing only peritoneal metastases patients, studies describing only colorectal liver metastases patients, articles reporting multiple types of malignancies, where differentiation between patients with colorectal cancer and those with other types of tumors was not possible, articles in which survival outcomes have not been clearly reported, article that failed to extract survival data comparing the peritoneal metastases + liver metastases group with the peritoneal metastases alone group, articles that failed to retrieve peritoneal metastases in combination with colorectal liver metastases data, or studies about debulking surgery alone or in combination with systemic chemotherapy. Out of 114 remaining studies, we found only 18 studies in which data on procedures and outcomes could be completely retrieved. A flow diagram of the literature search procedure according to the PRISMA guidelines is shown in Figure 1.

All 18 studies included in the review were published during the study period. In total, 4,719 patients were included in the study. Of these, 1,348 patients presented with synchronous PC + LM and had been treated with liver resection (or alternative therapy such as radiofrequency ablation—RFA) in combination with CRS and HIPEC. The remaining 3,371 patients presented with isolated PC and had been treated with CRS and HIPEC. In most of the studies, the PCI was comparable, and in all cases, it was below 20, which corresponds with clinical guidelines (Table 2). With the exception of the studies by Pinto et al. (28), Lo Dico et al. (40), and Jeon et al. (35), the studies in this review presented

TABLE 1 Surgical outcomes of available literature experiences.

	Study period	Patients		Operative time (min)		PO mortality (%)		Major PO morbidity (%)		Hospitalization (days)		Median Follow-up (months)	
		LM + PM	PM	LM + PM	PM	LM + PM	PM	LM + PM	PM	LM + PM	PM	LM + PM	PM
Allard 2013	1985–2010	30	NR	NR	NR	0	0	16.6	NR	NR	NR	63	NR
Blackham 2014	1991–2010	179	93	300	540	3.9	5.4	21	23	6	9	58	89
Alzahrani 2015	2003–2014	36	42	366	480	NR	NR	38.9	31	21.8	23.7	21.9	21.5
Randle 2015	1991–2013	32	201	528	510	6.5	2.8	18.5	22.5	13.6	14.2	75	120
Delhorne 2015	2007–2011	9	18	NR	NR	0	5	44.4	11.1	22	20.5	14	18
Berger 2016	2007–2014	103	166	379.3	316.9	5.8	6.7	24.3	18.1	8	6	18.2	18.2
Larimier 2016	1999–2011	22	36	586	456	1.9	11.1	54.5	38.8	22	19	60	60
Navez 2016	2007–2015	25	52	NR	NR	0	4	32	15.4	19	13	25.5	34.2
Saxena 2016	1996–2016	132	803	522	522	2.2	1.7	40.1	41.9	28	28	36	36
Morales Soriano 2017	2010–2015	16	45	456	420	0	4.4	56.3	26.6	23.1	14.4	20	20
Downs-Canner 2017	2005–2013	32	173	520.9	470.8	3.5	1.2	32.3	16.7	16	17.2	60.9	56.8
Mouw 2018	2005–2016	20	23	NR	NR	5	0	40	13.4	12.3	9.8	NR	NR
Cloyd 2018	2005–2016	100	1068	520.7	454.6	3	1.4	47	27.4	16.7	11.1	NR	NR
Jean 2019	2014–2018	22	NR	684	NR	4.5	NR	22.7	NR	25.6	NR	34	NR
Pinto 2019	2007–2016	33	76	420	420	0	0	42.4	39.4	28	25	30	30
Horvath 2019	2006–2016	37	NR	431	NR	0	NR	42	NR	9	NR	23	NR
Lo Dico 2020	1993–2017	437	NR	NR	NR	3.2	NR	40.2	NR	22.9	NR	60	NR
Lee 2020	2000–2017	83	575	504	429	NR	NR	81	60	NR	NR	23	23

LM, liver metastases; PO, post-operative; NR, not reported.

TABLE 2 Survival data and follow-up.

	Median PCI		Neoadjuvant therapy (%)		Adjuvant therapy (%)		Median OS		Median DFS		Recurrence rate (%)		HIPEC	CCR	
	LM + PM	PM	LM + PM	PM	LM + PM	PM	LM + PM	PM	LM + PM	PM	LM + PM	PM	LM + PM	LM + PM	PM
Allard 2013	2	NR	83,3	NR	100	NR	42	NR	NR	NR	83	NR	NR	NR	NR
Blackham 2014	N	NR	39	65	62	41	45.7	33.6	17.5	17.3	NR	NR	MMC	95	51.6
Alzahrani 2015	7	12	92	41	92	81	24.4	45.5	8.5	17.7	86	71	MMC/OX	97	93
Randle 2015	NR	NR	100	100	NR	NR	21.2	33.6	6.8	12	64.7	53.3	NR	42.2	45.7
Delhorne 2015	19	9	100	100	11	11	27.6	39.1	6.2	12	89	95	MMC or OX	100	100
Berger 2016	17.5	10	58.2	56.6	NR	NR	45.1	73.5	17.3	13.2	NR	NR	MMC	83.5	81.8
Lorimier 2016	15	10.5	86.2	86.2	90.9	83.3	36.1	25.2	9.5	12.6	NR	NR	MMC or LOHP	86.4	69.4
Navez 2016	10	6	90.5	57.7	52.4	87.5	27.5	59.2	6.7	18.4	81	NR	OX or MMC	100	100
Saxena 2016	NR	NR	NR	NR	NR	NR	32.3	30.5	14	14	NR	NR	NR	78	64.2
Morales Soriano 2017	10.6	9.9	81.3	73.3	NR	NR	36	33	12	12	11.4	NR	OX or MMC	100	100
Downs-Canner 2017	13.7	11.2	97	NR	69	63	13	20.5	9.9	7.6	22.6	NR	MMC	100	100
Mouw 2018	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	60	65.2	MMC/OX	100	82.61
Cloyd 2018	NR	NR	16	8.8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Jeon 2019	13	NR	90.9	NR	95.5	NR	16.7	NR	7.1	NR	81.8	NR	MMC	100	NR
Pinto 2019	9	6	100	88	54.5	36.8	31	65	21	24	66.6	51.3	OX	100	98.6
Horvath 2019	14	NR	78	NR	NR	NR	22	NR	59.5	NR	29.7	NR	Cisplatin/MMC/OX	100	NR
Lo Dico 2020	9.8	NR	79.8	NR	60.5	NR	44.8	NR	17.8	NR	77.9	NR	OX	100	NR
Lee 2020	12.8	12.8	59	44	NR	NR	20	25	NR	NR	NR	NR	NR	NR	NR

PCI, peritoneal cancer index; OS, overall survival; DFS, disease-free survival; HIPEC, hyperthermic intraperitoneal chemotherapy; LM, liver metastases; MMC, mitomicin C; OX, oxaliplatin; LOHP, oxaliplatin.

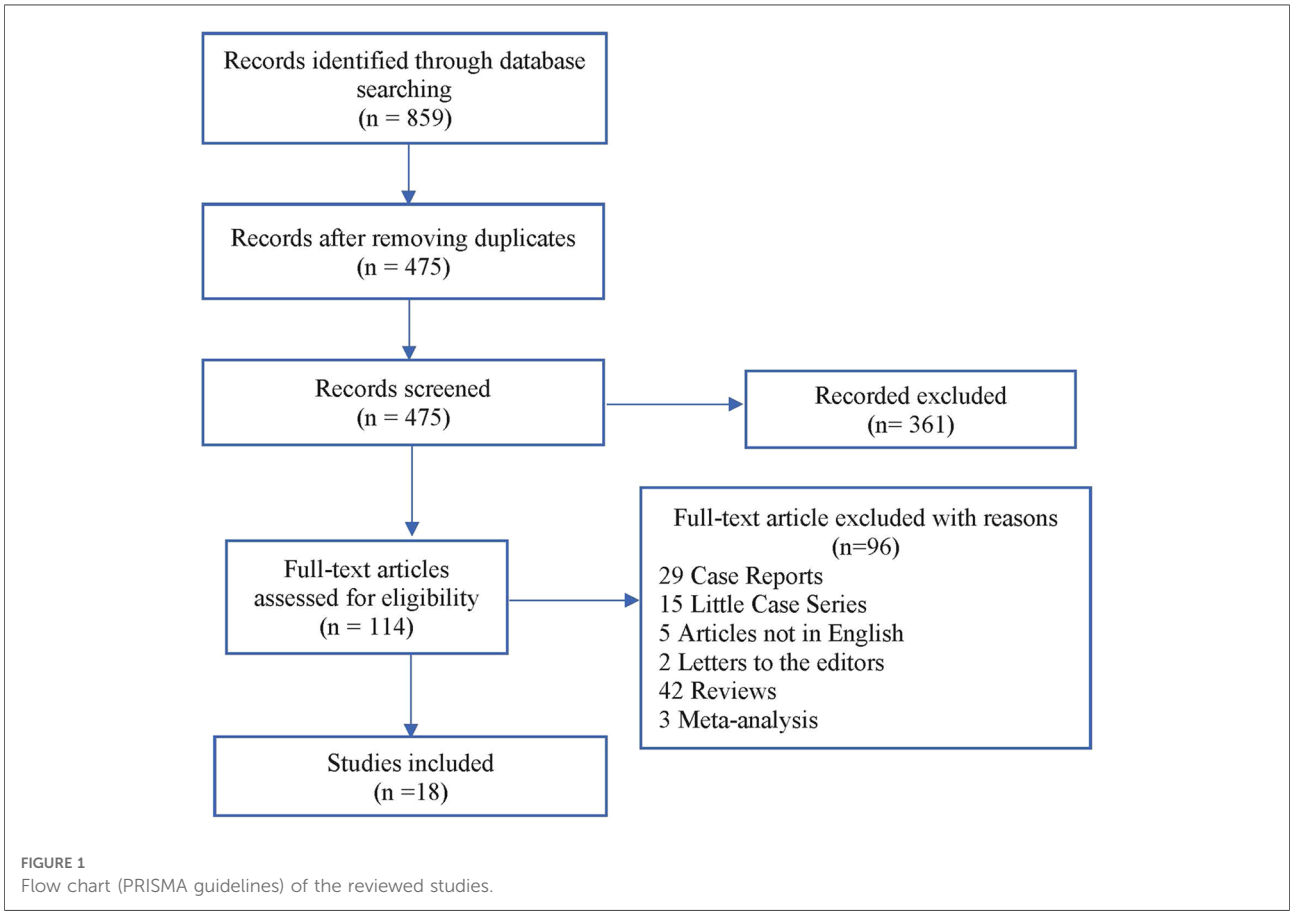

FIGURE 1
Flow chart (PRISMA guidelines) of the reviewed studies.

TABLE 3 Extent of liver disease and types of liver treatments.

Study	Extent of liver disease (No. of lesions)	LM treatment
Allard 2013	1: 391 pts 2:376 pts 3 or more: 397 pts	Resection
Blackham 2014	Mean 1.9	Resection and or RFA
Alzahrani 2015	<3: 25 pts >3: 11 pts	Resection
Randle 2015	Not recorded	NR
Delhorne 2015	Median 1	Resection and or RFA
Berger 2016	Not recorded	Resection
Lorimier 2016	Mean 1.9	Resection and or RFA
Navez 2016	<3	Resection and or RFA
Saxena 2016	1:34 pts 2–3: 30 pts 4 or more: 6	NR
Morales Soriano 2017	Mean 1.2	Resection and/or RFA
Downs-Canner 2017	1:16 pts 2: 7 pts 3 or more: 7	Resection and/or RFA
Mouw 2018	Not recorded	Resection
Cloyd 2018	Not recorded	Resection
Jeon 2019	Mean 3	Resection and/or RFA
Pinto 2019	Not recorded	Resection and/or RFA
Horvath 2019	1–2: 24 pts >2: 4 pts	Resection
Lo Dico 2020	Median: 1	Resection
Lee 2020	Not recorded	Resection

RFA, radiofrequency ablation; LM, liver metastases.

patients treated in a one-step procedure with CRS–HIPEC and liver resection/ablation performed during the same surgical procedure. Only a few studies reported the number of liver lesions. In most cases, liver resection was limited to small resection and RFA. Details of the liver treatment are presented in **Table 3**.

Discussion

This review shows that combined treatment of peritoneal and hepatic metastases for selected patients is feasible, resulting in a mean overall survival of 30 months. Combined CRS–HIPEC and liver resection can be an alternative for patients with limited diseases, leading to an improvement in terms of survival compared to patients who could receive only systemic therapy (42, 44). Despite the feasibility and safety of the combined LR and CRS–HIPEC in metastatic CRC reported from several studies (20, 22, 23, 27, 33, 36, 37, 39, 45), data on the matter show conflicting results, with updated studies and meta-analyses demonstrating evidence to the contrary (5, 21, 32, 34, 46). Razenberg et al. (47) reported a significantly lower median OS in patients with concomitant PC + LM treated with palliative chemotherapy compared to the patients treated with CRS and HIPEC (12.5 vs. 23.1 months). However, there could be a biased selection in interpreting this result as no data regarding the two groups (dissemination of the disease, history prior to treatment, and general conditions of the patients) were available. Lo Dico et al. (39), in their multicenter study, showed that extended surgical management with curative resection plus HIPEC in selected patients with PM + LM is feasible with acceptable morbidity and mortality rates (31% and 4%, respectively) and a better OS. These results are probably associated with a better selection of patients and with the choice of performing the combined procedure only if a minor LR was required. In fact, the study suggested performing a liver-first approach in the case of a two-step procedure and when a minor resection was not feasible. Our primary aim was to review the surgical and survival results of an extensive surgical approach including CRS + HIPEC and LR. Our updated literature review found worse perioperative outcomes (40% vs. 25%) among patients undergoing synchronous LR and CRS–HIPEC compared to the patients undergoing CRS–HIPEC alone. However, no data were available to clarify the risk factors to determine the difference in morbidity. Our results are in line with the findings of Cloyd et al. (35), who described that concomitant LR and CRS/HIPEC were associated with an increased number of postoperative complications and increased readmission compared to patients undergoing CRS/HIPEC alone. However, contradictory results of single-institution studies reporting no difference in postoperative morbidity have been published (3, 23, 27, 33). Lorimier et al. (27), in their monocentric retrospective study, showed better median OS in the PCLM group compared to the PC group only (36 and 25 months, respectively) but without significant statistical difference and with the same OS rate at 5 years (>40%). However, patients in the PCLM group had more hepatic and peritoneal recurrence than those in the PC group. Mortality linked to the surgical procedure was 6.8%, and global morbidity was 38%, without a significant difference between the two groups. In accordance with previous publications, the major postoperative complications occurred more frequently in patients with a PCI >20. Maggiori et al. also described a morbidity of 51% and mortality of 8% for patients undergoing the combined procedure, but almost half of the patients underwent major hepatectomy (48). Delhorme et al. (20) confirmed a significant morbidity rate (44%) when concomitant HIPEC and LS were performed compared with

HIPEC alone (11%). Navez et al. (23) described a morbidity rate of 32% when the combined procedure was performed and a median OS of 27.5 months (25). Major postoperative complications were higher in the study by Down-Canner et al. (34) as well (32% vs. 17%). Furthermore, most studies showed a trend toward a shorter median survival time in the PC + LM group and the median OS reported was 29 months. These adverse clinical outcomes should be considered when selecting patients for such aggressive treatment, given that it may provide minimal benefit in terms of prognosis. Nevertheless, other additional factors should be considered in the selection of the patients. For example, survival is also associated with PCI, which is used to evaluate disease extent in peritoneal surface malignancies. Low PCI and the completeness of cytoreduction (CC-0 or -1) were demonstrably associated with a survival benefit with an inverse linear relationship present between PCI and OS; PCI is in fact recognized as an independent prognostic indicator in patients with metastatic peritoneal disease (49). Maggiori et al. (48) reported a median OS of 40 months in patients with a PCI <12 and ≤2 LM, and a higher PCI and more LM were associated with a lower OS (17). Alzahrani et al. showed that the median survival for patients with PCI ≤ 7 and ≤ 3 LM was longer than those with a PCI > 7 and >3 LM (31). Soriano et al. recommended not to perform completeness of cytoreduction rate (CCR) + HIPEC in patients with a PC index higher than 18 points because of its elevated morbidity and poor survival and limited the simultaneous hepatic and peritoneal resection to patients with three or fewer liver lesions (41). Further research is necessary to determine the prognostic effect of these two variables and the relationship with other variables such as tumor histology, performance status, and lymph node metastasis. In a recent review, Lo Dico et al. reviewed all the available major experiences in the combined treatment of liver and peritoneal metastases from colorectal cancer, and their results suggested that patients with limited peritoneal disease (mean PCI of all the reviewed studies was 9.8) and those who need minor liver resections (defined as fewer than three hepatic segments) are the most likely to have better prognostic outcomes (39).

In the past, the presence of synchronous liver and peritoneal metastatic disease was considered a contraindication to surgical resection, and palliative chemotherapy was considered the only possible option (21). Systemic chemotherapy can improve the prognosis, achieving a median OS of 12–16 months (43, 50). Compared to classical chemotherapy regimens, the FOLFOXIRI regimen has shown better in metastatic CRC patients (51). By performing CRS with hyperthermic intraperitoneal chemotherapy, median OS can be brought up to 31–40 months with complete macroscopic resection, which could be increased even more through accurate patient selection (20). Regarding HIPEC role and toxicity, a recent prospective randomized multicenter phase III French trial (PRODIGE 7) has raised concerns about the benefits of adding HIPEC to CRS on survival in patients who underwent CRS + HIPEC compared to those who underwent CRS only (39). Regarding the results of our review, only a few papers report LR + CRS without HIPEC, and mostly, this happens when a minimal peritoneal disease is discovered accidentally and thus resected (29, 52). In larger experiences, the association of HIPEC to CRS correlates with a survival advantage and only a little increase in morbidity. HIPEC should be avoided only in cases where the expected increase in morbidity could be high (for example, patients with multiple comorbidities, renal, hepatic, or bone marrow failure, representing common contraindications to HIPEC) (39).

Certainly, drugs, regimens, and intraperitoneal (IP) perfusion duration influence results. Currently, two regimens are widely used: open-abdomen oxaliplatin ± irinotecan with concurrent intravenous 5-fluorouracil and folinic acid and open- or close-abdomen mitomycin-C, alone or in combination with other drugs (52). In these specific settings of patients, IP regimens with oxaliplatin seem to provide the best improvement in outcomes. Whether this improvement depends on the use of a specific drug or the different duration of IP perfusion (30 vs. 90 min) remains debatable (53).

However, in the reported experiences considered for this review, no increased toxicity of chemotherapeutic agents has been observed in patients who underwent LR compared to those who did not. Pinto et al. reported a median OS of 31 months for patients who underwent HIPEC + LR and received neoadjuvant chemotherapy, highlighting how the response or nonprogression during neoadjuvant treatment can be beneficial in selecting patients. He also proposed a two-step procedure for patients with bilobar metastases to avoid major hepatic resection during HIPEC, reducing postoperative morbidity and mortality rates (28). In fact, in the presence of hepatic metastases, the resectability rate can be increased by several surgical techniques, such as two-stage hepatectomy or portal vein embolization, even in patients with initially unresectable, multiple secondary diseases. LM may require only minor liver surgery procedures, usually performed at the same time as CRS and HIPEC, or it may require complex liver resection surgery that could be performed by two-step procedures; hence, HM management could be adapted depending on the extension of the metastatic disease and even the need for aggressive liver surgery such as major hepatectomy that could be performed in the simultaneous, delayed, and liver-first approach (14). Commonly, liver surgery is limited to minor resections in most of the experiences because cytoreductive surgery associated with major liver surgery, such as two-stage hepatectomy followed by HIPEC, seems to be correlated to unacceptable morbidity rates in the few papers that considered this approach (28–30). Other major liver procedures such as associating liver partition and portal vein ligation for staged hepatectomy

(ALPPS) are not described in the papers considered for this review. This review shows that combined integrated local treatment of peritoneal and hepatic metastases for selected patients is feasible, although its outcomes remain controversial. The survival rates of these patients suggest an advantage compared with patients who only received systemic chemotherapy. On the other hand, major morbidity rates seem to be worsened by the association of two major surgical procedures like LR and CRS + HIPEC. From this point of view, a key role is played by the extension of hepatic and peritoneal surgical resections that should represent a cornerstone in the preoperative evaluation of these patients, as more aggressive surgical procedures have been demonstrated to link with a higher rate of postoperative complications, as clearly reported by major experiences in the field (40). Aside from the surgical extension, specific organs resection also seems to be linked to the morbidity rate such as rectal resection or organ resections associated with upper quadrant peritonectomy (i.e., resection of the diaphragm, spleen, or pancreas) (33, 36, 54). As operative and patient factors both contribute to morbidity and mortality, additional factors that should be considered are the number of hepatic metastases, liver function tests, low or intermediate PCI scores, types of drugs and perfusion's duration of intraperitoneal chemotherapy, patient's characteristics such as age, performance status, and comorbidities, and tumor characteristics including tumor histology and grading (advanced tumors or signet ring cell histology), neoadjuvant therapy, and response to systemic chemotherapy (RECIST criteria). The incidence of major complications represents one of the most determinant factors limiting the results of this combined approach and the most relevant in worsening prognosis. Another significant factor impacting morbidity and hence prognosis is the number of liver metastases. An attempt to preoperatively estimate the expected survival after the combined procedure has been proposed by Elias et al. by the development of a nomogram including criteria such as the number of liver metastases, PCI, and type of surgery (CRS/HIPEC alone, LR alone, or concomitant LR and CRS/HIPEC) (20, 55). Patient selection and risk stratification may also be carried out by the use of risk scores in which an increased number of factors detected has been associated with decreased OS; factors proposed to assess the risk score are patient's age, primary tumor histology, number of liver lesions (single vs. multiple), and pathways of recurrence (38, 56–58). The median follow-up in our review was 32 months (20–63 months), and recurrence rates were respectively 81% and 71% in the PM + LM group and the PM group regardless of the additional use of neoadjuvant or adjuvant therapy. The incidence of postoperative mortality was 2.6% in the PM + LM group and 2.8% in the PM group. No studies showed a significant difference in postoperative mortality between the two groups. To date, neither patient selection nor patient management criteria have been standardized for combined treatment; considering the aforementioned survival rates and morbidity and mortality data, extensive surgical approaches including CRS and hepatic LR should not be defined as safe and risk-free, as some studies previously reported. Nevertheless, accurate patient selection and an individualized preoperative decision-making process should be considered fundamental steps in the initial management of patients selected for combined treatment (59, 60).

Conclusion

The role of combined surgical strategy (CRS + HIPEC and LR) in patients with synchronous liver and peritoneal metastases from colorectal cancer remains controversial. Survival rates and morbidity and mortality seem not in favor of this option. A strict and homogeneous selection of patients and a "tailored" surgical strategy (one-step vs. two-step liver surgery, extent of cytoreduction, and increasing use of laparoscopic techniques) (61–64) are mandatory to obtain the best results without increasing morbidity, and it would perhaps help improve the misleading results in this subgroup of patients with limited curative options.

Core statements

The role of combined surgical strategy (cytoreductive surgery with HIPEC and liver resection) in patients with synchronous peritoneal and liver metastases from colorectal cancer is promising but controversial.

Advantages in survival rates from the combined procedure seem encouraging, but high morbidity rates still limit the widespread of this approach.

Homogeneous patient selection criteria and preoperative decision-making processes are still lacking, even if some attempts in recent years have been made to standardize procedures and indications.

More efforts are needed to clarify which patients could really benefit from this complex combined strategy and which risk rates could be considered acceptable.

Author contributions

SDC, GC, SS, and LI provided substantial contributions to the conception and design of the work. VU, MF, PI, and FLR contributed to the acquisition, analysis, and interpretation of data for the work. LS, AF, and SD drafted the work. EF and PR revised it critically for important intellectual content. All authors provide their approval for publication of the content and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. 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.

The handling Editor GG declared a shared parent affiliation with the authors, GC, FLR, PI, LI, AF, and EF, at the time of review.

Publisher's note

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Transanal hemorrhoidal dearterialization (THD) for hemorrhoidal disease: An Italian single-institution 5-year experience analysis and updated literature review

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Background: Hemorrhoidal disease is a highly prevalent, chronic disorder that usually compromise patients' quality of life. Despite recent advances in pharmacologic and surgical therapeutic options, a clear treatment "gold standard" is lacking. Our aim is to analyze the outcomes following Transanal Hemorrhoidal Dearterialization (THD) procedure.
Methods: Patients who failed conservative treatment and underwent THD Doppler between 2017 and 2021 were enrolled. Follow-up interviews (consisting of clinical examination, Visual Analog Scale for pain—VAS, Vaizey incontinence score, Hemorrhoid Severity Score) were administered 1 week, 2 weeks, 1 month and 6 months after surgery.
Results: Forty-seven out of 75 patients were male, and the mean age was 50 (± 17.9) years. Hemorrhoids were classified as Goligher's degree II in 25 cases, III in 40 and IV, simple irreducible without ischemic changes, in 10. The mean operative time was 35 (28–60) minutes, and most procedures were performed with epidural anesthesia (80%). No intraoperative complications occurred, and 73 patients (97.3%) were discharged within post-operative day 1. Early post-operative pain and bleeding occurred in 37.3% and 8% of patients, respectively. No patients experienced anal incontinence and severe symptoms at 6 months after surgery. The overall success rate was 97.3%.
Conclusions: THD is safe and effective in hemorrhoidal disease at degree II if bleeding, III, and IV without ischemic changes, both as a first intervention and on recurrence. Physician and patient need to understand each other's expectations, weight the risks and benefits, and customize the treatment.

KEYWORDS

transanal hemorrhoidal dearterialization, hemorrhoids, recurrence, quality of life, outcomes

Introduction

Hemorrhoidal disease (HD) is a prevalent and debated proctologic condition (1). According to the severity of the disease (2), different treatment options, ranging from dietary-lifestyle measures to surgical treatment, have been proposed (3–5). However, the commonly adopted Goligher Classification (2) does not comprehensively consider the etiopathogenesis, the symptoms of the disease, their influence on the quality of life (QoL) (6), and need to be supplemented with clinical characteristics.

In the last few years, non-excisional surgical treatments have gained increasing popularity because they allowed to reduce most patients' discomforts, such as post-operative pain and recovery of working independence (7), with the advantage of keeping in place a physiologically useful tissue both for the defecation and continence. The Transanal Hemorrhoidal Dearterialization (THD), firstly described in 1995 (8), represents a valid choice in patients with II to IV degree HD (9), despite possible recurrences, whose risk is higher the greater the severity of the disease (10, 11).

Several variants of THD procedure have been described in recent years: doppler-guided hemorrhoidal artery ligation (DGHAL) (12), targeted mucopexy (13) and Anolift (14). The DGHAL allows the surgeon to identify and ligate the terminal branches of the superior rectal artery that feed the hemorrhoidal plexus. Frequently, the surgical indications are also expanded to the prolapses of hemorrhoidal tissue by carrying out standard mucopexy (12, 13) or recent Anolift procedure, conceived to overcome the inadequacy of the needle shape (14). However, no technical variant has been shown to be superior to the other while the surgeon's experience can improve the outcomes (5, 10, 15).

In 2018, the American Society of Colon and Rectal Surgeons (ASCRS) clinical practice guidelines listed DGHAL with mucopexy among surgical treatments for hemorrhoids (16). A consensus statement from the Italian Society of Colorectal Surgery (SICCR) (9, 17), aiming at establishing an evidence-based approach to HD, described THD and DGHAL techniques as associated with lower postoperative pain and faster recovery than excisional hemorrhoidectomy (i.e., Milligan-Morgan and Ferguson procedures, or radiofrequency hemorrhoidectomy), but carries higher recurrence rates [*Level of evidence 1, Grade of recommendation A* (18)]. The current recurrence rate ranged between 3% and 20%, with 4.1–17.8% of patients required reoperation (13).

The aim of the present observational study is to show the outcomes of the last 75 THDs performed in our center. We provide a critical review of the literature, giving evidence-based recommendations to improve patients' postoperative QoL.

Materials and methods

Study design

Between January 2017 and December 2021, a total of 75 patients underwent THD for HD in our center. All procedures were performed by the same colorectal surgeon (LV) and recorded in a prospectively maintained database. Demographic data, the type and severity of symptoms, anal continence status and procedural details including perioperative (comorbidities) and intraoperative data, length of hospital stay, readmission rate, and other short-term outcomes were analyzed.

The results of this study were reported as established by the Strengthening the reporting of observational studies in epidemiology (STROBE) statement for cohort studies (19).

The severity of disease was evaluated with a complete proctological examination, including both digital rectal examination and anoscopy, and graded according to the Goligher Classification (2).

Inclusion criteria were: (i) patients aged more than 18 years, (ii) hemorrhoids classified as degree II if bleeding, III, or IV if simple irreducible without ischemic changes, (iii) follow-up of at least 6 months (June 2022), (iv) failure to conservative or anal sparing treatments. Colonoscopy was performed to rule out inflammatory bowel disease, undiagnosed anal intraepithelial neoplasia, anal cancer, or other colorectal disease in patients with suspected symptoms or indications for screening (20, 21).

Exclusion criteria were: (i) fixed, fibrotic piles, degree IV hemorrhoids at advanced stage (irreducible hemorrhoids with ischemic changes and/or thrombosed), (ii) anorectal sepsis, (iii) hemorrhoids responsive to conservative treatments, (iv) previous anorectal surgery and/or anorectal cancer, (v) concomitant rectocele.

After enrolment (T0), all patients were outpatient-evaluated at 1 week (T1), 2 weeks (T2) and 1 month (T3) after surgery. Then, the follow-up was carried out with a telephone interview 6 months after the procedure (T4) (22, 23).

Subjective evaluations were obtained with the visual analog scale for pain (VAS) scores: 0 if "no pain" to 10 points if "worst imaginable pain". All post-operative complications were graded according to Clavien–Dindo Classification (CDC) (24). Recurrences were defined as a re-bleeding in case of degree II HD or re-bleeding with prolapse in case of degree III-IV HD, recorded during follow-up outpatient visits. Rectal tenesmus was defined as the feeling of being unable to empty the large bowel, even if there is no remaining stool to expel. Anal continence was evaluated at post-operative 1 week, 1 month and 6 months using Vaizey incontinence score (23). Vaizey score, based on the Wexner score which cross-tabulates frequencies and different anal incontinence presentations,

adds the use of constipating medication and the presence of fecal urgency, and ranged from 0 to 24. Hemorrhoid Severity Score (HSS), ranging from 4 to 20, was used both at the baseline, to quantify symptoms severity, and in post-treatment patient follow-up, to grade the response to treatment (22). The total HSS is obtained by the sum of the "PNR-Bleed" (more details in Appendix).

The study was conducted in accordance with the Declaration of Helsinki (1996) and International Conference on Harmonization-Good Clinical Practice guidelines (25). Internal Ethical Committee approved the study. Written informed consent was obtained from all the patients included in the study.

Surgical technique

The patient underwent general or spinal anesthesia. The procedure was performed (12) using the THD Doppler Kit (THD Slide® S.p.A., Correggio., Italy) (12). A prophylactic dose of cephazolin antibiotic was administered only pre-operatively. The patient was positioned in a lithotomy position. The surgeon precisely located terminal branches of the rectal arterial vessels, using Doppler ultrasonography (DGHAL), and ligated them, reducing excessive blood flow to hemorrhoid cushions. Thus, the surgeon repeated the procedure moving clockwise. If hemorrhoids were prolapsed outside the anus, the mucopexy aimed to reposition the hemorrhoidal mucosa in its anatomical position. A recommended oral dose of ketorolac tromethamine of 10 mg every 8 h, not exceeding 30 mg per day, was administered during the first 24 h after surgery. Moreover, patients were encouraged to prevent hard stool by taking stool softeners as well as a high-fiber intake diet during the first 30 post-operative days. Flebotonics were associated during the same latter period.

Statistical analysis

Descriptive statistics were reported as means ± Standard Deviation (SD) when normally distributed, and as median and interquartile range (IQR) if not normally distributed. Chi-squared test was used; a p-value < 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS version 26.0 software package (IBM Corp., Chicago, IL, USA).

Results

Patients

During the period of January 2017 and December 2021, a total of 120 patients underwent a non-conservative treatment for hemorrhoids. Overall, the Milligan-Morgan hemorrhoidectomy was performed in 33 patients (24 with degree III, 7 with degree IV non-circumferential thrombosed, 2 with circumferential thrombosed hemorrhoids), the Ferguson procedures in 8 patients with degree IV with ischemic changes, and the stapled hemorrhoidectomy in 4 patients with concomitant rectocele.

The present study included 75 (62.5%) non-consecutive patients underwent THD for HD degree II ($n = 25$, 33.3%), III ($n = 40$, 53.4%) and IV ($n = 10$, 13.3%). Most were males (62.7%), with a mean age of 50 years. Preoperative median HSS was 12 (7–16). The demographic and clinicopathology features were summarized in **Table 1**.

In-hospital outcomes (T0)

The median time for the actual surgical treatment was 35 min. No intraoperative complications occurred (**Table 2**). All procedures were carried out in Day Surgery regimen with a median length-of-stay of 1 day: particularly, 73 patients (97.3%) were discharged in post-operative day 1, and 2 patients (2.7%) in day 2.

Urinary retention happened in about 21.3% of cases limited to post-operative day 1 (16 patients). Only 1 patient (1.3%) experienced persistent bleeding soon after the procedure.

Post-operative outcomes (T1–T4)

Post-operative outcomes were classified in **Table 3**. Median length of registered follow-up in our cohort was 9 (6–15) months. Twenty-four patients (32%) referred at least one

TABLE 1 Patients' characteristics. SD, standard deviation; HSS, hemorrhoid severity score; IQR, interquartile range.

Patients (n)	75
Female/male (n, %)	28 (37.3%)/47 (62.7%)
Age (±SD)	50 ± 17,92
Haemorrhoidal degree (n)	II = 25 (33.3%)
	III = 40 (53.4%)
	IV = 10 (13.3%)
HSS (IQR)	12 (7–16)

TABLE 2 Procedural results (T0), number (percentage). IQR, interquartile range.

Epidural anesthesia/General anesthesia (n, %)	60 (80%)/15 (20%)
Median operative time (min) (IQR)	35 (28–60)
Hospital stay (days) (IQR)	1 (0–2)

TABLE 3 Postoperative complications (T1–T4): 1 week (T1), 2 weeks (T2), 1 month (T3), 6 months (T4) after surgery. VAS, visual analog scale; HSS, hemorrhoid severity score; IQR, interquartile range.

	T1	T2	T3	T4
Soiling (*n*, %)	24 (32%)	10 (13.3%)	4 (5.3%)	4 (5.3%)
Bleeding (*n*, %)	6 (8%)	1 (1.3%)	0	0
Itching (*n*, %)	37 (44%)	21 (28%)	13 (17.3%)	0
Tenesmus (*n*, %)	22 (29.3%)	19 (25.3%)	12 (16%)	6 (8%)
Pain (*n*, %), VAS (IQR)	28 (37.3%), 6 (0–8)	9 (12%), 4 (0–6)	1 (1.3%), 5	0
Recurrence (*n*, %)	0	0	0	2 (2.7%)*
Vaizey incontinence score (IQR)	5 (0–17)	–	3 (0–8)	0 (0–5)
HSS (IQR)	4 (4–5)	–	4	4

*Goligher's degree III.

episode of soiling, 6 (8%) occasionally bleeding, and 37 (44%) itching during the first post-operative week (T1). There were 22 (29.3%) patients with rectal tenesmus at T1; 6 patients (8%) experienced tenesmus for a longer time (T4), including 4 with degree III and 2 with degree IV ($p = 0.133$). Overall, 28 patients felt pain at T1 with a median VAS of 6 (0–8); 96.4% (27/28) of patients had no more pain at T3. Daily routines were resumed immediately by all our patients and each of them returned to their usual professional activity within one week, with no impairment. Complete remission of symptoms occurred in 65/75 (86.7%) patients within T4.

Median Vaizey incontinence score and HSS were showed in **Table 3**. Five patients (6.7%) experienced faecal urgency, alteration in lifestyle and/or the need to take antidiarrheal medications in the first post-operative week (T1). No patients referred anal incontinence at 6 months (T4) after surgery. No other kind of severe complications (CDC > 2) occurred.

Recurrences were registered in 2 patients with first HD degree III (2.7%, $p = 0.574$), both experiencing re-bleeding and prolapse 6 months after surgical procedure (T4). A second THD procedure was performed.

Discussion

Hemorrhoidal disease affects 50% of the over-50 people worldwide (1). Etiology is complex and not fully understood. In many cases, hemorrhoids are associated with conditions that increase pressure in the hemorrhoidal venous plexus, such as straining during bowel movements secondary to constipation. Other associations include obesity, pregnancy, chronic diarrhea, anal intercourse, cirrhosis with ascites, pelvic floor dysfunction, and a low-fiber diet (26).

The increase in prevalence in developed countries led to the need to organize fast-track procedures, with short operative times, very early discharge, and rapid return to work activities (27). Anyway, when conservative treatment fails, consisting of a diet rich in fiber, lactulose, and flavonoid mixture (diosmin, troxerutin, rutin, hesperidin, quercetin) (28), surgery is a feasible and suitable option, optimally improving the patient's QoL (9). Debate continues about the best surgical technique of management of mild-severe HD (12–14). Recent literature demonstrates that when compared to conventional hemorrhoidectomy, modern non-invasive surgical procedures for internal hemorrhoids, such as THD, reduce postoperative pain and facilitate a quicker discharge (7, 29). Indeed, although the "true" etiopathogenesis is still debated (mucosal prolapse (30) or "vascular hypothesis"), the THD technique would treat both causes. To date, the use of Doppler transducer is controversial (31). Nonetheless, while effective DGHAL reduces vascular flow to the hemorrhoid pads, mucopexy resolves the prolapse, resulting in THD being safe and effective in both primary and recurrent hemorrhoids (27).

The rationale of the potential clinical benefit of THD in HD is based upon three main cornerstones:

1. Therapeutic alternative in non-eligible patients. After rubber band ligation of hemorrhoids, secondary bleeding normally occurs in 10 to 14 days and patients taking anti-platelet and/or anticoagulant medication may have a higher risk, with some reports of massive life-threatening hemorrhage (32). However, Hite et al. reported that the risk of bleeding complication does not appear to be increased in patients taking clopidogrel (33). In 2016, Atallah et al reported similar rate of postoperative morbidity and hemorrhage between anticoagulated patients and who were not taking anticoagulant therapy (34), proving the safety of THD.
2. Low incidence of post-operative pain as well as other complications, and potential improvement in QoL. It is well known that THD technique is effective and safe for all degrees of hemorrhoids because of minor postoperative pain and low post-operative complication rate (7, 9, 35–37). Pain following THD was referred by up to 35% of operated patients. Yet, in most series, the incidence of postoperative pain was less than 10% (35). Postoperative bleeding was described up to 13% of patients and, in rare instances, required hospital admission and reintervention. A 2015 large meta-analysis (including 98 trials, 7827 participants, 11 surgical treatments for degree III- IV HD) suggested that THD had significantly less postoperative bleeding than other procedures and resulted in significantly fewer emergency reoperations (7). When compared with stapled hemorrhoidectomy, THD has similar early postoperative complications, but lower

postoperative pain and, globally, greater patient satisfaction (38–40). Other postoperative events include tenesmus, which is more frequent in patients who underwent mucopexy, hemorrhoidal thrombosis (8.6%) and anal fissure (0.6–1.5%). Transient fecal urgency has been also reported (9, 13). Additionally, patients returned to normal daily activities (7) and work earlier compared to patients who underwent stapled hemorrhoidectomy (36). Finally, pain resolution and no postoperative constipation at 1–6 months after surgery result in high satisfaction and improved QoL after surgery (41). Despite the QoL should be a main endpoint (42), there are not hemorrhoid specific QoL score. A study using SF-36 score showed that, in addition to a reduction of symptoms (bleeding, painful defecation, anal pain, constipation and tenesmus), QoL was improved 1-month after THD: patients had reduced limitations in usual daily and social activities through increased vitality and energy, reduced psychologic distress and well-being, and decreased physical and emotional problems (43). Ain et al. described that only 12.5% of patients were not satisfied with the procedure, most of them affected by recurrence. Interestingly, there was no correlation with gender, age, constipation, Goligher Classification or other symptoms (44).

3. Reduction of recurrence and reoperation. Although THD is a non-invasive and safe procedure with lower rate of postoperative bleeding and fewer emergency reoperations compared with other procedures (7), many trials described a significant recurrence rate compared to stapled hemorrhoidectomy (38, 40). In a 2018 meta-analysis on 1,077 patients, stapled hemorrhoidectomy and THD showed comparable postoperative morbidity, while the former seemed to have lower recurrence rate (38). Similarly, a recent study on 554 patients described persistent or recurrent HD in 13.2% and 6.9% patients after THD and stapled hemorrhoidectomy, respectively (40). Negative prognostic factors were younger age, degree IV disease, and high artery ligation (10).

Overall, the 2020 Practice Parameters for Management of Hemorrhoids (45) recommend THD in high- degree (II and III) hemorrhoids (2) and/or after medical therapy failure. No unanimous agreement has been reached regarding the efficacy and safety in degree IV hemorrhoids. Sobrado et al. emphasized that, due to its high rate of prolapse and bleeding, THD is not an effective option for the treatment of degree IV hemorrhoids (46). Genova et al. showed that Milligan-Morgan hemorrhoidectomy had similar clinical outcomes in degree III HD and better results in degree IV HD when compared with THD (47). Moreover, Ratto and Giordano suggested THD with mucopexy when symptoms are mostly transient, occasional, or limited in severity (48). A review of 28 prospective studies, including 2,904 patients with grade I to IV hemorrhoids, described a recurrence rate of 3–60%, with the highest for grade IV hemorrhoids. Therefore, only hemorrhoids classified as degree IV at initial stage were included in our series, while fixed, fibrotic piles, necrotic advanced hemorrhoids were treated first with excisional hemorrhoidectomy (Milligan-Morgan and Ferguson procedures). Despite the limited number of patients ($n = 10$, 13.3%), no one complained of disease recurrence (46–48).

In our series, we focused on four different points in time post-operatively: at 1 week = T1, at 2 weeks = T2, at 1 month = T3, and at 6 months = T4. We evaluated the occurrence of symptoms such as soiling, bleeding, itching, tenesmus, and pain as well as disease recurrences. Moreover, we measured the Vaizey incontinence score and the HSS at T1, T3 and T4. Overall, we found out that our patients moderately experienced bleeding (8% of patients at T1 and 1.3% at T2) and pain (37.3% of patients at T1% and 12% at T2), which decreased dramatically in the following controls. At T4 most of the symptoms were completely gone except for some patients who still experienced soiling (5.3%) and tenesmus (8%), thus documenting the absence of severe complications, such as bleeding and pain at T4. The novel Anolift technique may allow for a more even distribution of the tension along the suture lines and reduce the risks of creating a pocket in the rectal lumen, resulting in a lower rate of persistent rectal tenesmus (up to 1 in 10 patients at 6 months after surgery). Moreover, median Vaizey incontinence score decreased until reaching the minimum score at T4. Post-operative HSS highlights the efficacy of THD, which definitively results in improved QoL of patients. Lastly, recurrence rate was surprisingly low with only 2 cases (2.7%), probably as a result of a limited postoperative follow-up.

Interestingly, in our previous experience, neither 30-days severe postoperative complications nor postoperative readmission were registered; tenesmus occurred in 75% of patients underwent THD for degree II and III, which, however, solved spontaneously on the first postoperative day (27). Even though other studies had much higher number of patients to work on, the results of our study were somewhat similar to those of Ratto et al. showed even better outcomes in bleeding and pain 1 month after surgery and in recurrence rate (10). In the present study, THD has a low rate of symptom relapse and recurrence even in stage IV disease. We argue that high recurrence rate following THD, as reported in previous literature, could be influenced by technical experience (49).

Nowadays, the treatment of HD constitutes a narrow-minded approach that doesn't account for patients' needs, expectations and personal characteristics often leading to a blurry definition for success of surgical procedures in the long term and not compelling for an approach tailored to every single patient (50–52). The surgeon's experience seems to be the only key factor in the decision on surgical technique.

Consequently, it remains unclear how much the surgeon's skill affects the outcome of patients (8).

The THD is a safe and effective atraumatic technique associated, not influencing sphincter complex or anal function, with the best short-term clinical and surgical outcomes (rapid symptoms relief, lesser surgical site infection (53) and postoperative complications). Fast postoperative recovery, early discharge, and quickly return to normal daily activities and works substantially improves patient's QoL (54).

The main limitation of our observational study is a small cohort of enrolled patients, even given that all procedures were performed by the same expert surgeon, and a limited follow-up. Despite its exploratory nature, our study offers some insight into the "real" clinical practice. Further prospective studies are necessary to implement the paucity of evidence still available, investigating, on one hand, long-term outcomes, QoL and patients' satisfaction, and, on the other hand, predictive factors of recurrence.

Conclusion

THD is a safe and effective procedure for selected patients with hemorrhoids of every degree, with no significant differences in the rates of post-operative complications or recurrences, and improved patient's QoL. We recommend THD as a valid therapeutic option for Goligher's degree II and III hemorrhoids.

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 Area Vasta Sud Est (C.E.A.V.S.E.) Sezione di Siena Policlinico Le Scotte. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LV and GGa: conception and design. LC and LM: statistical analysis. GEP and OCS: analysis and interpretation of data. GGr, EB, GEP: acquisition of data. GGa, GGr and LC: drafting of the manuscript. LV and LM: critical revision of the manuscript. DM and FR: supervision. 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

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Appendix

The HSS is the total score obtained by the sum of the numerical grades of all four characteristics of hemorrhoids in "PNR-Bleed" classification:

- Degree of hemorrhoidal Prolapse (P): 1 point for no hemorrhoidal prolapse (Goligher's degree I), 2 prolapse upon straining that reduces spontaneously (Goligher's degree II), 3 prolapse upon straining that needs manual reduction (Goligher's degree III), 4 prolapsed and irreducible hemorrhoids but without ischemic changes (Goligher's degree IV), 5 prolapsed and irreducible hemorrhoids with ischemic (gangrenous) changes (Goligher's degree IV).
- Number of hemorrhoidal columns involved (*N*): 1 point for one column, 2 two, 3 three, 4 four, 5 circumferential (presence of secondary hemorrhoids along with the involvement of all primary hemorrhoids).
- Relation of the hemorrhoidal tissue to dentate line (R): 1 point for nil (normal anal cushions), 2 external hemorrhoids, 3 internal hemorrhoids, 4 interno-external hemorrhoids, 5 thrombosed external hemorrhoids.
- Bleeding: 1 point for nil, 2 mild—occasional episodes (during defecation), 3 moderate—frequent episodes (during defecation), 4 severe—persistent bleeding even without defecation with fall in Hb level (<10 gm/dl), requiring hematinics, 5 very severe—bleeding in the form of jets and splashes with severe fall in Hb level (<7 gm/dl), requiring blood transfusion.

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Preoperative tumor marking with indocyanine green prior of robotic colorectal resections

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This prospective case-series study aimed to assess the usefulness of preoperative colonoscopic marking of colorectal tumors using Indocyanine Green (ICG) fluorescence in patients that underwent robotic surgical colorectal resections. Consecutive patients that were eligible for colorectal resection with intent to cure in a single hospital (Athens Medical Center), from February 2022 to June 2022, were included. ICG solution was injected into the submucosal layer at 2 opposite sites (180 degrees apart) distal to the tumor, without submucosal elevation. Identification of the tumor marking was then performed after switching to near-infrared (NIR) fluorescence mode. During the robotic procedure, qualitative evaluation of fluorescence was performed by the surgical team (primary surgeon, first assistant, second assistant, research fellow). All 10 patients underwent robotic surgical approach and operations included right-sided colectomy ($n = 1$), left-sided colectomy ($n = 6$) and low anterior resection ($n = 3$). Visualisation of this dye with near-infrared light was very clear with bright intensity in all patients when the marking was performed one day prior of surgery. Preoperative tumor marking with ICG was identified intraoperatively in all cases and the techinque was easily reproducible.

KEYWORDS
colorectal surgery, indocyanine green, near-infrared fluorescence imaging system, fluorescent guided surgery, robotic surgery

Introduction

Minimally invasive robotic surgery for patients with colorectal cancer is increasingly being preferred over conventional surgery due to its comparable survival and recurrence rates along with improved visualisation and dexterity with which complex dissection can be carried out (1, 2). However, intraoperative detection of neoplasms has been challenging due to lack of tactile sensations (3). A variety of techniques have been used to detect colorectal tumors including barium enema, colonoscopic metallic

clipping, computed tomography colonoscopy, intraoperative colonoscopy as well as preoperative colonoscopy. Localization and marking of tumors preoperatively by endoscopists is of crucial significance and offers surgeons anatomical guidance especially in complex cases. Detection of colorectal lesions with endoscopic tattooing has been reported since 1975 (4).

India ink has been traditionally used to mark tumors *via* colonoscopic tattooing due to its effectiveness and accuracy in detection of small lesions. However, reports of side effects such as inflammation, local peritonitis, abscesses and adhesions have been recognized. Furthermore, a major disadvantage that has been observed is spillage of India Ink out of serosa. This agent cannot be eliminated and stays permanently in the tissues, potentially altering the surgical anatomical plane (5, 6).

Indocyanine Green (ICG) has been described as a potential agent for preoperative colonoscopic marking in animal models since 1989 (5–7). This fluorophore has several applications in colorectal surgery, such as assessment of bowel perfusion (8). ICG fluorescence imaging as tumor site marking in near-infrared (NIR) fluorescence has been reported as practical due to its lower surgical view interference by being less visible in white light (9–12). It is also safe with fewer and more tolerable side effects being observed in contrast to India Ink, although more comparative studies are needed. However, there are some facts that have not yet been predetermined regarding preoperative ICG tumor marking. The timing between local ICG injection and surgery for maximal visualization has not yet been defined. Moreover, several methods have been reported regarding the dosage and the technique used by endoscopists in order to inject this agent efficiently. In this study, we aimed to evaluate the usefulness of preoperative colonoscopic marking of colorectal tumors using ICG in robotic colorectal resections for cancer in a single hospital carried out by a single surgical team (Athens Medical Center).

Methods

Study design

From February 2022 to June 2022, consecutive patients from Athens Medical Center eligible for colorectal resection were enrolled in this prospective case-series study. Included patients were required to be at least 18 years old with histopathologically confirmed colorectal adenocarcinoma. They underwent preoperative colonoscopic tumor marking with ICG less than 24 h prior of the operation. Patient demographics were collected and included gender, age, body mass index, American Society of Anesthesiologist class and preoperative stage (**Table 1**). Patients who had previously experienced an adverse reaction to ICG and/or iodine, cases with obstructed colon requiring emergent operation, metastatic disease as well as pregnant women were excluded.

TABLE 1 Patient characteristics.

N	10
Sex ratio (Males:Females)	6:4
Age (years)[a]	67 (56–80)
Body Mass Index (kg/m²)[a]	25.3 (20.1–31.7)
Smoking: Yes, No	7, 3
ASA Classification	I:3
	II: 5
	III: 2
	IV: 0
Preoperative tumour staging	
T1	1 (10)
T2	2 (20)
T3	7 (70)
T4	0 (0)

ASA, American Society of Anesthesiologists.
Values in parentheses are percentages.
[a]Values are median (range).

Ethical statements

This study was approved by Athens Medical Center Institutional Review Board. Informed consent was obtained from all participants after comprehension and agreement with the study's protocol.

Study procedure

Under sterile conditions, solution of ICG was prepared by dissolving 25 mg of ICG (Verdye™) in 10 ml of sterile water (2.5 mg/ml solution). Using a 25-gauge needle, 0,1 ml of ICG solution was injected into the submucosal layer at 2 opposite sites (180 degrees apart) distal to the tumor. We did not use submucosal elevation with normal saline. The minimum volume that could be technically administered without difficulties was selected as the local injection dosage.

During the preoperative marking approach, patients were positioned in left lateral position and were marked by an expert gastroenterologist (D.K.). During surgery, entry to the peritoneum was approached using Hasson technique, with a 8-mm trocar to house the endoscope. Pneumoperitoneum was induced and maintained at 12 mm Hg. After the placement of trocars for working and assist ports, the robotic 30° camera

was inserted and the peritoneal cavity was explored using standard, high-definition, white light imaging. Identification of the tumor marking was then approached after switching to NIR fluorescence mode (Figures 1, 2).

Outcomes

Qualitative evaluation of fluorescence was performed by the surgical team (main surgeon, main assistant, second assistant, research fellow). Intensity of fluorescence of the marked colonic site was subjectively evaluated due to the lack of any objective technique for quantification.

Patient information, pre-operative radiological staging, type of operation, histological lymph node yields, and histological staging were also documented.

Results

During the study period, February 2022 to June 2022, ICG-enhanced fluorescence was used as tumor marking in 10 patients (4 females). Patient and tumor characteristics are presented in Table 1. All patients underwent robotic surgical approach and operations were categorised as right colectomy ($n = 1$), left-sided colectomy ($n = 6$) and low anterior resection ($n = 3$) (Table 2).

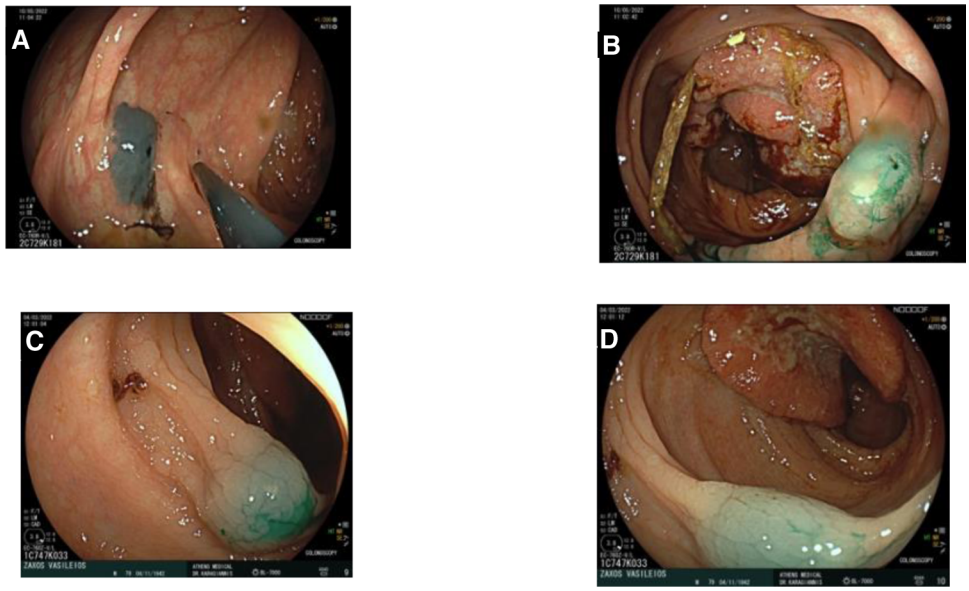

FIGURE 1
Endoscopic tattooing using indocyanine green in two patients. (A) Patient 1: Injection distally of tumor, one side. (B) Patient 1: Injection distally of tumor, other side. (C) Patient 2: Injection distally of tumor. (D) Patient 2: Injection distally of tumor.

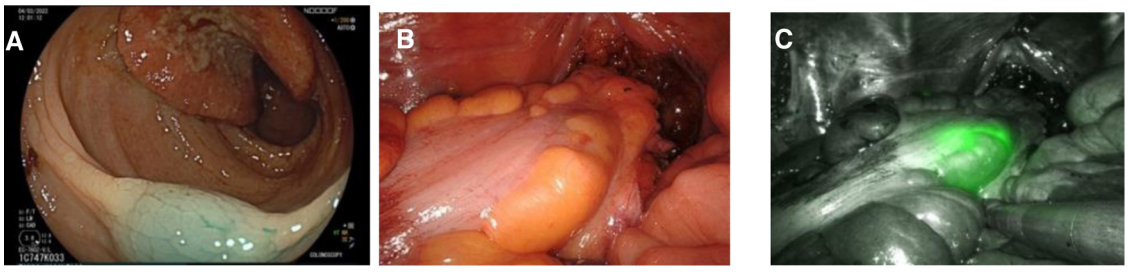

FIGURE 2
Three images of the same patient marked with indocyanine green. (A) Endoscopic view of marked tissue with Indocyanine Green. (B) Intraoperative view of rectosigmoid junction during robotic surgery under white light. (C) Intraoperative view of rectosigmoid junction during robotic surgery under Near-Infrared visualization mode.

TABLE 2 Operation type.

Right-sided Colectomy	1 (10)
Left-sided Colectomy	6 (60)
Low Anterior Resection	3 (30)

Values in parentheses are percentages.

All patients were marked solely with ICG. In all patients visualization of fluorescent tissues was adequate with bright intensity and clear separation of marked and non-marked sites (**Table 3**). Median time for tumor identification under NIR fluorescent mode was 2 min. All tumors were entirely removed, with negative resection margins. There were no complications attributed to the ICG as well as neither intraoperative nor postoperative adverse events or conversion to open surgery (**Tables 4**, **5**).

Discussion

During minimally invasive surgery, identifying lesions by palpation is impossible due to the fact that tactile feedback can not be achieved. The surgeon must rely on visual evaluation in combination with preoperative imaging in order to be guided for proper surgical resection. A variety of techniques have been described for detection of colorectal tumors including preoperative barium enema, CT scans, CT colonography, proctoscopy with stitch as well as colonoscopy with metallic clipping or tattoo (13–15). Barium enemas are ineffective in visualizing small tumours (15, 16). Metallic clip use is insecure due to occasional low visibility as well as migration to other tissues (14). Narihiro et al. observed the safety and effectiveness of near-infrared fluorescent clips and reported a detection rate 94.1% without adverse effects related to clip marking (17). Intraoperative colonoscopy can be used to identify GI lesions, however this extends the overall duration of the operation and can generate intestinal distention, which might limit the surgeon's surgical field (14, 18). Preoperative colonoscopy with simultaneous tumor marking using a dye may be necessary to precisely determine the level of the tumor and perform the appropriate excision. An alternative approach has also been described by using patients autologous blood instead of a dye (19–21). Kim et al. used 6–12 ml of autologous blood for endoscopic tattooing and reported a visualization rate of 92.2% with three patients (5.9%) experiencing endoscopic adverse effects related to the technique (19).

TABLE 3 Intraoperative ICG details.

- Identifiable Tumour: Yes	10 (100)
- Tumor marking intensity: Very Bright	10 (100)
- Timing for Tumour Identification (min)[a]	2 (1.5–5)
- Spillage of ICG: No (%)	10 (100)
- Adverse Events: No	10 (100)

ICG, indocyanine green.
Values in parentheses are percentages.
[a]Values are median (range).

TABLE 4 Perioperative clinical results.

Operation time (min)[a]	180 (120–350)
Estimated blood loss (ml)[a]	50 (30–100)
Complications: Clavien Dindo Classification	I: 3
	II: 1
	III: 0
	IV: 0
Hospital Stay (days)[a]	5 (4–8)

Values in parentheses are percentages.
[a]Values are median (range).

Preoperative colonoscopy with simultaneous injection of a dye in the intestinal wall is currently the most efficient and widely used way for identifying colorectal lesions. Multiple dyes that have been tested in animals including India ink, ICG, methylene blue, indigo carmine, toluidine blue, and isosulfan blue. However only India ink and ICG were detectable up to 48 h after marking (7, 22, 23). India ink has traditionally been used to mark tumors *via* colonoscopic tattooing due to its effectiveness and accuracy in detection of small lesions. Currently, it is the most commonly used agent for tattooing. However, reports of side effects such as inflammation, local peritonitis, abscesses and adhesions have been recognized. Furthermore, a major disadvantage that has been observed is in the case of spillage of India Ink out of serosa (5, 23, 24). This agent cannot be eliminated and stays permanently in the tissues confusing surgeons in the observation of the correct anatomical plane. The use of ICG gives an alternate means of correctly detecting and identifying the tumor to provide appropriate resection margins without the issues outlined above (5, 24, 25).

Several experimental research comparing ICG and India ink for colonic tattooing in animals found that India ink outperforms ICG due to its higher visibility and longer duration. A longer period is not usually required for surgical resection. In human cases, endoscopic tattooing with ICG was evident 36 h after injection in 12 individuals and resulted in relatively minor complications (5, 7, 22, 23).

In the current literature, different approaches have been described regarding the day of the tumor marking prior to

TABLE 5 Summary of results.

Age	Sex	Tumour Location	Operation	Preoperative Tumor Marking with ICG	Post operative Staging	Dissected Lymph Nodes
67	M	Sigmoid	LSC	Yes	T2N0M0 R0	18
71	F	Sigmoid	LSC	Yes	T2N1M0 R0	16
68	F	Sigmoid	LSC	Yes	T2N0M0 R0	20
72	M	Sigmoid	LSC	Yes	T2N1M0 R0	16
77	M	Rectum	LAR	Yes	T1N0M0 R0	17
69	F	Sigmoid	LSC	Yes	T3N1M0 R0	18
68	M	Cecum	RSC	Yes	T2N0M0 R0	19
73	M	Sigmoid	LSC	Yes	T3N1M0 R0	15
74	F	Rectum	LAR	Yes	T2N0M0 R0	20
69	M	Rectum	LAR	Yes	T2N0M0 R0	15

LSC, left-sided colectomy; LAR, low anterior resection; RSC, right-sided colectomy.

the surgery as well as the dosage and the concentration of the solution. According to Miyoshi et al., after injection of 1 ml of 1.25% ICG, it could be clearly detected in all 29 patients who underwent surgery within 8 days, whereas it was visible in only 2 of 10 patients who were operated after 8 days (24). Similar results were reported by Satoyoshi et al. who injected 0.1 ml of 0.5% ICG and evaluated a total of 100% visibility when the marking was performed within 6 days preoperatively as opposed to 60% and 0% when it was done between 7 and 9 and over 10 days, respectively (25). Watanabe et al. used 0.5 ml of 0.25% ICG which was sufficiently visible when the procedure was performed up to 7 days prior (11). Alternatively, Kim et al. injected 0.5–1 ml of 1.25% ICG a day prior of surgery and compared the measured outcomes to a group of non-tattooed patients, reporting a shorter operation time, hospital stay and postoperative oral ingestion period in favour of the tattooed group (18).

The purpose of this study was to evaluate the use of ICG as a preoperative tumor marking dye and describe the technique that we have been using in order to maximise the potential benefits of this procedure. As opposed to the currently standard method of tumor marking which is India Ink injection following submucosal elevation with saline test injection, we injected ICG directly to the submucosa without saline test injection. ICG may be managed more effectively than India Ink and injected straight into the submucosa without the need for a saline test injection due to the fact that it does not contain particles (18). The benefit of the direct injection technique is that there is no need of changing syringes. One of our findings is that visualisation of this dye with near-infrared light is very clear when the procedure was done one day prior of the surgery. Separation of marked and unmarked tissues was easily evaluated during laparoscopy and guided the surgeon for rapid recognition of anatomical landmarks. Injection of the minimum dosage (0.1 ml) of diluted solution (2.5 mg/ml) was performed in order to minimise the risk of spillage to surrounding tissues. This study adds to the little evidence available on the usefulness of ICG in this scenario.

There were no adverse events, which adds to the evidence that ICG is safe in minimally invasive colorectal surgery. This study provides preliminary evidence of the safety, feasibility and reproducibility of employing ICG to intraoperatively localize colorectal tumours.

However, this study has some limitations. It is an observational study which lacks comparison between techniques. Additionally, there is no specific method to accurately quantify the intensity of the signal and the interpretation of the images is under the surgical team's discretion. For that reason, subjective evaluation of fluorescence is still regarded as biased. An other limitation is the small sample size which reduces the power of the study. A randomised prospective comparative study, using as control group patients who have been preoperatively marked with India Ink, would be necessary in order to demonstrate whether the benefits of this technique are significant for tumor localisation and possible adverse events. In addition, more studies are required to also verify the optimal dosage of the fluorophores, as shown recently by an intercontinental experts Delphi consensus study (26).

Conclusion

Visualisation of preoperatively marked tumors with ICG offers a great choice that could potentially be considered by surgeons before colorectal procedures. The intraoperative view

of previously marked tissues under near-infrared light can be very clear with bright intensity. Separation of marked and unmarked tissues can be easily evaluated during laparoscopy and guide the surgeon throughout the operation.

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 Athens Medical Center. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization, MKK and AI; methodology, MKK, AI, MC; validation, MC, PV, NA, ISP, TP, KK; investigation, MKK; formal analysis, AI; resources, MKK, AI; data curation, AI; writing—original draft preparation, MKK; writing—review and editing, AI, MC, PV, NA, ISP, TP; visualization, MKK, AI; supervision, MC, PV, NA, KK; project administration, MKK. 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.

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Psychological states could affect postsurgical pain after hemorrhoidectomy: A prospective cohort study

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Background: Open hemorrhoidectomy is one of the standard procedures for grade IV hemorrhoids. Postsurgical pain is a common problem for patients. We aim to prospectively evaluate potential factors affecting postoperative pain among hemorrhoidectomy patients.
Methods: An observational study was conducted on 360 patients who had undergone Milligan-Morgan open hemorrhoidectomy. Details of the surgery and baseline information were recorded. Preoperative anxiety and depression were analyzed via the self-rating anxiety scale 20 (SAS-20) and self-rating depression scales 20 (SDS-20), respectively. Postoperative pain score was performed daily after surgery until the patient was discharged. The numerical pain score was evaluated by the visual analogue scale (VAS). The association between preoperative psychological states (anxiety or depression) and postoperative pain was analyzed using a generalized additive mixed model.
Results: A total of 340 patients eventually provided complete data and were included in our study. The average age was 43.3 ± 14.4 years, and 62.1% of patients were women. In total, 14.9% of patients had presurgical anxiety and 47.1% had presurgical depression. Postsurgical pain reached a peak point 1–2 days after surgery and went down to a very low level around 4–5 days after surgery. More excision of hemorrhoids could lead to more pain experience after surgery. Presurgical depression was associated with postsurgical pain. Patients who had presurgical depression had higher pain scores after surgery (2.3 ± 1.9 vs. 3.3 ± 1.9, $p = 0.025$).
Conclusion: Preoperative depression and the amount of excisional hemorrhoids are positively related to postsurgical pain.

KEYWORDS
hemorrhoids, postsurgical pain, psychological states, hemorrhoidectomy, depression

Introduction

Hemorrhoid disease is one of the most frequent complaints affecting a large population. In China, the prevalence rates were around 18% in the elderly population (1). Some researchers reported that 13.1% of all patients in the surgical outpatient department had hemorrhoids (2). According to the guideline statements from

different countries such as Italy (3), Japan (4), and many other countries (5–7), for patients with grade IV hemorrhoids, Milligan-Morgan open hemorrhoidectomy is still one of the standard procedures (8). The frequently encountered one after open hemorrhoidectomy is postsurgical pain (9, 10). In clinical practice, the size of the surgery area and the psychological states may all affect the degree of postsurgical pain (11). However, we still lack related data.

Previous studies have shown that emotional distress, such as presurgical anxiety and depression, is positively correlated with postsurgical outcomes (12, 13). In surgeries such as knee arthroscopy, bariatric surgery, and hip fracture repair, significant psychological influences on hospital stays and costs were reported (14). There are studies suggesting that the presence of preoperative anxiety is usually associated with poorer quality of life and cognitive performance (15). Also, patients with depression had worse perceptions of their shared decision-making process with their surgeon (10). However, in patients with hemorrhoids, the relationship between preoperative anxiety/depression and the development of postoperative pain has not been studied sufficiently.

We initiated this observational study to analyze which factors could affect subjective pain after surgery. Both the subjective and objective factors were taken into consideration. We aimed to figure out factors related to the degree of postsurgical pain. With the findings, we could predict the degree of pain after hemorrhoidectomy for everyone. Personalized pain management could then be adopted.

Patients and methods

This is a prospective study. From January 2019 to December 2021, 740 patients with a symptomatic fourth degree of hemorrhoids underwent Milligan-Morgan open hemorrhoidectomy. Patients who did not reach fourth-degree hemorrhoids were excluded. All patients had signed written informed consent. The local ethics committee and departmental internal review board approved this study. Patients who could not cooperate with data collection or had other postsurgical complications were excluded. Patients who had used opioids before admission to the hospital were excluded. Incidences of complications during the hospital stay period were recorded. Patients with serious complications shortly after surgery were excluded. Finally, 360 patients finished the study and provided eligible scales. Details are shown in **Figure 1**.

This is an observational study. Symptom onset, pain score, analgesic consumption, duration of hospital stay, and complications were recorded. A detailed preoperative consultation with a comprehensive information booklet for hemorrhoidectomy was provided to all the patients. The same surgeon performed all surgery. We did not use local anesthesia before surgery. The number of removed packs is listed in **Table 2**. High-frequency elytrotomy was used to stop bleeding during the surgery. Routinely, a single intradermal injection of methylene blue and ropivacaine was given to all patients right after surgery. Two millilters of 1% methylene blue and 8 ml of 10 mg/ml ropivacaine were mixed and injected into the surgical area (16, 17). We did not place a plug in the anal canal after surgery. The details of the surgery were immediately recorded after the operation. A standardized general anesthetic technique using propofol, fentanyl, and inhalation anesthesia was used. Laxatives were used the night before surgery, and oral enteral nutrition was used from the first day after surgery until the patients were discharged (4–5 days after surgery). An oral analgesic (tramadol hydrochloride

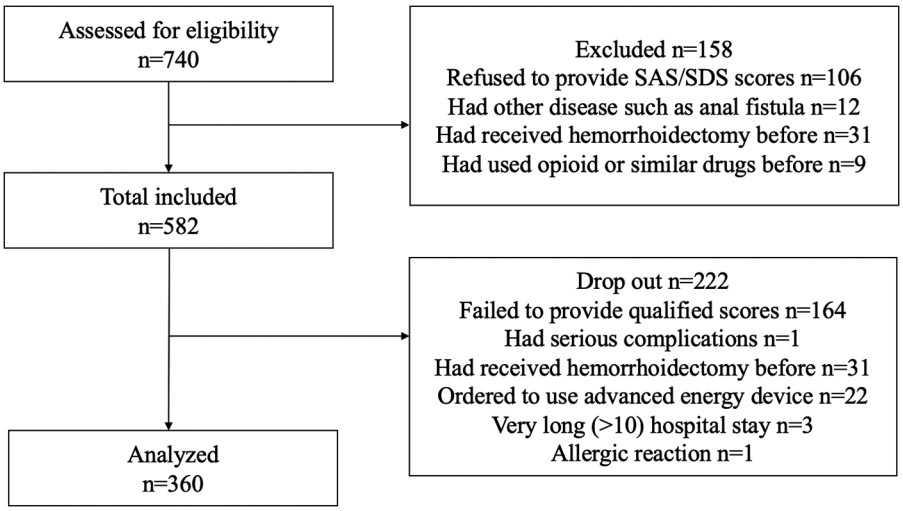

FIGURE 1

sustained release tablets) was given to the patients after surgery. Patients may take a pill when they feel hard to bear.

Assessment of psychological status

To assess whether psychological factors play a role, all patients were asked to finish the anxiety and depression questionnaire before surgery. Self-rating anxiety scale 20 (SAS 20) and self-rating depression scale 20 (SDS 20) were used to quantify the psychological status. High score values indicate high levels of anxiety or depression. By referring to the Chinese national norm, an SAS score <50 was considered normal for anxiety (18). An SDS score <53 was considered normal for depression (18).

Evaluation of postsurgical pain

Postsurgical pain was assessed every day after surgery. The visual analogue pain score system was used (19). Every day, a 10-cm linear analogue scale was used to assess. We evaluated the pain score three times a day and recorded the worst pain experienced on the day. The total number of analgesic tablets taken during the day was also recorded.

Statistical analysis

Baseline characteristics are presented as means ± SDs for normally distributed variables, medians (interquartile ranges) for non-normally distributed variables, and frequencies and percentages for categorical variables. Analysis of variance, the Kruskal–Wallis rank test, and the chi-square test were used to compare characteristics, clinical data, and postoperative pain scores where appropriate. In this study, longitudinal data were postoperative pain scores over time. The longitudinal changes in postoperative pain scores were analyzed using the generalized additive mixed model (GAMM), which is ideal for longitudinal data analysis because it is easy to accommodate unbalanced and unevenly spaced observations (20, 21). In these models, the dependent variable (i.e., postsurgical pain) was assessed during all follow-up visits, whereas the independent variables were only measured on the baseline visit. All models also included intercept and time as random terms. Random effects allowed each participant's starting value to vary from the population average (intercept) and the longitudinal trajectory to vary from the population average longitudinal trajectory (slope). All analyses were performed with R software version 3.4.3 (http://www.R-project.org; The R Foundation) and EmpowerStats version 2.20 (http://www.empowerstats.com; X&Y Solutions, Inc., Boston, MA). A *P*-value <0.05 was considered statistically significant (two-sided tests).

Results

Clinical characteristics

Finally, 340 patients provided qualified VAS scores and SAS/SDS questionnaires without any postsurgical complications. Table 1 shows the clinical baselines of the patients. The average age was 43.3 ± 14.4 years. There are 211 women (62.1%) and 129 men (37.9%) in the study. Fifty-one patients

TABLE 1 Demographics and clinical data at baseline.

Variables	Results Mean ± SD
Age, years	43.3 ± 14.4
BMI, kg/m^2	23.0 ± 3.0
HB, g/L	121.9 ± 24.7
ALB, g/L	43.4 ± 4.2
Sex, *n* (%)	
Female	211 (62.1%)
Male	129 (37.9%)
Education	
Illiteracy	31 (9.2%)
Elementary school	35 (10.3%)
Middle/high school	88 (26.4%)
University	184 (54.0%)
Unclear	31 (9.2%)
Smoking, yes, *n* (%)	12 (3.4%)
Drinking, yes, *n* (%)	27 (2.3%)
Diabetes, yes, *n* (%)	0 (0%)
Hypertension, yes, *n* (%)	27 (8.0%)
CVD, yes, *n* (%)	4 (1.1%)
Number of excisional hemorrhoids, *n* (%)	
1	91 (26.7%)
2	119 (35.0%)
3	125 (36.8%)
≥4	5 (1.4%)
Hematochezia, yes, *n* (%)	266 (78.2%)
Serious prolapse, yes, *n* (%)	235 (69.0%)
Anxiety, *n* (%)	
No (SAS score <50)	289 (85.1%)
Mild (SAS score 50–59)	35 (10.3%)
Moderate (SAS score 60–69)	16 (4.6%)
Severe (SAS score ≥70)	0 (0%)
Depression, *n* (%)	
No (SDS score <53)	180 (52.9%)
Mild (SDS score 53–62)	152 (44.8%)
Moderate (SDS score 63–71)	8 (2.3%)
Severe (SDS score ≥72)	0 (0%)

BMI, body mass index; HB, hemoglobin; ALB, albumin; CVD, cardiovascular disease; SAS, self-rating anxiety scale; SDS, self-rating depression scale.

(14.9%) had different levels of anxiety, and 160 patients (47.1%) had different levels of depression. Ninety-one patients (26.7%) received excision of one external hemorrhoid, 119 patients (35.0%) received two, 125 patients (36.8%) received three, and 5 (1.4%) received four. Twenty-two patients (6.1%) had continence problems, 1 patient (0.2%) had slight postoperative bleeding, and 15 patients (4.2%) had urine retention. Details are shown in Table 1 and Figure 1.

Postsurgical pain scores

The VAS system was used to quantify the pain degree. Pain score was the highest on the first day after surgery and slowly decreased afterward. On days 4–5, the degree of pain returned to a very low level. Patients were usually discharged on the fifth day after surgery. Details are shown in Table 2.

Consumption of oral analgesic

The total amount of oral analgesic consumed by the patients after surgery was recorded. Patients with anxiety took a higher amount of pain killer 2–3 days after surgery (day 2: 1.5 ± 0.7 vs. 3.4 ± 0.8, $p = 0.006$; day 3: 1.5 ± 4.4 vs. 2.5 ± 1.2, $p = 0.03$). Details are shown in Table 3.

TABLE 2 Demographic, clinical data, and postoperative pain score according to anxiety or depression.

Variables	Anxiety			Depression		
	No	Yes	*p*-Value	No	yes	*p*-Value
	289	51		180	160	
Age, years	44.2 ± 14.6	38.2 ± 12.3	0.165	45.9 ± 16.2	40.4 ± 11.5	0.074
BMI, kg/m^2	23.2 ± 3.1	22.3 ± 2.3	0.327	23.2 ± 3.3	22.9 ± 2.6	0.684
HB, g/L	120.7 ± 26.1	128.9 ± 11.6	0.289	121.7 ± 26.0	122.2 ± 23.3	0.925
ALB, g/L	43.3 ± 4.4	43.8 ± 3.4	0.688	43.2 ± 4.1	43.6 ± 4.5	0.704
Sex, *n* (%)			0.564			0.492
Female	176 (60.8%)	35 (69.2%)		106 (58.7%)	105 (65.9%)	
Male	113 (39.2%)	16 (30.8%)		74 (41.3%)	55 (34.1%)	
Education			0.428			0.046
Illiteracy	27 (9.5%)	4 (7.7%)		23 (13.0%)	8 (4.9%)	
Elementary school	31 (10.8%)	4 (7.7%)		20 (10.9%)	16 (9.8%)	
Middle/high school	55 (18.9%)	4 (7.7%)		16 (8.7%)	43 (26.8%)	
University	145 (50.0%)	10 (76.9%)		113 (63.0%)	70 (43.9%)	
Unclear	31 (10.8%)	0 (0.0%)		8 (4.3%)	23 (14.6%)	
Smoking, yes, *n* (%)	12 (4.1%)	0 (0.0%)	0.46	8 (4.3%)	4 (2.4%)	0.626
Drinking, yes, *n* (%)	8 (2.7%)	0 (0.0%)	0.549	4 (2.2%)	4 (2.4%)	0.934
Hypertension, yes, *n* (%)	23 (8.1%)	4 (7.7%)	0.959	22 (15.2%)	5 (0.0%)	0.069
CVD, yes, *n* (%)	4 (1.4%)	0 (0.0%)	0.673	4 (2.2%)	0 (0.0%)	0.342
Number of excisional hemorrhoids, *n* (%)		0.476			0.84	
1	80 (27.7%)	11 (21.6%)		39 (21.7%)	52 (32.5%)	
2	95 (32.9.1%)	24 (47.1%)		63 (34.8%)	56 (35.0%)	
≥3	114 (39.4%)	16 (31.4%)		78 (43.5%)	52 (32.5%)	
Hematochezia, yes, *n* (%)	219 (75.7%)	47 (92.3%)	0.181	141 (78.3%)	125 (78.0%)	0.981
Serious prolapse, yes, *n* (%)	199 (68.9%)	35 (69.2%)	0.982	125 (69.6%)	109 (68.3%)	0.898
Postoperative pain score						
POD1	4.3 ± 2.3	4.1 ± 2.5	0.71	4.2 ± 2.2	4.4 ± 2.4	0.8
POD2	3.1 ± 1.9	3.7 ± 1.5	0.286	2.9 ± 2.0	3.5 ± 1.6	0.169
POD3	2.6 ± 2.0	3.6 ± 1.8	0.09	2.3 ± 1.9	3.3 ± 1.9	0.025
POD4	2.4 ± 1.7	3.0 ± 2.1	0.259	2.1 ± 1.8	2.9 ± 1.7	0.05
POD5	2.4 ± 1.8	2.6 ± 1.4	0.713	2.4 ± 2.0	2.4 ± 1.4	0.911

BMI, body mass index; HB, hemoglobin; ALB, albumin; POD, post operation days; CVD, cardiovascular disease.

TABLE 3 The amount of oral analgesic consumed by the patients during hospital stay after surgery.

Variables	Anxiety			Depression		
	No	Yes	*p*-Value	No	yes	*p*-Value
No. of patients	289	51		180	160	
No. of pills consumed						
POD1	2.8 ± 1.1	2.9 ± 0.9	0.412	2.9 ± 1.0	2.8 ± 1.1	0.922
POD2	1.5 ± 0.7	3.4 ± 0.8	0.006	1.7 ± 0.6	1.9 ± 0.8	0.312
POD3	1.5 ± 1.4	2.5 ± 1.2	0.03	1.5 ± 0.5	1.8 ± 0.7	0.074
POD4	1.6 ± 0.5	1.7 ± 0.6	0.728	1.4 ± 0.3	1.5 ± 0.5	0.522
POD5	0.9 ± 0.4	1.1 ± 0.5	0.922	0.8 ± 0.6	1.0 ± 0.4	0.621

POD, postoperation day.
Data are shown as mean ± SD.

Preoperative psychological characteristics and postsurgical pain

The preoperative feeling of anxiety and depression was evaluated by SAS 20 and SDS 20. Before surgery, in 340 patients, 51 patients (14.9%) had abnormal levels of anxiety. A total of 160 patients (47.05%) were assessed to have depression. Details are shown in Table 2. Gender, education, and the number of external hemorrhoids did not differ between the normal and abnormal groups, except that patients with a higher education level seem to have a higher burden of depression ($p = 0.046$). There were no significant differences in terms of pain scores between patients with and without anxiety. On the third day after surgery, patients with depression had significantly higher pain scores (2.3 ± 1.9 vs. 3.3 ± 1.9, $p = 0.025$).

Other characteristics correlated to postsurgical pain

We recorded the number of excisional hemorrhoids. We also studied the educational background, alcohol/tobacco consumption, and clinical symptoms such as prolapsus and hematochezia. Patients who underwent more hemorrhoid excision had higher pain scores after surgery. No differences were found in terms of other factors. Details are shown in Supplementary Table S1.

Association between preoperative psychological state and postoperative pain

The GAMM model showed that the postoperative pain score decreased significantly with time in the crude model (β: −0.52; 95% CI: −0.63 to −0.41; $p < 0.001$) and fully adjusted model (β: −0.53; 95% CI: −0.65 to −0.42; $p < 0.001$). In the crude model (model 1), compared with patients without depression, those with depression have higher postoperative pain. However, it was not statistically significant (β: 0.50; 95% CI: −0.12 to 1.11; $p = 0.118$). In model 2 adjusted for age, sex, education, and patients with depression were independently and significantly associated with postoperative pain (β: 0.77; 95% CI: −0.13 to 1.41; $p = 0.021$). In the full model (model 3), further adjusted fo the number of excisional haemorrhoids, the association between depression and postoperative pain was close to the margin of statistical significance (β: 0.61; 95% CI: 0.01 to 1.21; $p = 0.05$). However, we did not observe significant anxiety and postoperative pain in all models. Details are shown in Table 4.

Discussion

In this study, we aimed to study the effect of psychological state on postsurgical pain after open hemorrhoidectomy. Since the factors affecting pain are too complicated, we set several restrictions. Only patients with fourth-degree hemorrhoids were recruited for our research. Also, patients who had taken opioids or other psychotropic drugs before admission to the hospital were excluded. Thus, the patients had similar conditions before surgery. Patients with serious postsurgical complications (serious infection, anal fissure, anorectal stenosis, serious bleeding) were excluded. We found that the pain score was highest on the first day after surgery and slowly decreased afterward. The GAMM model showed that the postoperative pain score decreased significantly with time in the crude model. There are no significant differences in terms of pain scores between patients with and without anxiety. However, patients with anxiety took higher amounts of pain killer 2–3 days after surgery. On the other hand, patients with depression had significantly higher pain scores on the third day after surgery than others. In the fully adjusted model adjusted for age, sex, education, and the number of excisional hemorrhoids, we still found that patients with depression were independently and significantly associated with postoperative pain. Together, our data suggested that depression could promote postsurgical pain after Milligan-Morgan open hemorrhoidectomy.

Before we started this research, we analyzed the sample size using statistical Software G*Power 3.1.7 for Windows (https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower.html). Considered an effect size (f) of 0.30, error probability alpha of 0.05, power (1 – error probability beta) of 0.90, the number of groups of 2, the number of measurements of 5, a correlation among repeated measures of 0.5 for F tests (ANOVA: repeated measures), the calculated total sample size was 74. We finally had 340

TABLE 4 Preoperative anxiety and depression and postoperative pain score in a linear mixed-effects regression model.

	Model 1		Model 2		Model 3	
	β (95%CI)	*p* value	*β* (95%CI)	*P* value	*β* (95%CI)	*p* value
Preoperative anxiety						
Anxiety	0.53 (−0.33, 1.39)	0.228	0.57 (−0.29, 1.43)	0.2	0.40 (−0.40, 1.21)	0.328
Time	−0.52 (−0.63, −0.41)	<0.001	−0.52 (−0.63, −0.41)	<0.001	−0.53 (−0.65, −0.42)	<0.001
Preoperative depression						
Depression	0.50 (−0.12, 1.11)	0.118	0.77 (0.13, 1.41)	0.021	0.61 (0.01, 1.21)	0.05
Time	−0.52 (−0.63, −0.41)	<0.001	−0.52 (−0.63, −0.41)	<0.001	−0.53 (−0.65, −0.42)	<0.001

Model 1: Crude model.
Model 2: adjusted for age, sex. and education.
Model 3: further adjusted for the number of excisional hemorrhoids.

patients. In addition, a post hoc power analysis was conducted by using the same statistical software. Considering an effect size (f) of 0.30, error probability alpha of 0.05, the total sample size of 340, the number of groups of 2, the number of measurements of 5, a correlation among repeated measures of 0.5 for F tests (ANOVA: repeated measures), the calculated power (1 – error probability beta) was 0.95. Thus, based on the results of priori power analyses and posthoc power analyses, we believe that this study has an adequate sample size.

In this study, we chose to perform Milligan-Morgan open hemorrhoidectomy. Milligan-Morgan surgery is a classic surgery and is widely performed (22). This surgery has a very low medical cost and recurrence rate. Although new techniques such as stapled hemorrhoidopexy and DGHAL did reduce postsurgical pain, they required higher medical fees and had higher recurrence rates for grade IV hemorrhoids (23). Restriction of the medical fee also restricts the use of the type of energy. The LigaSure system and Ultrasonic Scalpel were recommended in many studies (24, 25). We had used the device in some cases. The clinical results were excellent. These equipment could reduce operation time, blood loss, and postoperative pain (26). However, due to the limitation of the medical insurance policy, to reduce the medical cost to meet the demand of Diagnosis-Related Groups (DRGs), we only used the normal high-frequency elytrotomy to stop bleeding during hemorrhoidectomy in all the cases in our study.

In our study, we used VAS to investigate postsurgical pain. It is very important in terms of sensitivity and the ability to detect changes in pain over time. VAS is more valid for detecting changes in pain intensity (27). That is why we chose VAS in our study. Also, in many similar studies, VAS was also used to examine postsurgical pain after hemorrhoidectomies (28, 29). Indeed, there are limitations to the self-reporting scales. There are many other scales for rating anxiety and depression. Both SAS/SDS 20 and HADS were widely used, and many clinical studies adopted either of the scales. We tried both scales. HADS contained fewer questions and occupied less time. However, we found that there are two problems. First, sometimes, the patients were not careful enough and did not provide accurate answers. Second, many patients were elderly people. They could not understand the questions in the HADS. SAS/SDS 20, however, had a design of reverse scoring. We could check the scale and found it obvious. The patients were then asked to finish the scale again. In this way, the scores were more reliable. Thus, we chose SAS/SDS 20 for our study.

In our study, the median pain score was the highest on day 1. Some studies mentioned that many patients had defecatory pain after surgery. This happened around days 3–4 after surgery (30). In our medical center, we used laxatives before surgery and oral enteral nutrition after surgery instead of a normal diet. This largely retarded the defecation time after surgery, and we did not observe significant pain complaints during this period.

We found that patients with fewer excisional hemorrhoids had less pain 1 and 2 days after surgery ($p = 0.021$, $p = 0.002$). This finding was not surprising because more excisional hemorrhoids would lead to more surgical trauma in the local site. Also, this would cause postoperative spasm of the anal sphincter and leave the inflammation reaction around the anal. Thus, unlike malignant diseases, the surgical concept for hemorrhoids should be as less as possible. Also, we validated the affection of pre-surgical symptoms, such as hematochezia and prolapsus. Moreover, the results were negative.

In addition to the surgery itself, the perception and the psychological status of the patient are also very important. Previous studies suggested that anxiety and depression prior to surgery were correlated with postsurgical pain (12). These patients had higher analgesic requirements. Moreover, pain may also aggravate the status of depression/anxiety. These changes may trigger each other and finally lead to a vicious circle. We found that patients with anorectal disease usually had abnormal psychological states. Our data suggested that 14.9% of all patients had different levels of anxiety and 47.1% had different levels of depression. It seemed that patients with grade IV hemorrhoids properly had depression.

To study whether anxiety and depression may affect postsurgical pain, the generalized additive mixed model was used for the study. In a systematic review, 8 studies reported a significantly effect and 10 studies did not demonstrate a significant difference between patients with and without depression (15). In our study, we did not observe significant differences in terms of anxiety. However, on the other hand, patients with depression had prolonged pain duration. After excluding the effects of age, gender, education, and the number of excisional hemorrhoids, patients with depression still had higher pain scores. Our finding suggested that presurgical depression did contribute to more pain complaints after surgery. Depression is commonly associated with cognitive impairment, and this could lower the threshold for acute postoperative pain (31). Also, in depression disorders, the immune system of the patient is suppressed and there might be higher chances of infection. After hemorrhoidectomy, this might promote pain.

We also recorded the amount of oral analgesic each patient taken during their hospital stay. Interestingly, it seemed that although patients with anxiety did not have higher pain scores, they consumed higher amounts of the drugs than others (**supplementary Table S2**). Since the effects of the drug could last for 4–6 h, the worst pain experience of the day could still be recorded and not affected. This finding suggested that patients with anxiety seemed to take more drugs than other patients under similar pain burdens.

In our study, the length of hospital stay (LOS) was usually 4–5 days after surgery. The LOS varied very much due to the different situations in different countries. Some surgeons even showed that the LOS could be nearly a month (25). Other reports from China indicated that LOS is 7–13 days (32). Others suggested that it is usually 1–2 days (28). Some groups even performed the surgery in the outpatient setting (33). Despite the fact that there are big differences in terms of LOS, other studies and our groups agreed that it would take almost 7–30 days for the patients to return to normal activity (34, 35). Those who left hospital very early after surgery still require medical support after they went home. It seems that in a place with less community medical support, patients chose to stay in the hospital for longer.

There are several limitations to our study. First, we only record the pain score of hospitalized patients. Thus, we lack the related data when patients were discharged. Second, this is an observational study, and there is no additional intervention treatment. More study is required to figure out advanced therapies. Also, patients with different expectations of the operation may have different readouts in terms of pain degree. As a result, the pain score from the patients may not be very accurate. To weaken the affection, we only recorded the data on patients with symptomatic fourth-degree hemorrhoids. Still, this is not objective enough and advanced methods are required for further study. In addition, there are now advanced devices to help reduce postsurgical pain and there are many reports. In our study, due to the restriction of medical insurance and Diagnosis-Related Groups (DRGs), we only use the normal high-frequency elytrotomy. The results may change when an advanced device is adopted.

In conclusion, our study suggested that the amount of excisional hemorrhoids correlates with the pain of postsurgical pain. In addition, psychological states could also affect the complaints of postsurgical pain. Presurgical depression could increase the degree of postsurgical pain.

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.

Ethics statement

The studies involving human participants were reviewed and approved by this study was approved by the institutional review board of Tongji Medical College of Huazhong University of Science and Technology. Both written and oral consent was obtained before the data were collected. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GW designed the study and wrote the manuscript. YW analyzed the clinical data. YC and RZ helped with the design and data collection. KT provided suggestions for the data analysis, and Linfang Wang supervised the whole study and worked as the surgeon for all patients. All authors contributed to the article and approved the submitted version.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.1024237/full#supplementary-material.

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Restructuring surgical training after COVID-19 pandemic: A nationwide survey on the Italian scenario on behalf of the Italian polyspecialistic young surgeons society (SPIGC)

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Introduction: The COVID-19 pandemic has led to the disruption of surgical training. Lack of communication, guidelines for managing clinical activity as well as concerns for safety in the workplace appeared to be relevant issues. This study aims to investigate how surgical training has been reorganized in Italy, almost 2 years after the outbreak of COVID-19 pandemic.

Materials and methods: A 16-item-electronic anonymous questionnaire was designed through SurveyMonkey© web application. This survey was composed of different sections concerning demographic characteristics and impacts of the second COVID-19 pandemic wave on surgical and research/didactic activities. Changes applied in the training programme and activities carried out were also investigated. The survey was carried out in the period between June and October 2021.

Results: Four hundred and thirty responses were collected, and 399 were considered eligible to be included in the study analysis. Three hundred and thirty-five respondents continued working in Surgical Units, with a significant reduction (less than one surgical session per week) of surgical sessions in 49.6% of them. With concern to didactic and research activities, 140 residents maintained their usual activity, while 116 reported a reduction. A sub-group analysis on resident moved to COVID-19 departments showed a reduction of research activities in 35% of them. During the period considered in this survey, the surgical training program was not substantially modified for most of participants (74.6%).

Conclusion: Our survey demonstrated that surgical residency programs haven't improved 2 years after the beginning of the pandemic. Further improvements are needed to guarantee completeness of surgical training, even in emergency conditions.

KEYWORDS

surgical training, COVID-19 pandemic, trainee, training programme, survey

Introduction

In January 2022, COVID-19 globally reached almost 350 million cases, accounting for around 5.5 million deaths (1). Following UK, France, Russia and Turkey, Italy was the fifth European state for total COVID-19 cases, recording more than ten million people that tested positive and 144,000 deaths (2).

The first COVID-19 outbreak lead Health Systems to face a burden never seen before. The drastic changes in human resources negatively impacted healthcare workers everyday life. Surgical units suffered an unavoidable impact, with discontinuation of elective non-oncological procedures, outpatient clinics, and endoscopy services (3–6). Considering the above, also surgical education programs were drastically affected by the pandemic (7, 8).

In 2020, an international survey-based study, including 15 specialities and 34 countries, assessed the global impact of the COVID-19 pandemic on surgical training (9), demonstrating a severe impact on all of its aspects. Interestingly, trainees from Europe reported worse consequences than those from Asia and Australia.

In our previous survey (10), among 800 responses collected, almost 35% and 27% of respondents declared they were experiencing, respectively, complete interruption of surgical and clinical activities. A subgroup analysis, comparing the COVID-19 impact on clinical activities with demographics data demonstrated a statistically significant difference regarding the various surgical specialities and Italian regions.

Lack of communications and coordination from the institutions, and guidelines for managing clinical activities during the pandemic have been identified as significant negative factors for surgical training during COVID-19 pandemic (11, 12).

Overall, anxiety for rising difficulties in career progression and concerns for safety on the workplace related to COVID-19 pandemic were underlined as relevant issues potentially affecting residents' training (13, 14).

The present study aims to investigate how surgical training was reorganised in Italy almost 2 years after the outbreak of COVID-19 Pandemic.

Methods

This survey was carried out between June and October 2021 by the Italian Polyspecialistic Society of Young Surgeons (SPIGC). It consists of an anonymous questionnaire created through SurveyMonkey© web application (SVMK Inc., One Curiosity Way, San Mateo, United States) (15). The aim of the survey was explained to all participants with a brief introduction. Participants were asked to sign a privacy policy consent. Survey participation was voluntary, and no incentives were offered. No institutional review board approval was required. This survey was registered in clinicaltrias.gov (NCT04338945).

The survey was composed of three sections. The first section included 5 Questions (Q) concerning whether or not participants belong to a surgical training programme, demographics, level of training and type of surgical activity routinely performed (Q1–Q7). The second section was concerned with the impact of second wave of the COVID-19 pandemic on clinical, surgical and research activities (Q8–Q10). The third section focused on the activities carried out during the second wave, the changes applied in the training programme and COVID-19 vaccine (Q11–Q16).

These questions were selected and collected by the authors, with the aim of providing an accurate scenario of COVID-19's impact on trainees' activities.

The survey was promoted through a mailing list, instant message services, and through the SPIGC official Facebook, Instagram, and LinkedIn accounts.

Italian surgical residents coming from any surgical specialty and attending all years of training program were considered eligible for the survey's analysis. The eligibility has no relation to the residents' curricular activities. As previously done (10), the study sample aimed to reach approximately 5% of Italian residents in surgical specialties concerning the annual number of residency scholarship places from 2014 to 2019, and the annual drop-out percentage of surgical trainees (16). All participants were informed that the results of the survey would have been used for further statistical evaluation and scientific publication. Anonymity was guaranteed by study design.

Results of the survey were reported according to the CHERRIES Guidelines (17).

Statistical analysis

All the answers collected and included in the study were processed, and results were summarized as numbers (n) and percentages (%), separately for each question. A p-value < 0.05 was considered statistically significant. All the analyses were

performed with RStudio (Version 1.1.463-© 2009–2018 RStudio, Inc.).

Results

Study population

Out of 430 participants, 399 (92.7%) were included in the study. The response rate for specific questions ranged from 92.2% to 100%.

Overall, trainees answering to this survey were in 49.1% of cases male ($n = 196$) and in 50.9% female ($n = 203$). Most residents (56.4%) were attending a training program in general surgery, followed by plastic surgery (7.77%). The complete subdivision according to surgical specialties has been reported in Table 1. One hundred ninety-four (49.2%) responders were 28 (27–30) years old, 136 (34.5%) were 26 (25–27) years old, and 63 (16%) were aged over 30 years.

At the time of questionnaire administration, 381 residents were equally distributed during the 5 years of surgical training, as showed in Table 2. In 51.9% of cases ($n = 207$), trainees were attending the training program in hospitals in the Northern regions of Italy (Table 3).

Regarding the type of surgery performed in each center, 230 (60.5%) out of 380 responders worked in surgical oncology units, 75 (19.7%) performed surgery only for benign conditions and 51 (13.4%) worked in an emergency surgery departments. Less than 10% of the participants attended

TABLE 1 Subdivision according to surgical specialty.

Surgical speciality	Percentage (%)	Number of participants
General surgery	56.4	225
Obstetrics and gynecology	18	72
Plastic surgery	7.7	31
Thoracic surgery	4.7	19
Orthopedics	3.7	15
OHNS otolaryngology-head and neck surgery	2.5	10
Maxillo-facial surgery	1.8	7
Ophthalmology	1.8	7
Urology	1.2	5
Vascular surgery	1	4
Cardio surgery	0.3	1
Neurosurgery	0.3	1
Pediatric surgery	0.3	1
Others	0.3	1
Dentistry	0.0	0
Total		399

TABLE 2 Subdivision of respondents according to year of residency and activities usually performed.

Attended year of surgical residency (381)
1st year: 76 (19.95%)
2nd year: 81 (21.26%)
3rd year: 77 (20.2%)
4th year: 75 (19.69%)
5th year: 72 (18.9%)
Main surgical activity performed (380)
Elective surgery for oncological pathologies (60.53%)
Elective surgery for benign pathologies (19.74%)
Emergency surgery (13.42%)
Transplant surgery (5.26%)
Surgery which requires post-operative anaesthesiologic care (1.05%)

TABLE 3 Italian regions in which the respondents work ($n = 399$ respondents).

Italian region	Percentage (%)	Number of participants
Lazio	23.55	94
Lombardia	16.54	66
Friuli Venezia Giulia	12.03	48
Emilia Romagna	8.52	34
Veneto	6.77	27
Puglia	6.27	25
Sicilia	5.26	21
Piemonte	5.01	20
Sardegna	3.51	14
Toscana	3.01	12
Calabria	2.76	11
Liguria	2.5	10
Umbria	1.5	6
Abruzzo	1.25	5
Campania	1	4
Valle d'Aosta	0.26	1
Trentino Alto Adige	0.26	1
Basilicata	0.00	0
Marche	0.00	0
Molise	0.00	0

organ transplants departments or worked in a surgical unit requiring post-operative anesthesiologic care (Table 2).

Impact of COVID-19 second wave on research/didactic and surgical weekly activities

Among 378 responders (94.7%), 335 (88.6%) declared to have continued working in Surgical Units, while a limited proportion of them (5.3%) were moved to a non-surgical unit (Table 4). In this subgroup, 15 (75%) were residents attending general surgery at the fourth year of the training program (35%; Figure 1) and working in northern regions of Italy (90%).

Considering the impact of second COVID-19 pandemic wave, there was a statistically significant difference in residents maintaining the usual activity when comparing those belonging to the first 3 years and at last 2 years of the training program ($p = 0.019$) (Table 5).

Considering the impact of the pandemic on surgical activities, 189 out of 381 responders (49.61%) reported a reduction of surgical sessions despite one or more planned surgical procedures per week; in 29.6% of cases there were no relevant changes in routine surgical activity; a complete interruption of surgical activities occurred in 3.41% of cases; Interestingly, seven residents (1.84%) declared to have performed an increased number of surgical procedures (Table 4).

Influence of COVID-19 second wave on training and research

Concerning didactic and research activities, among 380 responders (95.2%), 140 (36.8%) declared to have maintained the usual activity, while 116 (30.5%) reported a reduction. Interestingly, 59 residents (15.5%) reported not being involved in didactic and research activities even before COVID-19 pandemic. Forty-seven residents reported an increased

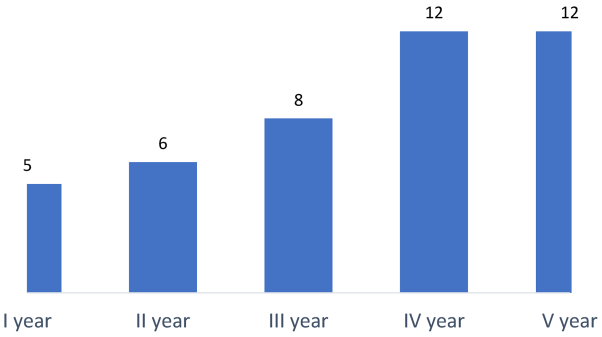

FIGURE 1
Graphical representation of 43 respondents who left their surgical training divided according to the attended year of residency.

TABLE 5 Impact of COVID-19 second wave on active participation to clinics according to the attended year of residency.

	I–III (%)	IV–V (%)
I maintained my usual activity	91.8	83.5
I have been moved to a non-surgical unit	3.9	7.5
I voluntarily interrupted my Residency Program to take part of a COVID-19 emergency unit	0.9	4.2
I interrupted all clinical activities	0.4	0.0
I interrupted all clinical activities because I started feeling COVID-19 related symptoms	0.0	2.1
I interrupted all clinical activities following the residency program board directives	3	2.7

TABLE 4 Impact of pandemic on clinical, surgical and research activities.

Impact of COVID-19 second wave on clinical activities (378)	Impact of COVID-19 second wave on surgical activities (381)	Impact of COVID-19 second wave on training and research activities (380)
Maintenance of usual activity (88.62%)	No relevant modifications (29.66%)	Maintenance of usual activity (36.84%)
Transfer to a non-surgical unit (i.e., COVID ward, internal medicine ward, emergency department) (5.29%)	Reduction of surgical sessions but at least one or more weekly planned surgical sessions (49.61%)	Increase of usual activity (12.37%)
Voluntary Interruption of residency program to take part in COVID-19 emergency unit (in the same hospital or in another) (2.12%)	A significant reduction with less than one surgical session per week (15.49%)	Decrease of usual activity (30.53%)
Interruption of all clinical activities beforehand (0.26%)	Complete interruption of all surgical activities (3.41%)	Interruption of usual activity (4.74%)
Interruption of all clinical activities because of feeling COVID related symptoms (0.79%)	Increase of surgical activity (1.84%)	Usually not performed this activity (15.53%)
Interruption of all clinical activities following the residency program board directives (2.91%)		

activity, 25 of them (53.2%) attending the first 3 years of the residency program (Figure 2). Most of the participants (250, 65.7%) carried out their didactic and research activities in different fields, while 121 (31.9%) and 9 (2.4%) were partially or totally focused on research or didactic activities related to COVID-19 pandemic.

Influence of COVID-19 second wave on the surgical training program organization

During the period considered in this survey, the surgical training program was not substantially modified for most participants (74.65%); 5.93% of responders ($n = 22$) declared an improvement in training with virtual reality and 8.63% of them in using surgical simulators. Notably, 57 participants (15.36%) reported following "remote" training courses led by experts in a specific field.

Among 371 respondents, 124 (33.42%) reported a complete interruption of surgical training. In 43.13% of cases there was a decrease of the training program activities, although 54 participants (14.56%) defined the training program as "sufficient". On the other hand, according to 28 respondents (7.55%), the program remained unchanged with respect to before the COVID-19 pandemic; surprisingly, the surgical program was considered improved for 5 residents (1.35%).

Out of 371 residents, 107 (28.8%) decided to take part in the national COVID-19 vaccination campaign, and 13 (3.5%) participants were involved as part of the residency school program. Nevertheless, most trainees (67.7%) did not take part to the national vaccination campaign (Figure 3).

The residency program resulted improved or partially improved for 6.5% (24 answers) and 40.7% (151 respondents) respectively. However, the program was considered "not improved" by 196 residents (52.8%) completing this survey.

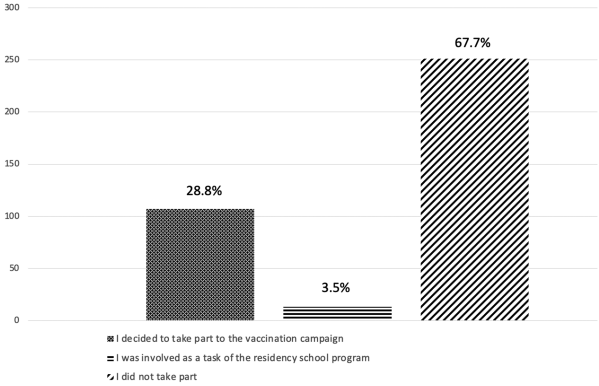

FIGURE 3
Involvement in national vaccination campaign.

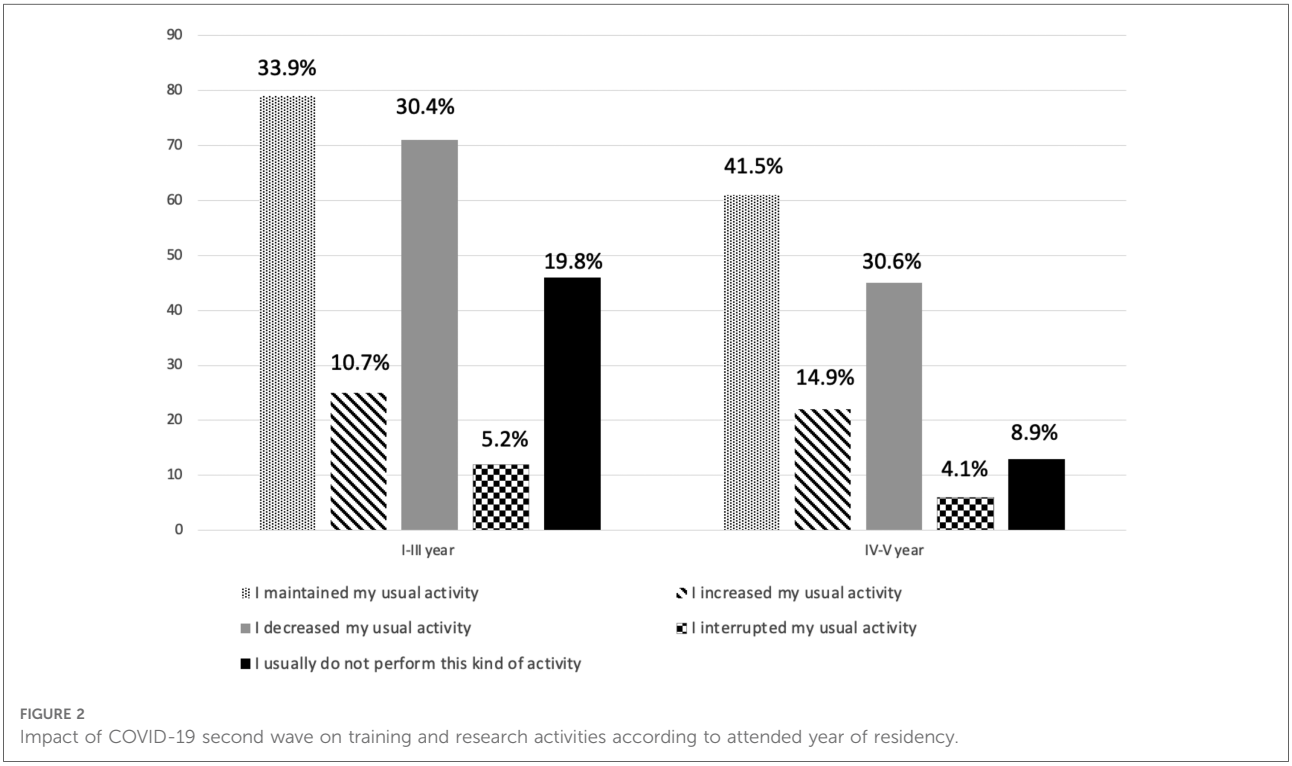

FIGURE 2
Impact of COVID-19 second wave on training and research activities according to attended year of residency.

Discussion

During the first COVID-19 pandemic wave, several articles have analyzed the impact of COVID-19 in different educational teaching programs (18). As reported by Aziz et al., a positive impact of COVID-19 pandemic was related to an improvement in resident educational programs; particularly, these authors reported that residents had a shift to online lessons, leading to global increase in overall teaching time during the pandemic (19).

Unfortunately, less attention has been paid to training programs during the second COVID-19 pandemic wave, as demonstrated by the lack of reports on this topic. This situation can also be highlighted by the number of responses to this survey, which were about half compared to the previous proposal during the first COVID-19 pandemic wave (10).

General surgery residents seem to be sensitive to this topic; this has been underlined by their extensive participation to this survey, making general surgery the most common surgical specialty performed by the participants (**Table 1**). During the first COVID-19 wave, the problems related to COVID-19 pandemic involved, in particular, responders from the northern regions of Italy (deeply affected by first months of pandemic); notably, also the findings obtained in the current survey confirmed this trend (51.9% of cases); nevertheless, analyzing data from specific regions, 23.3% of the responses were working in the Lazio region (**Table 3**), one of the most affected areas in Italy.

In comparison to the last survey (10), experience in terms of resource management developed during the first wave of Covid-19 has led to a decreased reallocation of surgical specialists to a medical area from 14.8% to 5.3%. Surprisingly, a higher number of older trainees were reassigned to non-surgical wards compared to younger residents ($p = 0.019$). This finding, in contrast with the previous survey, could be partly explained by to the lower pressure exerted by COVID-19 pandemic on the health care system, which, therefore, led to a reduced workload, thus allowing the recruitment of staff with more experience (20).

Further confirmation of the improved capacity of the health care system to deal with the pandemic is represented by the decreased number of centers in which surgical activity has been suspended and by a relative increase in those able to maintain their usual surgical activity (21). Concerning the participation to surgical activity, trainees reported a general decrease in attendance to surgical procedures, although in very few cases a complete interruption of the operating activity was observed (**Table 4**).

Unfortunately, research activity did not benefit from the experience of the first COVID-19 pandemic wave. In fact, 30.5% of respondents to our survey reported a decrease in their research activity. Furthermore, a high percentage (about 33%) of residents declared that their scientific activity was mainly focused on COVID-19. These findings seem to show how in the past 2 years, scientific research in the surgical field has been negatively influenced.

A positive aspect recorded during the second COVID-19 wave was represented by the lack of significant impact on the surgical programming, differently from the previous wave.

Overall, the COVID-19 pandemic greatly affected residency educational programs, particularly those related to surgical areas and organized by centers with reduced clinical experience and case volume (22). The experience from the first wave showed the importance of having a flexible surgical training program due to multiple emergent aspects related to pandemic. The possibility to practice on a simulator has been demonstrated to be crucial, especially at the beginning of training (23). From data reported in this survey, unfortunately, 74.6% of respondents reported that training activities during second wave did not have a relevant improvement in comparison to the previous experience during the first COVID-19 pandemic wave. Improvements to training were reported by some participants, as the introduction of virtual training (5.93%), the adoption of surgical simulators (8.63%), and remote training (15.36%).

The growth of several alternative didactic approaches, such as webinars, e-group discussions, educational videos, podcasts, telemedicine, virtual and augmented reality simulation (especially with the presence of a trainer and not self-driven), represented a positive novelty; Interestingly, several authors advise their incorporation into standard surgical training curricula (11, 24–27). These alternative didactic approaches may represent a good tool contributing to overcome the lack of training and hopefully could be introduced in the education program after the pandemic period.

As further evidence of limited learning flexibility of the surgical training system during COVID-19 pandemic, 33.4% of respondents reported a new interruption of surgical activities during the second wave. The low adhesion by some trainees (only 28.8%) to take part in vaccination programs can be considered as a lack of efforts done by the residency programs in underlining the importance of managing the national emergency. It should also be reported, however, that the vaccination campaign, like other initiatives to fight COVID-19, have been interpreted by some organizations as an opportunity to obtain earnings, thus preventing its broad adhesion among healthcare workers. Considering the importance of vaccines for the restoration of elective surgical activity, there should be serious changes in this direction (28).

The present study has some limitations. The heterogeneity of the sample, in terms of experience and demographics, and the impossibility of quantifying the number of trainees who received the survey represent the major limitation. Another possible limitation is that 20% of responders was at the first

year of residency with limited knowledge of the level of surgical and research activities before COVID-19. Furthermore, some items did not receive 100% of responders.

Conclusion

Our study shows how the residency programs were considered improved by about half of the respondents which, undoubtedly, represents an unsatisfactory result, especially after the first wave.

Moreover, most of the respondents did not have the opportunity to participate in alternative training programs, such as virtual reality or tele-mentoring. Consequently, further improvements are needed to guarantee the completeness of surgical training even in extreme emergency conditions such as the COVID-19 pandemic.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: privacy. Requests to access these datasets should be directed to *arcangelopicciariello@gmail.com*.

Author contributions

GG, APi, DP and RM all contributed equally to this study in terms of contributions to the conception and design of the research project; acquisition, analysis, and interpretation of data for the study; drafting and revising the project critically; final approval of the version to be published; agreement to be accountable for all aspects of the research in ensuring that questions related to the accuracy and integrity of any part of the study are appropriately investigated and resolved. EG, FB and AC contributed equally to this study; agreement to be accountable for all aspects of the research in ensuring that questions related to the accuracy and integrity of any part of the study are appropriately investigated and resolved Drafting the work and revising it critically for important intellectual content. APa: Substantial contributions to the conception and design of the study; acquisition, analysis, and interpretation of data for the work; Final approval of the version to be published. 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.

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Appendix A

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Downsizing of rectal cancer following neoadjuvant radiotherapy (5 × 5 Gy) and long interval surgery evaluated using MRI semiautomated volumetric measurements, a retrospective study

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Introduction: Neoadjuvant conventional chemoradiation (CRT) is the standard treatment for primary locally non-curatively resectable rectal cancer, as tumor downsizing may allow R0 resectability. Short-term neoadjuvant radiotherapy (5x5 Gy) followed by an interval before surgery (SRT- delay) is an alternative for multimorbid patients who cannot tolerate CRT. This study examined the extent of tumor downsizing achieved with the SRT-delay approach in a limited cohort that underwent complete re-staging before surgery.

Methods: Between March 2018 and July 2021, 26 patients with locally advanced primary adenocarcinoma (>uT3 or/and N+) of the rectum were treated with SRT-delay. 22 patients underwent initial staging and complete re-staging (CT, endoscopy, MRI). Tumor downsizing was assessed by staging and re-staging data and pathologic findings. Semiautomated measurement of tumor volume was performed using mint Lesion^{TM} 1.8 software to evaluate tumor regression.

Results: The mean tumor diameter determined on sagittal T2 MRI images decreased significantly from 54.1 (23–78) mm at initial staging to 37.9 (18–65) mm at re-staging before surgery ($p < 0.001$) and to 25.5 (7–58) mm at pathologic examination ($p < 0.001$). This corresponds to a mean reduction in tumor diameter of 28.9 (4.3–60.7) % at re-staging and 51.1 (8.7–86.5) % at pathology. Mean tumor volume determined from transverse T2 MR images mint Lesion^{TM} 1.8 software significantly decreased from 27.5 (9.8 – 89.6) cm^3 at initial staging to 13.1 (3.7 – 32.8) cm^3 at re-staging ($p < 0.001$), corresponding to a mean reduction of 50.8 (21.6 – 77) %. The frequency of positive circumferential resection margin (CRM) (less than 1mm) decreased from 45,5 % (10 patients) at initial staging to 18,2 % (4 patients) at re-staging. On pathologic examination, the CRM was negative in all cases. However, multivisceral resection for T4 tumors was required in 2 patients (9%). Tumor downstaging was noted in 15 of 22 patients after SRT-delay.

Conclusion: In conclusion, the observed extent of downsizing is broadly comparable to the results of CRT, making SRT-delay a serious alternative for patients who cannot tolerate chemotherapy.

KEYWORDS

total tumor volume measurement, short-term radiation with delayed surgery, tumor downsizing, neoadjuvant therapy, rectal cancer

Introduction

Colorectal carcinoma is one of the most common malignant tumors of the digestive tract and a relevant cause of cancer-related deaths. It is the third most common tumor disease in both sexes worldwide and the second leading cause of death among all cancers (1).

In rectal cancer, local recurrence is an important problem that affects not only oncologic outcomes but also quality of life.

The establishment of the concept of total mesorectal excision (TME) as a standard procedure (2) and the introduction of neoadjuvant therapy for locally advanced tumors have contributed to the improvement of local control in rectal cancer in recent decades (3–5).

In terms of oncologic outcome in locally advanced, resectable rectal cancer, short-term neoadjuvant irradiation (5 × 5 Gy) (SRT) and surgery the following week were shown to be equivalent to long-term neoadjuvant chemoradiation (28 × 1.8 Gy, 5-fluorouracil, and leucovorin) and surgery after 4–6 weeks (CRT) (6).

For primary locally non-curatively resectable tumors with infiltration of the pelvic wall or floor, adjacent organs, or sphincter, conventional long-term neoadjuvant chemoradiation remains the standard of care, as tumor downsizing may allow R0 resectability or sphincter-preserving resection (7, 8). Recently, even more aggressive concepts of total neoadjuvant therapy have been introduced, achieving complete remission in up to 30% of cases, even in extensive tumors (9–11).

However, a proportion of elderly multimorbid patients do not tolerate even standard long-term neoadjuvant chemoradiation. Therefore, a concept of short-term neoadjuvant radiotherapy (5 × 5 Gy) followed by a 4–8-week interval before surgery (SRT-delay), with the goal of tumor regression, was developed for these patients.

The feasibility of the SRT-delay approach has already been demonstrated in studies without evidence of increased complication rates (12–14).

The extent of downsizing achieved with this approach has not yet been systematically studied.

The few reports of tumor regression with SRT-delay are mainly based on pathologic findings compared with initial clinical and radiologic staging. To date, there are no tumor downsizing data with this neoadjuvant approach in the context of re-staging data, particularly no data measuring total tumor volume.

The aim of this study was to evaluate the extend of downsizing of locally advanced rectal cancer in the SRT-delay approach in a limited cohort undergoing complete re-staging in the interval before surgery. In addition, we aimed to investigate the total tumor volume to assess the downsizing of rectal cancer after this neoadjuvant approach.

Patients and methods

Patients

Between March 2018 and July 2021, 26 patients were treated with the concept of neoadjuvant radiotherapy (5 × 5 Gy) and delayed surgery (SRT-delay) for rectal cancer at Ruppin-Brandenburg University Hospital. All patients had locally advanced primary adenocarcinoma (≥uT3 or/and N+) in the lower or middle third of the rectum. In addition, patients with locally advanced upper third rectal cancer whose main tumor mass appeared caudal to the promontory on sagittal MRI view were included.

Patients were assigned to this form of neoadjuvant therapy because they either could not tolerate conventional neoadjuvant chemoradiation due to their comorbidities or refused chemotherapy.

Short-term neoadjuvant radiotherapy included five fractions of 5 Gy in one week (5 × 5 Gy), followed by an interval of about 8 weeks before surgery.

22 of the 26 patients underwent initial staging (CT, endoscopy, MRI) and complete re-staging before surgery. 4 of 26 patients had to be excluded from the study because of insufficient re-staging. In 2 of these 4 cases, inserted hip arthroplasties caused poor MRI quality. MRI was not possible in one patient, and re-staging endoscopy was not performed in the remaining patient.

The clinical data of the 22 patients enrolled in the study are shown in Table 1.

The study was approved by the ethics committee of the Brandenburg Medical School (No. E-02-20210930).

Tumor downsizing after neoadjuvant therapy was assessed by comparing staging and re-staging data on MRI and endoscopy and by comparing initial staging data with pathological findings.

MRI

The largest tumor diameter was determined using pelvic MRI in mercury technique in sagittal T2 images as crania-caudal

TABLE 1 Clinical data of patients included. mrCRM, circumferential resection margin at primary staging MRI.

Age (years)	72.3 (mean)	51–84 (range)
	Male	Female
Sex (%)	68.2	31.8
SRT-delay (weeks)	8.1 (mean)	4.3–10.9 (range)
UICC Stage (%)	**I**	1 (4.5)
	II	6 (27.3)
	III	14 (63.6)
	IV	1 (4.5)
Primary T staging	**2**	1
	3a	3
	3b	3
	3c	12
	3d	2
	4a	0
	4b	1
Primary N staging	0	7
	1	14
	2	1
Tumor height		
Low (<6 cm)	4	
Mid (6–12 cm)	14	
High (>12 cm)	4	
	<1 mm	**>1 mm**
mrCRM (%)	45.5	54.5

extension. Tumor diameters were defined as D1 at initial staging and D2 at re-staging before surgery.

The distance of the tumor to the mesorectal fascia (MRF) was assessed in the transversal T2 images and classified as greater or less than 1 mm.

In addition, tumor volume was determined at initial staging (V1) and re-staging (V2).

For semiautomated volume measurement, the entire tumor margins were marked by an experienced radiologist using mint Lesion^{TM} 1.8 radiology software (Mint Medical, Dossenheim, Germany) on three transverse T2 images of the tumor: the most cranial, the most caudal, and one additional (**Figure 1**).

The mint Lesion^{TM} software interpolated the tumor margins in the remaining, non-manually marked transverse T2 images and calculated the corresponding volume. In case of differences between the interpolated margins and the actual tumor margins, the interpolated margins were manually corrected.

MRI images were evaluated by two experienced radiologists who independently assessed tumor diameter and total tumor volume. The mean value of both examiners was used for further analysis.

Endoscopy

Rigid and flexible rectoscopy were used at baseline and re-staging to assess the tumor and the distance of the aboral tumor margin from the anal verge.

For semiquantitative assessment of tumor downsizing after neoadjuvant therapy, the endoscopy was performed by the same investigator.

The endoscopist evaluated tumor changes comparing staging and re-staging using the following classification:

0 - no changes/progression
1 - moderate regression up to 25%.
2 - significant regression 25–75%
3 - extensive regression > 75%

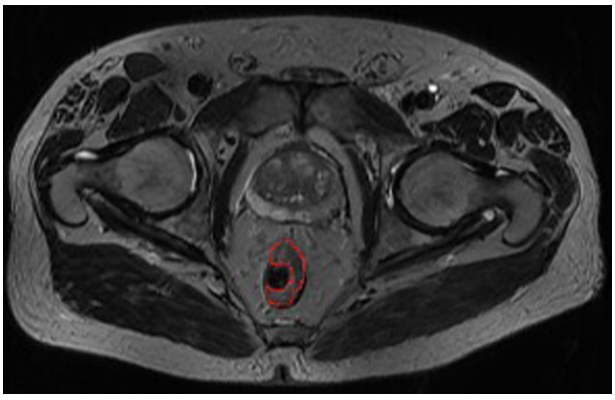

FIGURE 1
Entire tumor margins marked (red)—one of three marked transverse images for semiautomated volume measurement using mint lesion^{TM} 1.8.

4 - not assessable

Category 4 concerned stenosing tumors that were also stenosing at re-staging. Possible changes could not be assessed endoscopically in these cases.

Pathological examination

Circumferential resection margin (CRM) was defined as negative if the distance of the tumor from the margin was more than 1 mm. Histopathological tumor regression to neoadjuvant radiotherapy was evaluated according to the Dworak scoring system (15). The quality of the TME was evaluated using the protocol introduced by Quirke (16).

Statistical evaluation

Statistical analysis was performed using GraphPad Prism 9 (GraphPad Software, LLC, San Diego, CA). Descriptive statistics in the form of mean and standard deviation were obtained and presented as tables and box plots. Changes in tumor size etc. were analyzed using the paired t test. When more than two groups were compared, a one-way ANOVA was performed with Tukey's multiple comparisons test. Interobserver correlations were calculated using the Pearson correlation coefficient. The overall significance level was set at $\alpha = 0.05$ and marked with an * in the graphs. A significance level of $\alpha = 0.01$ was marked with ** and $\alpha = 0.001$ with ***.

Patients follow-up

Patient follow-up was scheduled according to the German guideline for colorectal cancer. Follow up included a medical history and physical examination, blood tests such as serum carcinoembryonic antigen (CEA), sonography, rectoscopy every 6 months. Computed tomography of the chest, abdomen, and pelvis and colonoscopy were performed annually. Patients who did not show up for examinations were followed up by telephone.

Results

Of the 22 patients enrolled in the study, 7 were women and 15 were men. The mean age was 72 (51–84) years. The interval between radiotherapy and surgery averaged 8.1 (4.3–10.9) weeks. Oncologic (low) anterior resection of the rectum with total mesorectal excision and central lymphadenectomy (low tie of inferior mesenteric artery) was performed in 18 patients. One patient underwent intersphincteric resection followed by hand-sewn coloanal anastomosis.

Multivisceral resection was required in 3 patients, *en bloc* hysterectomy in one patient, and *en bloc* resection of the urinary bladder in another. The third patient underwent extended abdomino-perineal excision with *en bloc* partial vaginectomy.

Fifteen patients underwent laparoscopic surgery, and 7 patients had open surgery.

MRI

The mean value of the largest tumor diameter, determined as cranio-caudal extent in sagittal T2 images, decreased significantly from 54.1 (23–78) mm at initial staging (D1) to 37.9 (18–65) mm at re-staging before surgery (D2) ($p < 0.001$) (Figure 2). This corresponds to a mean reduction in cranio-caudal tumor diameter of 28.9 (4.3–60.7) %.

Evaluation of the distance of the tumor from the mesorectal fascia in transverse T2 images showed that it was less than 1 mm in 10 patients (45.5%) at initial staging, but only in 4 patients (18.2%) at re-staging.

Metastatic lymph node involvement was detected in 15 patients at initial staging and in 7 patients at re-staging.

Semiautomated volume measurement using mint Lesion™ 1.8 software revealed a significant decrease in mean tumor volume from 27.5 (9.8–89.6) cm^3 at initial staging to 13.1 (3.7–32.8) cm^3 at re-staging ($p < 0.001$) (Figure 3). This equates to a mean reduction in tumor volume after neoadjuvant radiotherapy of 50.8 (21.6–77) %.

Analysis of interobserver reliability revealed a Pearson correlation coefficient of r = 0.95 for tumor diameter D1 on MRI 1 and r = 0.97 for D2 on MRI 2. Regarding tumor volume, the Pearson correlation coefficient was r = 0.99 for V1 in MRI 1 and r = 0.97 for V2 in MRI 2.

Endoscopy

Semiquantitative endoscopic assessment of the tumor after neoadjuvant therapy revealed moderate regression (up to 25%) in 5 patients, significant regression (25%–50%) in 8 patients, and extensive regression (>75%) in another 5 patients.

Endoscopic assessment of tumor changes after neoadjuvant therapy could not be performed in 4 patients because the tumors were stenosing at both initial and re-staging.

Pathological examination

R0 resection of the tumor was achieved in all 22 patients. The circumferential resection margin was negative in all cases and not smaller than 1 mm.

The mean tumor size at pathological examination was 25.5 (7–58) mm (Figure 2).

This corresponds to a significant reduction in mean tumor diameter compared to initial staging MRI (D1) ($p < 0.001$) of 51.1 (8.7–86.5) % on average.

Lymph node metastases were found in the specimens of 6 patients.

Tumor regression according to the Dworak classification was grade 1 in 10 patients, grade 2 in 8 patients, and grade 3 in 3 patients. Only in one patient, no histopathological tumor regression could be observed after neoadjuvant radiation (Dworak grade 0).

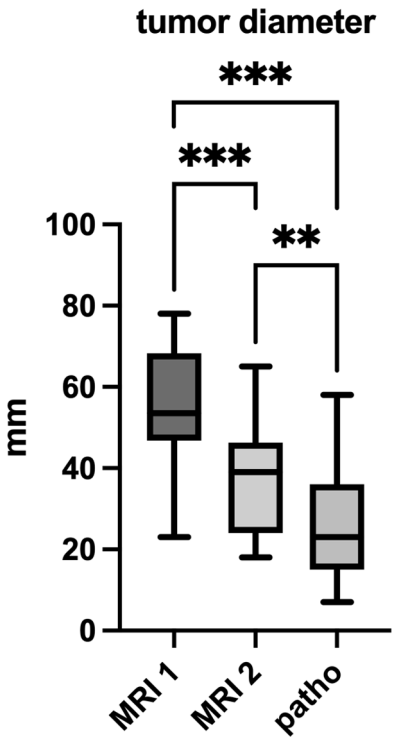

FIGURE 2
Tumor diameter in mm in staging MRI 1, MRI 2 and pathological examination. ** significance level $\alpha = 0.01$, *** $\alpha = 0.001$.

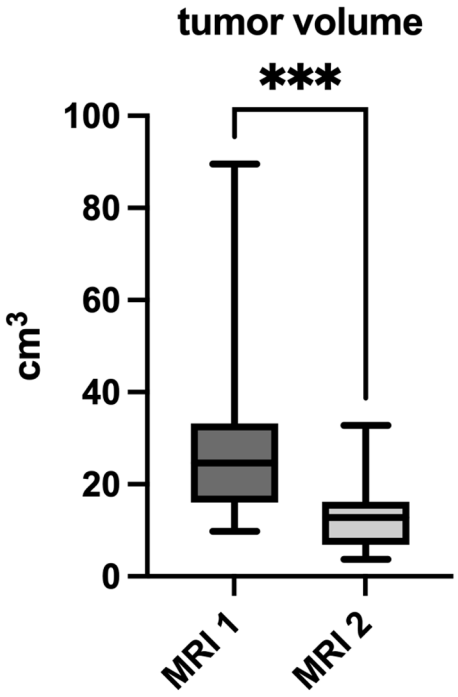

FIGURE 3
Tumor volume in cm3 measured in primary- and re-staging MRI. *** significance level $\alpha = 0.001$.

At pathological staging, tumor downstaging was noted in 15 of 22 patients after neoadjuvant therapy compared with initial staging (**Figure 4**).

Follow up

After a mean follow-up of 34.6 (14–54) months, 3 of 26 patients had died unrelated to tumor. Another patient had died from multiple distant metastases. 3 other patients developed distant metastases, 2 of whom had solitary metastases that were surgically resected. One patient had a recurrence of rectal cancer. On pathologic examination, the tumor was found to have grown from an HGIEN polyp. Therefore, it was considered a *de novo* metachronous second rectal cancer rather than a local recurrence. In 18 of 26 patients, there was no evidence of new tumor manifestations. Of the above patients, 2 did not show up for scheduled examinations and were therefore followed up by telephone.

In summary, with a mean follow-up of 34.6 (14–54) months, disease free survival was seen in 18 of 26 patients (69,2%) and overall survival in 22 of 26 patients (84,6%).

Discussion

Neoadjuvant radiotherapy has become the standard of care for locally advanced rectal cancer, as both hyperfractionated radiotherapy and conventional chemoradiation (CRT) have been shown to reduce the rate of local recurrence (3–6). These results are also consistent in the cohort of patients treated with the surgical standard of TME (4, 17). The most important risk factors for locoregional recurrence are involvement of the circumferential resection margin and positive lymph node status (5, 18). The quality of surgery (controlled TME, number of lymph nodes retrieved) influences the latter. However, in noncuratively resectable tumors with infiltration of the mesorectal fascia, pelvic wall or floor only downsizing following neoadjuvant therapy may enable resection with a sufficiently wide negative (>1 mm) circumferential margin.

From this perspective, evaluation of the chances of short-term neoadjuvant radiotherapy (5 × 5 Gy) with delayed surgery (SRT-delay) as an alternative to conventional chemotherapy in patients who cannot tolerate chemotherapy depends on the extent of tumor downsizing achieved with this approach. In addition, the subgroup of patients responding to neoadjuvant therapy with tumor downstaging was shown to have a survival benefit (14, 19, 20).

For SRT-delay, reports of tumor regression are mainly based on pathologic findings compared with initial clinical and radiologic staging (12–14). However, MRI is known to have limitations in predicting tumor and lymph node category with a tendency to overstaging. On the other hand, prediction of mesorectal fascia involvement and positive CRM by MRI is considered very accurate (21).

In our study, the frequency of positive CRM decreased from 45% (10 patients) at initial staging to 18% (4 patients) at re-staging. On pathologic examination, the circumferential resection margin was negative in all cases. However, in 3 patients (14%) with T4 tumors requiring multivisceral *en bloc* resection for negative CRM, the mesorectal fascia (MRF) remained infiltrated. This issue of correct terminology in initial staging positive MRF vs. positive CMR and extended surgery to achieve negative CRM in MRF-infiltrating tumors has been discussed previously (22).

Our finding is consistent with the report of Pettersson et al., who described a significant decrease in CRM-positive cases of 50% at initial staging vs. 14% at pathologic examination (13). For CRT, Bahadoer et al. reported a decrease to 9% CRM-positive cases on pathology in a high-risk population with 30% cT4 tumors and 60% CRM-positive cases at initial staging (9).

When evaluating tumor downsizing based on re-staging data, a partial response is defined as regression of the tumor by at least 30% according to RECIST criteria (23). For SRT delay, there is only one study reporting on tumor downsizing at re-staging. Pettersson et al. described tumor regression in 74% of patients on re-staging MRI, but without quantifying the extent (13).

We found a significant reduction in tumor size at restaging after neoadjuvant radiotherapy in our patients, which translated into a mean reduction in craniocaudal tumor diameter of 29% and tumor volume of 51%. Accordingly, endoscopic re-staging described significant regression (25%–50%) in 36% of patients and extensive regression (>75%) in another 23% of patients. The mean reduction in tumor diameter from initial staging to pathologic examination was more pronounced (51%) than the decrease according to restaging data (29%).

This fact may be caused by both overstaging on MRI due to fibrotic thickening or edema (21) and shrinkage of specimens after formalin fixation (24).

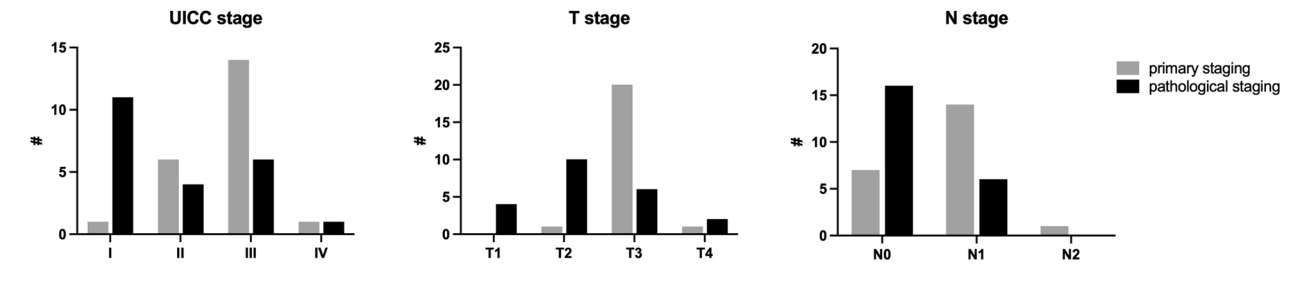

FIGURE 4
UICC, T and N stage in primary staging and pathological findings.

With CRT, Yu et al. reported a mean reduction in craniocaudal tumor length of 33% after MRI re-staging, which is similar to our results after SRT-delay (20).

Furthermore, Yu et al. demonstrated that patients with >50% tumor reduction after CRT showed a survival benefit in addition to the intended improvement in local tumor control. Tumor downsizing of this extent was seen in about 24% of patients in their study (20). In our study, only 14% of patients had a tumor reduction >50% as determined by tumor diameter at MRI re-staging.

On the other hand, no tumor response to SRT-delay was observed in only one patient (5%) in our study, which manifested as pathological regression Dworak grade 0.

In this context, Petterson et al. reported upstaging in 11% of patients after SRT-delay, comparing initial staging with pathologic stage (13). However, further related data based on pathological tumor regression are not available for SRT-delay.

The assessment of response to treatment of solid tumors according to the RECIST criteria focuses on the unidimensional evaluation of the longest tumor diameter (23).

With the increasing availability of novel radiological segmentation software, semi-automated tumor volumetry is a potentially useful additional assessment tool for better detection of tumor response that has been used in several solid tumors (25, 26).

In rectal cancer, measurement of total tumor volume has been shown to be more accurate than measurement of one- and three-dimensional size in assessing response to neoadjuvant treatment (27).

In our study, semiautomated volume measurement documented a mean 51% reduction in tumor volume after neoadjuvant radiotherapy, which is more pronounced than the reduction observed with unidimensional assessment of tumor diameter.

To date, there are no volumetric data on response to SRT-delay on which to benchmark our results. For CRT, Martens et al. reported a mean 65% reduction in total volume and a mean 36% reduction in tumor length (27) (**Table 2**).

Downstaging, as determined by comparing the initial staging with the pathologic stage, was observed in 68% of patients in our study, although none showed a complete response.

With an interval of 4–5 weeks to surgery after neoadjuvant radiotherapy, Pach et al. reported downstaging in 44% of patients and complete response in 10% (14). The difference in complete response is presumably related to the number of patients in our study.

However, complete response is observed more frequently with CRT, in 12%–20% of patients (7, 9, 10, 20, 27).

Regarding the goal of neoadjuvant treatment to increase the frequency of sphincter-preserving surgery by tumor downsizing, our study cannot provide data as the majority of tumors in our cohort did not have a critical distance to the anal verge. Pach et al. reported no improvement in the rate of sphincter preservation at 4–5 weeks after neoadjuvant radiotherapy with a 2 cm rule for the distal margin (13). In contrast, an increase in sphincter-preserving surgery was noted in up to 25% of patients after CRT (28).

Our study has several limitations, notably the retrospective design, the number of patients included, and the range of the time interval before surgery.

Because of these limitations, the results should be interpreted with caution.

TABLE 2 Downsizing of rectal cancer following neoadjuvant therapy evaluated in restaging MRI. Reduction of tumor diameter, Regression of total tumor volume. CRT, conventional chemoradiation; SRT-delay, short-term radiotherapy with delayed surgery; n.d., not done.

Author	Neoadjuvant regimen	Tumor diameter	Tumor volume
Yu et al. (20)	CRT	−33%	n. d.
Martens et al. (27)	CRT	−36%	−65%
present study	SRT-delay	−29%	−51%

Conclusion

The present study demonstrated that SRT-delay can lead to significant downstaging and downsizing of locally advanced rectal cancer. The observed extent of downsizing is broadly comparable to the results of CRT, making SRT-delay a serious alternative for patients who cannot tolerate chemotherapy. In our study, semiautomated measurement of total tumor volume was a feasible and accurate tool for assessing downsizing after SRT-delay.

The extent to which SRT-delay in very low rectal cancer may increase the number of sphincter-preserving procedures needs further investigation in an appropriate cohort and design. Also, to investigate whether the extent of downsizing after SRT-delay results in a survival benefit comparable to that of CRT.

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 Ethics committee of the Brandenburg Medical School. The patients/participants provided their written informed consent to participate in this study.

Author contributions

HCA, SW, and CS: collected and analyzed the data and wrote main parts of the manuscript. SG and HCA: designed the study and completed the manuscript. All authors meet the criteria of the International Committee of Medical Journal Editors (ICMJE) regarding the definition of authorship. All authors contributed to the article and approved the submitted version.

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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

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Clinical significance and related factors of rectal hyposensitivity in patients with functional defecation disorder

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Background: Rectal hyposensitivity (RH) is not uncommon in patients with functional defecation disorder (FDD). FDD patients with RH are usually unsatisfied with their treatment.

Aims: The aim of this study was to find the significance of RH in patients with FDD and the related factors of RH.

Methods: Patients with FDD first completed clinical questionnaires regarding constipation symptoms, mental state, and quality of life. Then anorectal physiologic tests (anorectal manometry and balloon expulsion test) were performed. Rectal sensory testing (assessing rectal response to balloon distension using anorectal manometry) was applied to obtain three sensory thresholds. Patients were separated into three groups (non-RH, borderline RH, and RH) based on the London Classification. The associations between RH and clinical symptoms, mental state, quality of life, and rectal/anal motility were investigated.

Results: Of 331 included patients with FDD, 87 patients (26.3%) had at least one abnormally elevated rectal sensory threshold and 50 patients (15.1%) were diagnosed with RH. Patients with RH were older and mostly men. Defecation symptoms were more severe (p=0.013), and hard stool (p<0.001) and manual maneuver (p=0.003) were more frequently seen in the RH group. No difference in rectal/anal pressure was found among the three groups. Elevated defecatory desire volume (DDV) existed in all patients with RH. With the number of elevated sensory thresholds increasing, defecation symptoms got more severe (r=0.35, p=0.001). Gender (male) (6.78 [3.07–15.00], p<0.001) and hard stool (5.92 [2.28–15.33], p<0.001) were main related factors of RH.

Conclusion: Rectal hyposensitivity plays an important role in the occurrence of FDD and is associated with defecation symptom severity. Older male FDD patients with hard stool are prone to suffer from RH and need more care.

KEYWORDS

functional defecatory disorder, rectal hyposensitivity, Bristol stool formation scale, age, male

Introduction

Approximately 50% of patients with functional constipation have difficulty in defecating (1) and may have the functional defecatory disorder (FDD) (2). FDD significantly affects productivity, mental health, and quality of life (QOL) (3).

Intact rectal sensation and motility are critical to normal bowel movement and defecation. The presence of sufficient stool and intact sensation will trigger the perception of rectal fullness through rectal afferent pathways (4). Rectal hyposensitivity (RH) refers to a blunted sensation of mechanical distension, which is indicated by the elevation of sensory thresholds beyond the normal range (5). As sensation and motility are inextricably linked, alteration in one domain can affect the other. RH, rectal motor dysfunction, and altered recto-anal reflex activity are particularly associated with FDD (6).

Patients with RH commonly present with constipation (48%) (7), and about 18%–68% of constipated patients have RH (8). It is reported that RH is more common in patients with functional disorders (i.e., dyssynergic defecation) rather than structural diseases (i.e., rectocele and intussusception) (9). Our team has found that RH is associated with defecation symptoms and specifies an eventual diagnosis of FDD over delayed gut transit (10).

Rectal hyposensitivity is associated with constipation, but its clinical importance remains unclear. In addition, little is known about the characteristics of FDD patients with RH and the related factors of RH in these individuals. Given the above deficiencies, we carried out this study to explore the influence of RH on constipation symptoms, mental state as well as QOL, and related factors of RH in an FDD population.

Methods

Participants

This is a cross-sectional study. We enrolled patients with FDD (Rome IV core criteria defined) who were referred to our gastrointestinal motility clinic between January 2014 and May 2021. Patients with pregnancy, drug-induced constipation, secondary constipation due to other diseases, a history of the prior bowl or anorectal surgery, or an abuse history were excluded. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital with Nanjing Medical University (2022-SR-210).

All of our target patients underwent high-resolution anorectal manometry (HR-ARM) and balloon expulsion test (BET) and completed the required questionnaires.

High-resolution anorectal manometry

A high-resolution solid-state anorectal manometry device (Manoscan AR 360; Given Imaging, Yokneam, Israel) with 12 sensors was adopted to evaluate patients' defecation function. The absolute parameters were assessed as follows: anal resting pressure (20–30 s), anal sphincter length, duration of the sustained squeeze, anal pressure during squeeze (three attempts for a maximum duration of 20–30 s), rectal pressure, and anal residual pressure during attempted defecation (typically 20–30 s, three times, with a 2-min rest interval). Comprehensive parameters were also collected for analysis including manometric defecation index (MDI), recto-anal pressure gradient (RAG), and anal relaxation rate during attempted defecation (11).

The rectal sensation was evaluated by incrementally distending the rectal balloon by 10 mL from 0 to 400 mL, and the thresholds for first constant sensation volume (FCSV), defecatory desire volume (DDV), and maximum tolerable volume (MTV) were recorded.

Upper limits of normal rectal sensation (95%)

A previously published dataset of 54 healthy individuals (35 women) assessed by our motility center (Table 1) was used to define the upper limits of normal (95%) for three sensory thresholds (men and women have different upper limits of normal) (10). The healthy individuals did not have any surgical history related to constipation and they all had normal bowel movements.

Diagnostic criteria for RH

According to the London Classification published in Jan 2020, RH is defined as an abnormal elevation of ≥2 sensory thresholds while borderline RH refers to one of the three sensory thresholds exceeding the upper limit of the normal range (12).

Balloon expulsion test

A 4-cm long balloon filled with 50 mL of warm water was placed in the patient's rectum while the patient was seated on a commode and was asked to expel the balloon, in privacy. If the subject could not expel the balloon after 1 min of straining, it was deflated and removed and the result was identified as abnormal (13).

TABLE 1 Rectal sensory thresholds (mLs) in 54 healthy individuals (35 women) by gender.

Rectal sensory thresholds [upper limits of normal (95.0%)]	Females (n =35)	Males (n=19)
FCSV (mL)	90	70
DDV (mL)	170	120
MTV (mL)	320	250

FCSV: first constant sensation volume; DDV: defecatory desire volume; MTV: maximum tolerable volume.

Abbreviations: RH, Rectal hyposensitivity; FDD, Functional defecation disorder; QOL, Quality of life; HR-ARM, High-resolution anorectal manometry; BET, Balloon expulsion test; MDI, Manometric defecation index; RAG, Recto-anal pressure gradient; FCSV, First constant sensation volume; DDV, Defecatory desire volume; MTV, Maximum tolerable volume; SBMs, Spontaneous bowel movements; BSFS, Bristol Stool Formation Scale; PAC-SYM, Patient assessment of constipation symptoms; GAD-7, General anxiety disorder 7-item; PHQ-9, Patient health questionnaire-9; PAC-QOL, Patient assessment of constipation quality of life.

TABLE 2 Demographic characteristics of patients stratified by rectal sensation in 311 patients with FDD.

Demographics	Non-RH (*n*=244)	Borderline RH (*n*=37)	RH (*n*=50)	*p*
Age(yr), mean ± SD[a]	47.54 ± 16.78	53.73 ± 15.73	54.82 ± 16.81	0.005
Gender, male/female(%)[b]	81/163 (33.2)	15/22 (40.5)	38/12 (76.0)	<0.001
BMI(kg/m^2), median (interquartile range)	21.97 (3.77)	21.88 (5.37)	22.86 (3.73)	0.212
Constipation Duration(yr), median (interquartile range)	6.00 (9.50)	3.00 (5.75)	5.00 (6.63)	0.148

BMI: body mass index; yr: year.
[a]The patients in RH and Borderline RH groups were significantly older than those in Non-RH group (post hoc $p = 0.005$ and $p = 0.036$, respectively).
[b]More males were observed in RH group than those in Non-RH and Borderline-RH group (*v* value is defined to be a "discovery" using a Bonferroni procedure for multiple tests which controls the false discovery rate at 0.05).

Defecography

Patients who were suspected to suffer from rectal structural diseases such as rectocele or intussusception underwent defecography. The presence of poor opening of the anorectal angle, poor relaxation of the anal canal, or poor expulsive effort generated which is related to retention of more than 50% contrast was defined as abnormal (14).

Questionnaires

Constipation symptoms

Patients with FDD were asked about their spontaneous bowel movements (SBMs) (times per week), defecation duration, and stool consistency evaluated by Bristol Stool Formation Scale (BSFS). In addition, Rome IV core criteria for functional constipation were adopted to evaluate symptoms including fewer bowel movements (<3 times per week), straining, feeling incomplete defecation, anal blockage, lumpy or hard stool, and manual maneuvers during the last 6 months (15). In addition to collecting the typical symptoms, we used Patient Assessment of Constipation Symptoms (PAC-SYM) (16) to measure patients' subjective feelings about constipation, with higher scores indicating more severe symptoms.

Mental health

General Anxiety Disorder 7-item (GAD-7) (17) and Patient Health Questionnaire-9 (PHQ-9) (18) were adopted to measure anxiety and depression symptoms, respectively. Higher scores suggested more severe symptoms and a score of >5 indicated anxiety or depression state.

Quality of life

The Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire specifically assesses constipated patients' QOL (19). It contains 28 items divided into four subscales (physical discomfort, psychosocial discomfort, worry/anxiety, and satisfaction with treatment). Higher scores showed poorer constipation-related QOL.

Statistical analysis

Statistical analyses were conducted with SPSS version 26.0. Continuous variables were presented as the mean ± SD or median (interquartile range). Categorical variables were given as relative frequencies. A one-way ANOVA test was used to compare normally distributed variables while a rank-sum test was used to compare non-normally distributed variables. Fisher's exact test was adopted to analyze categorical variables. The Spearman correlation analysis was applied to find associations between clinical manifestations and three rectal sensory thresholds. And logistic regression was applied to explore related factors of RH in patients with FDD. *p*-values were corrected for multiple tests with the Bonferroni procedure. *p*-values less than 0.05 were considered statistically significant.

Results

Demographics

We enrolled 331 patients with FDD in total, of which 87 (26.3%) had at least one abnormally elevated rectal sensory threshold and 50 (15.1%) had two or three thresholds above the 95% normal upper limit. According to the latest published London Classification of anorectal function, these patients were divided into three groups (non-RH: n = 244 [73.7%]; borderline RH: n = 37 [11.2%]; and RH: n = 50 [15.1%]). Patients in the three groups were similar in BMI and constipation duration. Patients in RH and borderline RH groups were significantly older than those in the non-RH group ($p = 0.005$ and $p = 0.036$, respectively). In addition, more male patients were found in the RH group (male/female: 38/12, $p < 0.001$) compared to those in the non-RH group and borderline RH group. Detailed data are listed in Table 2.

Functional tests

Analysis of grouped data suggested that all three rectal sensory thresholds were significantly high in the RH group (*P*s < 0.001) but no difference was observed between borderline RH and RH groups (Table 3). Patients with RH showed the lowest anal relaxation rate ($p = 0.017$), especially lower than those in the non-RH group ($p = 0.013$). However, the parameters regarding anorectal pressure and pelvic coordination did not differ among the three groups (all *P*s > 0.05), which could be referred to in Table 3. As regards to BET, FDD patients with more abnormally elevated sensory thresholds were more likely to fail it, but no significant difference was seen ($p = 0.073$).

As shown in Table 4, FDD patients with RH were more likely to suffer abnormally elevated FCSV ($p = 0.008$), DDV, and MTV compared to patients with borderline RH, especially in DDV and MTV (both *P*s < 0.001), which indicated that most patients with FDD

TABLE 3 Comparisons of rectal/anal pressure, pelvic coordination and rectal sensory thresholds of patients stratified by rectal sensation in 311 patients with FDD.

HARM metrics	Non-RH (*n*=244)	Borderline RH (*n*=37)	RH (*n*=50)	*p*
Anal resting pressure (mm Hg), mean ± SD	88.67 ± 24.46	89.55 ± 20.86	85.97 ± 20.79	0.670
Maximum squeeze pressure(mm Hg), median (interquartile range)	218.35 (92.65)	227.00 (99.15)	241.05 (149.53)	0.405
Duration of sustained squeeze (s), median (interquartile range)	19.25 (9.00)	19.80 (7.80)	15.30 (14.72)	0.296
Rectal defecation pressure (mm Hg), median (interquartile range)	36.15 (23.28)	38.70 (24.35)	37.00 (42.15)	0.894
Anal residual pressure (mm Hg), median (interquartile range)	93.40 (44.67)	94.80 (52.40)	96.55 (42.55)	0.190
Anal relaxation rate(%), median (interquartile range)[a]	−4.05 (42.49)	−4.74 (47.00)	−19.58 (50.86)	0.017
RAG (mm Hg), mean ± SD	−55.14 ± 34.91	−59.30 ± 28.77	−62.16 ± 37.98	0.382
MDI, median (interquartile range)	0.40 (0.29)	0.36 (0.19)	0.38 (0.34)	0.566
Abnormal BET, *n* (%)	231 (94.67)	36 (97.30)	50 (100.00)	0.073
FCSV (mL), median (interquartile range)[b]	40.00 (20.00)	50.00 (50.00)	90.00 (70.00)	<0.001
DDV (mL), median (interquartile range)[b]	90.00 (40.00)	150.00 (115.00)	200.00 (115.00)	<0.001
MTV (mL), median (interquartile range)[b]	130.00 (70.00)	230.00 (60.00)	350.00 (170.00)	<0.001

RAG: recto-anal pressure gradient; MDI: manometric defecation index; BET: bollon expulsion test; FCSV: first constant sensation volume; DDV: defecatory desire volume; MTV: maximum tolerable volume.

[a]Anal relaxation rate of patients in RH group was significantly lower than that in Non-RH group($p = 0.013$).

[b]FCSV, DDV and MTV of patients were higher in Borderline RH and RH groups compared to those in Non-RH group ($p < 0.001$).

[a b]*p* value is defined to be a "discovery" using a Bonferroni procedure for multiple tests which controls the false discovery rate at 0.05.

TABLE 4 Comparison of the occurrence of each abnormally elevated rectal sensory threshold between Borderline RH and RH groups.

Abnormally elevated threshold	Borderline RH (*n*=37)	RH (*n*=50)	*p*
FCSV, *n* (%)	13 (35.1)	32 (64.0)	0.008
DDV, *n* (%)	17 (45.9)	50 (100)	<0.001
MTV, *n* (%)	7 (18.9)	34 (68)	<0.001

FCSV: first constant sensation volume; DDV: defecatory desire volume; MTV: maximum tolerable volume.

tended to have abnormally elevated DDV (45.9% in borderline RH group and 100% in RH group) rather than FCSV and MTV. In the RH group, nearly one-third (n = 16, 32%) of patients with FDD had three elevated rectal sensory thresholds.

There were only weak links between FCSV and anal resting pressure ($r = -0.155$, $p = 0.005$), maximum squeeze pressure ($r = -0.109$, $p = 0.047$), as well as anal residual pressure ($r = -0.148$, $p = 0.007$). No other links between rectal sensory thresholds and motility parameters were found.

Clinical manifestations

Higher score for defecation symptoms (including straining, incomplete or failed defecation, and low stool weights) in PAC-SYM ($p = 0.013$), lower score for BSFS ($p = 0.019$), greater proportion of assistance for defecation ($p = 0.003$), and higher presence of hard stool ($p < 0.001$) were reported by patients with RH (Table 5). However, no difference in GAD-7, PHQ-9, or PAC-QOL scores was shown in the three groups (all *P*s > 0.05). A weak correlation was found between defecation symptoms and mental state (GAD-7: $r = 0.329$, $p = 0.002$; PHQ-9: $r = 0.371$, $p < 0.001$). In addition, the score for defecation symptom was moderately related to PAC-QOL score ($r = 0.570$, $p < 0.001$) as well as scores for sub-scales in PAC-QOL (Physical Discomfort: $r = 0.434$, $p < 0.001$; Psychosocial Discomfort: $r = 0.50$, $p < 0.001$; and Worry/Anxiety: $r = 0.499$, $p < 0.001$).

Related factors of RH and rectal sensory thresholds

According to our findings that some variables (age, gender, hard stool, manual maneuvers, feeling incomplete evacuation, feeling anal obstruction) made statistically significant changes at the 10% level and anxiety/depression could also interact with rectal sensation (20), we included them in the logistic regression model. Logistic regression revealed that gender (male) and hard stool were closely related to the occurrence of RH (Figure 1). Furthermore, spearman correlation analysis of clinical manifestations and rectal sensory thresholds suggested that FDD patients with older age and lower BSFS score (indicating hard/lumpy stool) were more likely to suffer abnormally elevated FCSV and DDV. In addition, older patients with higher PHQ-9 scores were prone to have abnormally elevated MTV. No correlation was observed among the PAC-SYM score, SBMs, GAD-7 score, and three rectal sensory thresholds (Table 6). An increasing number of abnormally elevated thresholds suggested a linear relationship with more severe defecation symptoms in PAC-SYM ($r = 0.35$, $p = 0.001$).

TABLE 5 Constipation symptoms and defecation characteristics of 311 patients with FDD in 3 groups.

Constipation symptoms	Non-RH (*n*=244)	Borderline RH (*n*=37)	RH (*n*=50)	*p*
SBMs (times per week), median (interquartile range)	2.0 (4.0)	3.0 (4.0)	2.0 (3.0)	0.638
BSFS, median (interquartile range)[a]	2.0 (3.0)	2.0 (3.0)	1.5 (1.0)	0.019
Defecation duration, median (interquartile range)	3.0 (1.0)	3.0 (1.0)	2.0 (2.0)	0.114
<3 defecations/week, *n* (%)	140 (57.4)	17 (45.9)	30 (60)	0.367
Hard stool, *n* (%)[b]	135 (55.3)	22 (59.5)	44 (88)	<0.001
Manual maneuvers, *n* (%)	65 (26.6)	2 (5.4)	19 (38)	0.003
Straining, *n* (%)	123 (50.4)	22 (59.5)	22 (44.0)	0.362
Feeling incomplete evacuation, *n* (%)	147 (60.2)	20 (54.1)	38 (76.0)	0.065
Feeling anal obstruction, *n* (%)	78 (32.0)	5 (13.5)	16 (32)	0.069
PAC-SYM Score				
Abdominal symptoms, median (interquartile range)	1.00 (1.00)	1.00 (1.38)	0.50 (1.50)	0.523
Rectal symptoms, median (interquartile range)	0.33 (1.00)	0.33 (0.67)	0.33 (1.00)	0.277
Defecation symptoms, median (interquartile range)[c]	2.40 (1.20)	2.20 (1.20)	2.80 (0.85)	0.013
Total score, median (interquartile range)	1.50 (0.92)	1.33 (0.42)	1.42 (0.68)	0.097

SBMs: spontaneous bowel movements; BSFS: Bristol stool formation scale.
[a]The score for BSFS in RH group was significantly higher than that in Non-RH group ($p = 0.016$).
[b]More patients suffered hard stools in RH group than those in Non-RH and Borderline-RH group.
[c]The score for Defecation Symptoms in RH group was significantly higher than that in Borderline RH group ($p = 0.010$).
[a b c]*p* value is defined to be a "discovery" using a Bonferroni procedure for multiple tests which controls the false discovery rate at 0.05.

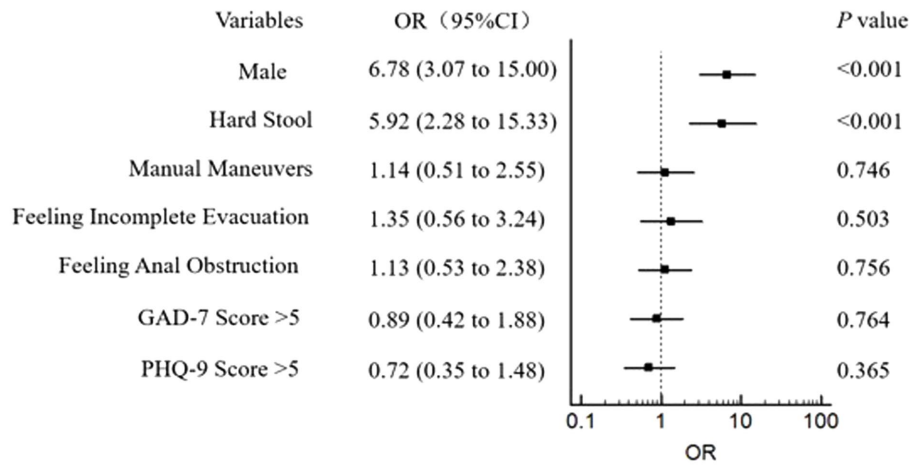

FIGURE 1
Associations between RH and gender, symptoms of constipation, and mental state in 331 patients of FDD. RH: Rectal hyposensitivity; FDD: Functional defecation disorder; GAD-7: General anxiety disorder 7-item; PHQ-9: Patient health questionnaire-9. The outcome was adjusted for the potential confounding factors: age (years), BMI, and constipation duration.

Discussion

Rectal hyposensitivity was reported in almost 25% of adult patients with chronic idiopathic constipation (21, 22). RH was associated strongly with pelvic floor dysfunction other than abnormal motility. A recently published study revealed that patients with three abnormally elevated sensory thresholds suffered almost two times as frequent defecation disorder as patients with normal rectal sensation (44.3% vs. 23.2%) (23). However, in a study that enrolled 107 patients with FC (37.4% had RH), no significant difference in RH was observed between the non-FDD and FDD groups (24). The impaired rectal sensation may be negatively associated with abnormal rectal/anal pressure and paradoxical pelvic contraction. Biofeedback therapy (BFT) is the first-line treatment for FDD but patients with RH poorly respond to it (10). Our study might help physicians identify patients with both FDD and RH timely in order to manage them more individually.

We detected RH in 50/311 (15.11%) and borderline RH in 37/331 (11.18%) of patients with FDD. More than a quarter of patients with FDD had one or more abnormally elevated sensory thresholds. This finding is consistent with an observational study where 163 of 667 constipated patients (24.4%) had one or more elevated thresholds (5). It is also suggested that there is a smaller proportion of constipated

TABLE 6 Relationship between clinical manifestations and 3 rectal sensory thresholds of 311 patients with FDD.

	FCSV (mL)		DDV (mL)		MTV (mL)	
	r	*p*	*r*	*p*	*r*	*p*
Age	0.121	0.028	0.152	0.005	0.130	0.018
SBMs	−0.053	0.333	−0.050	0.369	−0.050	0.360
BSFS	−0.176	0.001	−0.116	0.036	−0.085	0.123
Abdominal symptoms	0.028	0.606	−0.032	0.564	−0.041	0.459
Rectal symptoms	0.002	0.972	0.049	0.374	−0.043	0.436
Defecation symptoms	0.079	0.153	0.086	0.116	0.073	0.185
PAC-SYM score	0.032	0.561	0.015	0.779	−0.002	0.970
GAD-7	0.040	0.469	0.023	0.681	0.053	0.334
PHQ-9	0.019	0.737	0.055	0.320	0.122	0.026

SBMs: spontaneous bowel movements; BSFS: Bristol stool formation scale; FCSV: first constant sensation volume; DDV: defecatory desire volume; MTV: maximum tolerable volume; PAC-SYM: patient assessment of constipation symptoms; GAD-7: general anxiety disorder 7-item; PHQ-9: patient health questionnaire-9.

patients with ≥2 elevated sensory thresholds (13–17%) (23, 25). However, we did not find that patients with FDD suffered more RH than generalized constipated patients.

The underlying mechanism of how RH causes anorectal disorders is still unknown. The intact rectal sensation is fundamental to recto-anal and pelvic floor coordination (26). Some scholars hypothesize that individuals with RH have altered recto-anal reflexes and/or sensorimotor response, and the balloon volumes for inducing their rectoanal inhibitory reflex and contractile reflex were higher (27). Another study showed that patients with RH have reduced rectal wall contractility in response to distension, which likely contributes to failed defecation (28). However, we only found that the anal relaxation rate was lowest in the RH group but no difference in anorectal pressure or presence of pelvic floor disorder was observed among the three groups. As to comparisons of three rectal sensory thresholds, the presence of abnormally elevated FCSV, DDV, and MTV were all higher in patients with RH compared to those with borderline RH and non-RH, especially for DDV which was elevated in all patients with RH. We speculated that DDV might be a useful indicator for impaired rectal sensation. Only weak correlations were seen between FCSV and anal resting pressure, maximum squeeze pressure, and residual pressures, which is of limited clinical significance.

It is demonstrated that an increasing number of elevated sensory thresholds was associated with a more severe constipation phenotype (23). In our study, FDD patients with RH had more severe defecation symptoms. Meanwhile, the BSFS score was lower in these patients, indicating that they suffered from the lumpy or hard stool. The hard stool is closely related to RH in patients with FDD. Thus, more patients with RH needed manual maneuvers to help defecate. The conscious withdrawal of attention from rectal sensations or habitual suppression of the desire to defecate may contribute to impaired call to stool, which could cause rectal impaction and secondary dilatation of the rectum, leading to RH (29–31). The longer stool stays in the colon and rectum, the harder it may become, which could explain the lumpy or hard stool which patients with RH frequently have. Thus, these patients with FDD experience more severe defecation symptoms and need to use digital assistance or enema. Defecation symptom severity was correlated to QOL in these patients, which needs more attention.

We found that patients with RH were older and age was positively correlated to three rectal sensory thresholds, suggesting the decreased rectal sensation might be related to aging. Age-related impairment in the mechanoreceptors of the rectal wall and the pelvic afferent nerves might play a role in this relationship (32). A previous study by our team had a similar finding in a general functional constipation population (10). In addition, the proportion of male patients was high in the RH group. It is known that female patients are prone to constipation but most of them suffer slow transit constipation compared with male patients. A previous study found that constipated male patients were significantly more likely to suffer from defecation disorder than female patients (33). Additionally, our team has found that male patients tended to have much more paradoxical anal sphincter contraction and impaired anal sphincter relaxation (34). We speculated that male patients might have higher stress and various pressure than female patients and they are inclined to suppress the stool calling, which could lead to RH and FDD. Based on the analysis of a large patient cohort, older age and male sex were associated with higher rectal sensory thresholds (35), which agrees with our findings. However, the pathophysiological mechanism is still unknown and warranted to be explored in future studies.

The visceral sensation may be influenced by personality profile, autonomic nervous system function, and psychological phenotype (36, 37). However, little evidence has yet to be found directly in patients with RH. In our study, depression symptom was positively related to MTV, though the link is weak. But anxiety symptom was not related to any sensory threshold. The concept of the brain-gut axis is well recognized and peptide hormones (neuropeptide Y, peptide YY, glucagon-like peptide 1, etc.) released from the gut play a critical part in the interaction between the brain and digestive system (38, 39). Our results revealed that GAD-7 and PHQ-9 scores were positively related to defecation symptom severity. Patients with irritable bowel disease (IBS) (40) mostly have acute rectal feelings and psychological distress may aggravate IBS symptoms (41). It is established that anxiety can enhance visceral feelings (42, 43) but the effect of depression on sensation is controversial. According to our findings, we speculate that depression rather than anxiety plays an important role in blunt rectal sensation. However, logistic regression revealed that anxiety or depression was not related to the occurrence of RH. The association between mental state and RH in patients with FDD has been rarely studied and needs to be explored in future research.

We acknowledged that there are some limitations regarding our study. First, our study focused on patients with FDD in a single tertiary center, which unavoidably ended up with a highly selected population so the results could not be generalized to a wider primary care

population. Second, volumetric balloon distension instead of barostat was used to test patients' rectal sensory thresholds. Constipated patients with RH usually have persistent dilatation of the rectum and greater volumes will be required to stimulate the rectum (44). Thus, constipated patients with RH who have elevated volume thresholds might not have impaired rectal sensation actually. Recording pressure thresholds with barostat rather than volume thresholds is of more physiological significance (45). Nevertheless, in routine clinical practice, volumetric balloon distension is well accepted and often used (12, 46). In the future, testing rectal pressure thresholds with barostat may be a better and more rigorous method to identify RH. Finally, the link between constipation and RH is well established, but the cause–effect relationship in observational studies is still unclear. RH could lead to harder stool and more difficult defecation and long duration or severe constipation may result in a dilated rectum and abnormal rectal wall compliance which impairs rectal sensation and vice versa. Advanced prospective researches and cohort studies are in need.

This study has summarized the characteristics of FDD patients with RH by investigating symptomology, mental state, QOL, and functional tests. It is shown that patients with RH are older, more male patients, and vulnerable to suffering more severe defecation symptoms. Elevated DDV is most frequently seen in FDD patients with RH. Although abnormal motility and sensation may interact with each other and induce defecation disorder, we did not find specific links between them. Older age, gender (male), and lumpy or hard stool are related factors of RH in FDD and depression is associated with elevated MTV. The above findings may help physicians identify high-risk patients more efficiently. Thus, FDD patients with RH could get much better management in time.

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.

Ethics statement

Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

YJ and YT designed the study. YJ, YW, and MW collected and analyzed the data. YJ wrote the manuscript. YJ, YT, and LL revised the manuscript. All authors contributed to the article and approved the submitted version.

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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

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Bundles reduce anastomosis leak in patients undergoing elective colorectal surgery. A propensity score-matched study

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Background: anastomosis leak still being a handicap in colorectal surgery. Bowel mechanical preparation and oral antibiotics are not a practice recommended in many clinical practice guides. The aim is to analyse the decrease in frequency and severity of postoperative complications, mainly related to anastomotic leak, after the establishment of a bundle.
Methods: Single-center, before-after study. A bundle was implemented to reduce anastomotic leaks and their consequences. The Bundle group were matched to Pre-bundle group by propensity score matching. Mechanical bowel preparation, oral and intravenous antibiotics, inflammatory markers measure and early diagnosis algorithm were included at the bundle.
Results: The bundle group shown fewer complications, especially in Clavien Dindós Grade IV complications (2.3% vs. 6.2% $p < 0.01$), as well as a lower rate of anastomotic leakage (15.5% vs. 2.2% $p < 0.01$). A significant decrease in reinterventions, less intensive unit care admissions, a shorter hospital stay and fewer readmissions were also observed. In multivariate analysis, the application of a bundle was an anastomotic leakage protective factor (OR 0.121, $p > 0.05$)
Conclusions: The implementation of our bundle in colorectal surgery which include oral antibiotics, mechanical bowel preparation and inflammatory markers, significantly reduces morbidity adjusted to severity of complications, the anastomotic leakage rate, hospital stay and readmissions.
Register study: The study has been registered at clinicaltrials.gov Code: nct04632446.

KEYWORDS

bundle, anastomosis leakage, colorectal surgery complicatios, bowel mechanical preparation, inflammatory marker

Introduction

The safety of patients undergoing colorectal surgery has significantly improved during the past 50 years due to the progress in preoperative preparation, surgical technique and postoperative treatment. Even so, there are still postsurgical complications, with a current morbidity of close to 40% in elective surgery (1).

Among the complications of colorectal surgery, Surgical Site Infection (SSI) is the most important one, reaching up 20% (2) and represents the highest rates in all major abdominal surgery. This is probably due to the influence of Organ-Space Infection, which includes anastomosis leak (AL) and whose origin seems to differ from Incisional SSI. Organ-space

SSI alone accounts for 23% of re-hospitalizations, 60% of reoperations and 29% of admissions to Intensive Care Units (ICU), trebling hospital stay (3). The incidence of AL varies between authors, from 2 to 14% in colon surgery and from 2 to 29% in rectal surgery (4).

Due to the frequency and severity of SSI in elective colorectal surgery, specific guidelines have been prepared in order to reduce this type of complications by using bundles or a series of measures aimed at improving postoperative results. Today, there is not just one bundle, but different groups (5–7) and societies (8) who have implemented different measures succeeding in significantly reducing SSI. Mechanical bowel preparation (MBP) and oral antibiotic prophylaxis have been two of the most frequently used measures. Although there is a broad consensus that antibiotic prophylaxis is essential before colorectal surgery, there is still controversy about whether antibiotics should be administered intravenously, orally, or combined. On the other hand, the role of MBP alone or with oral antibiotics has been extensively discussed.

The purpose of this study is to evaluate the improved frequency and severity of complications and the morbidity associated with anastomosis leak after de use of a bundle in patients undergoing elective colorectal surgery.

Methods

We conducted a study before and after implementing a bundle with 5 new measures. The Pre-bundle cohort consisted of 95 consecutive patients undergoing elective colorectal surgery with anastomosis, from October 1, 2017 to May 30, 2018. The incidence of complications of these patients was recorded and their C-Reactive Protein (CRP) reference levels were obtain as a marker for early diagnosis of anastomotic dehiscence by applying the ROC curves and calculating the pathological reference value using the Youden's index (>15 mg/dl on the third postoperative day, >10 mg/dl on the fourth postoperative day and >9 mg/dl on the fifth postoperative day) (9). These values were used in the bundle for early diagnosis of complications.

The sample size of the patients in the Bundle group was calculated for a decrease in serious complications (grades IV and V of the Clavien-Dindo Classification) to 6%, having the Pre-bundle group as a reference.

The inclusion criteria were: patients over 18 years old, signed the informed consent and underwent elective colorectal surgery due to malignant or benign neoplasia with anastomosis during surgery. Patients who required transfer to another center or those with fatal evolution (death) before the third postoperative day, were excluded from the study. Finally, the Bundle group consisted of 139 patients.

The bundle consisted on preoperative and postoperative measures (Table 1) and included an algorithm for the early diagnosis of anastomosis leak (Figure 1). All our patients are assessed daily by a coloproctology unit surgeon, since the first postoperative day, and a CRP were measured ant 3rd, 4th and 5th postoperative day.

The asymptomatic patients with CRP below the calculated cut-off point were discharged on the third or fourth postoperative day. Patients with mild symptoms (such as feeding intolerance, absence of intestinal transit or abdominal discomfort) and markers within normal ranges, had another blood test performed after 24 h. Patients with serious symptoms (like fever, hemodynamic instability or peritoneal irritation signs) and normal markers had an abdominal and pelvic Computed Tomography scan (CT-scan) with double or triple contrast performed. Patients with high inflammatory markers had a CT-scan performed, whether they had symptoms or not. All the patients of the Pre-Bundle group received IV Cefminox 2gr within the hour prior to surgery and oral MBP, with sodium picosulfate.

The study was single-center. Patient selection, data collection, and later follow-up were conducted prospectively during the first 30 days after surgery. The preoperative, intraoperative and postoperative variables of all patients were collected.

Data processing and statistical analysis were performed using SPSS 24.0. In order to obtain two comparable homogeneous groups, a propensity score matching analysis was performed. Confounding variables used to set the propensity score were age, sex, Charlson index, American Society of Anaesthesiologists (ASA) classification, preoperative steroids and surgical approach. On the basis of multi-factor logistic analysis, the propensity score was calculated with a caliper width of 0.2, obtaining two groups with 84 patients in the Pre-bundle Group and 139 in the Bundle group (Figure 2). At first, a univariate analysis was performed to compare the groups by using chi-squared distribution for discrete variables (considering standardized residual in tables bigger than 2×2); and Students' t-distribution for continuous variables (using Levene's test to assess the distribution of variances). For the purpose to avoid any bias, a subgroup analysis was performed according the colon condition (benign or malignant).

In order to assess the possible prognostic factors of the severity of morbidity, ICU stay and presence of anastomosis leak, a multivariate analysis was conducted using backward stepwise logistic regression to describe the significant variables for our study.

TABLE 1 Measures implemented in the bundle.

Preoperative measures	Postoperative measures
Mechanic bowel preparation	**Regular blood tests on the 3rd, 4th and 5th postoperative day** (hemogram, venous blood gas, biochemical profile and CPR)
Oral antibiotic prophylaxis (Neomycin 1 gram and Metronidazole 1 gram in 3 doses on the day prior surgery, at 13, 14 and 23 h)	**Implementation of the algorithm for early diagnosis of AL**
Single dose intravenous antibiotic therapy (Cefminox 2 grams)	

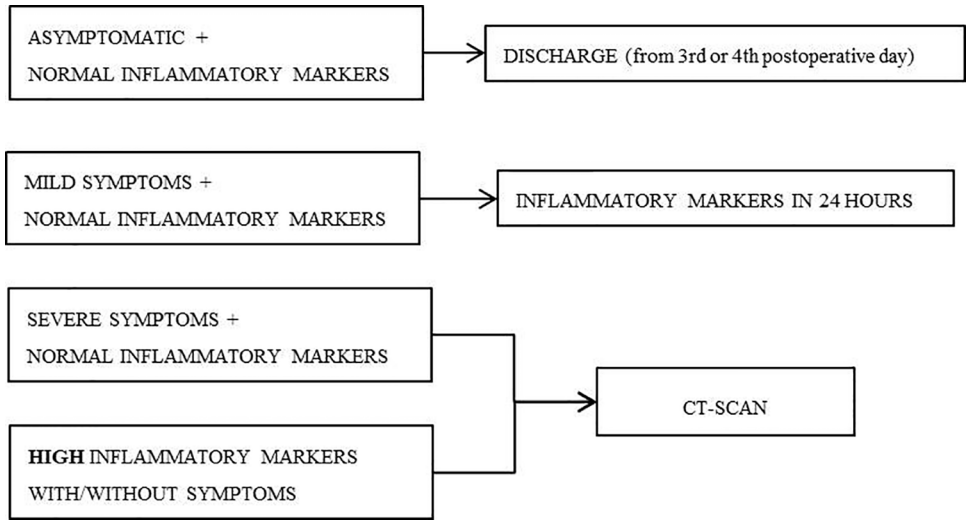

FIGURE 1
Algorithm for the early diagnosis of anastomotic leak.

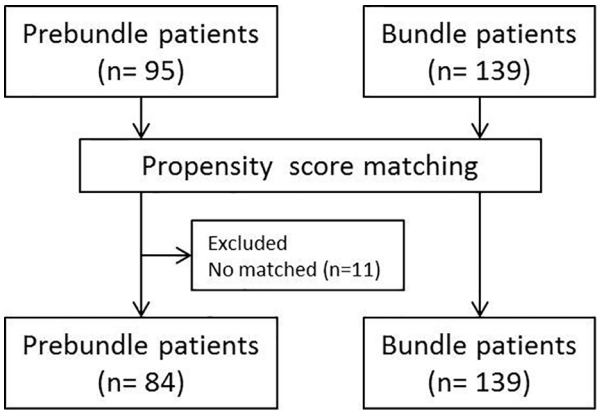

FIGURE 2
Study population and flowchart showing patient group before and after propensity score matching.

The study has been approved by the appropriate institutional ethics committee and have been performed in accordance with the ethical standards as laid down in the 1,964 Declaration of Helsinki and its later amendments or comparable ethical standards. Patients have consented to participate and to publication.

Results

The 84 patients of the Pre-bundle group were compared with a cohort of 139 patients subjected to the bundle (Bundle group), operated between March 2019 and May 2020. Adherence to the bundle was 99.3% for mechanic preparation and 95.7% for oral antibiotic prophylaxis. However, the adherence to the implementation of the diagnostic algorithm for postoperative complications was 87%.

Both groups were homogeneous (sex, age and BMI, among others), although the Bundle group presented with higher Charlson Index (Table 2). Both were also homogeneous regarding surgical approach, procedure, surgical team, ostomy confection, metastasis, carcinomatosis and Possum score (Table 3).

The percentage of patients who presented with complications in the Bundle group was lower than in the Pre-bundle group (34.5% vs. 46.4%), without reaching statistical significance, but when analyzing the distribution of the complications according to their gravity, we observed that the Bundle group mainly presented with mild complications, grade I of Clavien-Dindo classification (77% vs. 20.5% $p = 0.001$), whereas in the Pre-bundle group the rate of severe complications, grade IV of Clavien-Dindo classification, was significantly higher (23% vs. 6.2%, $p = 0.001$). Moreover, the incidences of Organ-space SSI (and therefore of AL), acute respiratory failure and dynamic ileus were lower in the Bundle group, $p < 0.05$. Mortality was similar in both series (2.4% in the Pre-bundle group vs. 2.1% in the Bundle group) (Table 4).

Hospital stay for the Bundle group was shorter (6.3 vs. 11.4 days, $p = 0.001$), as well as the need for ICU (4.3% vs. 15.5%, $p = 0.004$), the re-hospitalization rate (4.3% vs. 13.1%, $p = 0.017$) and the need for imaging tests during the postoperative period, despite complying with the diagnostic algorithm (15.1% vs. 29.8%, $p = 0.009$), were significantly lower (Table 5).

On the other hand, the laparoscopic approach was associated with less incidence of complications (18.8% vs. 47.5%, $p = 0.001$) and of severe complications (grades IV and V of Clavien-Dindo classification) than open surgery (4.1% vs. 11.9%, $p = 0.001$). However, these differences were not significant regarding AL, whose incidence was similar in both approaches (Table 6).

When analyzing the variables of the subgroups according to the condition (benign vs. malignant), we have obtained that both are also homogeneous with no differences in the preoperative and operative variables. Moreover, the morbidity, mortality, all

TABLE 2 Univariate descriptive analysis of the preoperative variables comparing both groups.

		Pre-bundle	Bundle	*p*
Total patients		84	139	N/A
Sex	Male	56 (66.7%)	86 (61.9%)	0.471
	Female	28 (33,3%)	53 (38.1%)	
Age (years)		64,65 (±13.8)	64,51 (±14.6)	0.940
Charlson Index		**3.06 (±1.9)**	**4.43 (±2.7)**	**0.001**
BMI (kg/m2)		27.25 (±5.0)	27.66 (±4.6)	0.538
Albumin levels (g/dl)		4.22 (±0.48)	4.26 (±0.56)	0.608
ASA	I	9 (10.7%)	5 (3.6%)	0,102
	II	50 (59.5%)	82 (59%)	
	III	24 (28.6%)	46 (33.1%)	
	IV	1 (1.2%)	6 (4.3%)	
Smoking		15 (17.9%)	38 (27.3%)	0.107
Corticotherapy		1 (1,2%)	2 (1.4%)	0.876
Neoadjuvant therapy		4 (5.3%)	6 (5.6%)	0.966
Diagnosis	Colon neoplasia	59 (62.4%)	85 (61.2%)	0.128
	Rectal neoplasia	16 (19%)	22 (15.8%)	
	Sigmoid volvulus	0	2 (1.4%)	
	Reconstruction after Hartmann procedure	1 (1.2%)	7 (5%)	
	FAP	3 (3.2%)	0	
	Diverticular disease	4 (4.8%)	18 (12.9%)	
	Inflammatory disease	1 (1.2%)	5 (3.7%)	
Stage (T)	Tis-T2	33 (43.4%)	58 (54.2%)	0.303
	T3	35 (46.1%)	42 (39.3%)	
	T4	8 (10.5%)	7 (6.5%)	

N, number of patients; *p*, statistical significance; N/A, not applicable; ASA, American society of anesthesiologists; FAP, familial adenomatous polyposis; T, tumor size according to TNM staging for colorectal cancer; Tis, carcinoma *in situ*.

TABLE 3 Comparative analysis of the intraoperative variables.

		Pre-bundle	Bundle	*p*
Approach	Open surgery	44 (52.4%)	57 (41%)	0.098
	Laparoscopy	40 (47.6%)	82 (59%)	
Procedure	Right hemicolectomy	36 (42.9%)	55 (39.6%)	0.301
	Left hemicolectomy /Sigmoidectomy	26 (31%)	49 (35.4%)	
	Low anterior resection	17 (20.2%)	22 (15.8%)	
	Subtotal colectomy	4 (4.8%)	3 (2.2%)	
	Bowel transit reconstruction	1 (1.2%)	8 (5.8%)	
	Segmental resection	0 (0%)	2 (1.2%)	
POSSUM score		10.9 (±1.4)	10.95 (±1.2)	0.176
Surgeon	Colorectal	71 (84.5%)	123 (88.5%)	0.394
	General	13 (15.5%)	16 (11.5%)	
Protective stoma		15 (17.9%)	18 (12.9%)	0.317
Carcinomatosis		1 (1.2%)	0 (0%)	0.197
Liver metastasis		6 (7.1%)	6 (4.3%)	0.365

N, number of patients; p, statistical significance.

complications and postoperative results were similar to the overall series both in benign and malignant subgroups.

The multivariate analysis included the variables related to AL occurrence: sex, age, ASA, Charlson Index, BMI, surgical approach and bundle implementation. The bundle itself was a protective factor for AL occurrence [OR 0.121,—CI 95% (0.033–0.446)]. Moreover, male sex was associated with a significantly higher risk of AL (OR 9.350, CI 95% 1.190–73.488).

Discussion

Due to the high risk and repercussion of SSI and AL in colorectal surgery, many have been the strategies used throughout history to try to reduce them. In 1934, Poth (10) concluded that MBP on its own did not succeed in reducing the bacterial content in the colon; therefore, oral non-absorbable antibiotics were introduced (11, 12). Later on, with the detection of anaerobic microorganisms in the colon (13), an anaerobicidal agent, such as metronidazole, was added to neomycin, which, in combination with MBP, succeeded in reducing aerobic and anaerobic bacteria outgrowth in the sample (14), and reduced the incidence of SSI and AL (15), thus consolidating the principles of bowel preparation.

This trend has continued in the United States and Canada since the 80s (5–7, 16–31) with good results regarding SSI decrease. But this is not the case in Europe (32–36), where the ERAS® program (37) and the guidelines of the British National Institution of Health and Clinical Excellence 2008 (38) reject MBP and advocate the superiority of intravenous prophylaxis for SSI prevention, reporting an increased incidence of pseudomembranous colitis and antibiotic resistance associated with oral prophylaxis (39).

Due to the high morbidity resulting from the AL and the disparity of the results of the published works regarding how to avoid it, we decided to monitor the complication rate in our unit, which resulted in an incidence of infection of the surgical wound (superficial and deep) of 2.4% and an AL rate of 15.5%. Not only the overall incidence of complications but also their grade of severity was high, with 23% of grade IV complications according to Clavien-Dindo classification and 5.1% of grade V. Moreover, the mean hospital stay was 11 days with 13.1% of re-hospitalizations. After being aware of these figures, we created a bundle that allowed for decreasing

TABLE 4 Comparative analysis of postoperative complications.

		Pre-bundle	Bundle	*p*
Overall morbidity		39 (46.4%)	48 (34.5%)	0.07
Mortality		2 (2.4%)	3 (2.1%)	0.635
Clavien-Dindoa	I	8 (20.5%)	37 (77%)	**0.001***
	II	17 (43,6%)	3 (6.2%)	
	III	3 (7.7%)	2 (4.1%)	
	IV	9 (23%)	3 (6.2%)	
	V	2 (5.1%)	3 (6.2%)	
Type of complication	Surgical wound infection (superficial and deep SSI)	2 (2.4%)	7 (5%)	0.362
	Organ-space SSI	14 (16.7%)	5 (3.6%)	**0.001***
	Anastomotic dehiscence	13 (15.5%)	3 (2.2%)	**0.001***
	Hemoperitoneum	6 (7.1%)	3 (2.2%)	0.067
	Lower gastrointestinal bleeding	5 (6%)	5 (3.6%)	0.536
	Intestinal ischemia	1 (1.2%)	0 (0%)	0.197
	Acute renal failure	6 (7.1%)	6 (4.3%)	0.365
	Acute respiratory failure	7 (8.3%)	3 (2.2%)	**0.031***
	Febrile illness	15 (17.9%)	22 (15.8%)	**0.693**
	Postoperative adynamic ileum	27 (32.1%)	22 (15.8%)	**0.004***
	Phlebitis	1 (1%)	9 (6.5%)	**0.001***

N, number of patients, P, statistical significance, SSI, surgical site infection.
[a]Calculated based on patients with complications.

TABLE 5 Comparative analysis of reoperations, re-hospitalizations, ICU management and stay.

	Pre-bundle	Bundle	*p*
Reoperation	11 (13.1%)	5 (3.6%)	**0.008***
CT-scan after surgery	25 (29.8%)	21 (15.1%)	**0.009***
ICU management	13 (15.5%)	6 (4.3%)	**0.004***
Re-hospitalization	11 (13.1%)	6 (4.3%)	**0.017***
Hospital stay	11.4 (±10.42)	6.3 (±4.17)	**0.001***

N, number of patients; p, statistical significance; CT-scan, computed tomography scan; ICU, intensive care unit.

the incidence of such complications and reducing their severity and repercussion on the patient.

With the implementation of the new bundle, we obtained a decrease in morbidity from 46.4% to 34.5%, although without reaching significant values. However, the severity of complications did change considerably in both groups. Most of the complications in the Bundle group were grade I of Clavien-Dindo classification (77% vs. 20.5% in the Pre-bundle group), and grade IV complications of Clavien-Dindo classification were significantly higher in the Pre-bundle group (23% vs. 6.2% in the Bundle group). Therefore, we can say that the implementation of the new measures drastically reduced the severe complications of elective colorectal surgery. The most relevant difference was the incidence of organ-space infection (16.7% to 3.6%) and particularly the incidence of anastomosis leak, which significantly decreased from 15.5% to 2.2% in the Bundle group ($p = 0.001$).

TABLE 6 Comparative analysis of the approach in relation to the postoperative complications and their seriousness.

		Open surgery	Laparoscopy	*p*
No complications		**45 (44.6%)**	**91 (74.6%)**	**0.001***
Complications other than AL		**48 (47.5%)**	**23 (18.8%)**	
AL		8 (7.9%)	8 (6.6%)	
Seriousness of complications (Clavien-Dindo)	Grades 0-III	**89 (88.2%)**	**117 (95.9%)**	**0.001***
	Grades IV–V	**12 (11.9%)**	**5 (4.1%)**	

p, statistical significance; AL, Anastomosis leak.

Other authors have published similar results on the decrease of SSI after the implementation of bundles. Lutfiya et al. (5) who, after implementing the measures of the American College of Surgeons "ACS NSQIP" (8), obtained a decrease in overall SSI at the expense of superficial and deep incisional infection (21.15% to 6.67%, $p = 0.001$). Weiser et al. (40) in 2018 conducted a study before and after the implementation of a bundle, in which they divided the patients according to their risk of SSI. The incidence of SSI decreased from 11% to 4.1% at the expense of the groups with intermediate or high risk of SSI. These differences were significant in the superficial and deep incisional infections. A much smaller range of measures than "ACS NSQIP" (8) was implemented in our study, thus facilitating compliance (7).

Studies such as Gorgun et al. (22) also found a decrease in overall SSI when implementing their bundle (11.8% to 6.6%, $p = 0.001$), associated with decreased organ-space infection (5.5% vs. 1.7%, $p = 0.001$). Likewise, Mulder et al. (24) also succeeded in significantly reducing overall SSI and AL, thus reducing hospital stay from 8 to 7 days. Like in our study, a laparoscopic approach was most frequently used in the group after the bundle implementation. In this line, we also observed that a laparoscopic approach yielded a lower complication rate, particularly severe complications (grade IV and V of Clavien-Dindo classification), than an open approach (4.1%vs.11.9%). It is worth noting that Mulder et al. administered oral antibiotic prophylaxis and intravenous prophylaxis, without mechanical bowel preparation. In our study, we opted for a combination of antibiotics and MBP

because we found little evidence in favor of the use of oral antibiotics without mechanical bowel preparation. Hoang et al. (23) also implemented a bundle including mechanical preparation and dual antibiotic therapy together, which resulted in a significant decrease in overall SSI. We found striking that Hoang's study included patients undergoing emergency surgeries, in which cases it is difficult to administer mechanical bowel preparation and oral antibiotic therapy.

In our study, besides the decreased infectious complications, there was also a significant decrease in other medical complications such as respiratory failure (8.3%vs.2.2%) and adynamic ileus (32.1%to15.8%). Other studies obtained similar results (25, 28), as opposed to the ERAS® protocols (37), which recommended against mechanical preparation because they considered that it provided no benefits but posed a greater risk of paralytic ileum after surgery.

In addition to trying to reduce SSI with preoperative measures, we included in our bundle some postoperative measures that allowed us for an early diagnosis of severe intra-abdominal infectious complications. After confirming the usefulness of CRP as a biologic marker for the early diagnosis of AL in the Pre-bundle group, we created an algorithm to facilitate the early detection of this complication and proceed accordingly, and to be able to early and safely discharge those patients who had that marker below the pre-established values.

Although we performed CT-scan based mostly on the results of blood tests, the number of them performed was significantly lower than in the Pre-bundle group (29.8% vs. 15.1%); therefore, our measures not only do they decreases the AL rate but allowed for a better selection of patients who required a CT-scan during the postoperative period also. Besides, we succeeded in significantly reducing the number of reoperations from 13.1% to 3.6% ($p = 0.008$), the need of ICU management from 15.5% to 4.3% ($p = 0.004$) and re-hospitalizations from 13.1% to 4.3% ($p = 0.017$), which resulted in a 5-day decrease in hospital stays (11 vs. 6 days $p = 0.001$). These results show that the implementation of a bundle also decrease healthcare costs. Other studies such as the one by Keenan et al. (6) show similar results.

In our study, after conducting the multivariate comparative analysis, we found that the implementation of our bundle proved to be a protective factor from the most important complication in colorectal surgery.

Limitations

A potential limitation of our study is to be a before-after, single-centre study, rather than a randomized and multicenter one which would provide more reliable results. A larger sample size would have allowed to find more relations between risk factors and complications. Finally, it is a heterogeneous sample, since it encompasses a range of pathologies in colorectal surgery as colorectal cancer, diverticulosis and inflammatory disease, but we wanted to have a clinically representative population sample.

Conclusions

The implementation of our bundle significantly reduces morbidity adjusted to the severity of complications, the AL rate, hospital stay and re-hospitalizations.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository and accession number can be found below: 10.6084/m9.figshare.17009111&lt.

Ethics statement

The studies involving human participants were reviewed and approved by CEI-CEIm Hospital General Universitario José María Morales Meseguer. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All the authors have contributed substantially to the design of the study, acquisition, analysis and interpretation of data. Likewise, everyone has revised critically the draft and approval the final document. Specifically: BM, VN, PF and AA: have designed the study. BM, SA, MB, GM and BB: have collect all the data. BM and VN: have made the statistical analysis. All the authors have analyzed and interpreted the data, discussed the results and approved the paper. All authors contributed to the article and approved the submitted version.

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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.

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Safety and efficacy of Levorag emulgel in the treatment of anal fissures using a validated scoring system

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Introduction: Anal fissure is one of the most common anal disease characterized by intense anal pain, and deterioration of patients quality of life. Treatment is mainly based on the topical administration of calcium antagonist or nitric oxide ointments, and in cases refractory to medical treatment patients can undergo surgery. This study aims to assess the efficacy and safety of Levorag emulgel in the treatment of acute and chronic fissures using of a validated scoring system.
Material and Methods: A prospective observational study was carried out on patients with anal fissures between February and May 2022. The efficacy of the treatment was evaluated using the REALISE score, a new validated scoring system that rates VAS for pain, NSAID use, pain duration, bleeding, and quality of life (QoL), recorded after 10, 20 and 30 days from the beginning of treatment.
Results: Forty patients (median age 46 years, IQR 29–57, 70% women) with acute (22, 55%) or chronic (18, 45%) anal fissures entered the study. The median anal pain score according to the VAS scale decreased significantly from 7 (IQR 4.7–8) at baseline to 1 (IQR 0–3.2, $p = 0.05$) after 20 days. At the 30-day proctological examination, 22 patients (61%) were pain free (median VAS of 0, IQR 0–1.2, $p < 0.05$). Pain duration after defecation measured according to the REALISE score, showed a significant decrease after 10 days, from a median value of 2 (IQR 1–4) to 1 (IQR 1–1.2) ($p < 0.005$). The median value of the REALISE score decreased significantly, from 15 (IQR 11–19.25) at first proctological evaluation to 4 (IQR 4–6, $p = 0.139$) after 30 days of treatment. At day 30, complete fissure healing was achieved in 30 patients (80%). The healing rate was 82% and 78% in patients with acute and chronic anal fissures, respectively.
Conclusion: The use of Levorag® Emulgel may represent a safe and effective non-invasive first line treatment in patients affected by acute or chronic anal fissure.

KEYWORDS
anal fissure, topical treatment, anal pain, scoring system, healing

Introduction

Anal fissure (AF) is one of the most common anal disease characterized by intense and prolonged anal pain after defecation, bleeding, and considerable deterioration of patient's quality of life (1). AF is often caused by the passage of hard stools or prolonged diarrhea (2). Spontaneous healing rarely occur because the reactive spastic contraction of the internal anal sphincter, decreases blood flow to the affected area (1–4). In fact, treatment strategies aim to reduce this uncontrolled spasm, using topical creams based on calcium antagonists (such as diltiazem) or nitric oxide donors (such as glycerin trinitrate) (5, 6)

or by injections of botulinum toxin A (7) allowing restoration of blood flow to the anoderm (8) and to facilitate evacuation by using stool softeners.

When conservative treatments fail, surgical options including internal anal sphincterotomy, anal advancement flap, and anal stretch/dilation may be considered (9, 10).

None of these medical treatments are completely free from side effects such as headaches, migraines, and pruritus ani, while surgical approach can cause bleeding, abscesses, fistulas, and considerable risk of fecal incontinence (11–13).

This study aims to evaluate the safety and effectiveness of Levorag® Emulgel, a topical ointment which favors pain relief, microperfusion of the anoderm and the reepithelization process (11, 14), in the treatment of acute and chronic anal fissures assessed by a new validated scoring system.

Material and methods

A prospective observational study was carried out in a tertiary proctology unit on patients with anal fissures between February and May 2022. After receiving approval from the local ethics committee, patients of both sexes aged 18 to 85 years with acute or chronic anal fissures were enrolled. Exclusion criteria included previous medical or surgical treatment, perianal Crohn's disease, previous anorectal operations, prolapsed hemorrhoids, rectal prolapse, functional disorders of the defecation and continence, and pregnancy. Acute fissures were defined as recent (within 6 weeks) ulcerations of the anoderm, while chronic anal fissures persisted for more than 6 weeks, with sentinel tags and/or induration of the lateral margins of the fissure and/or exposure of the internal anal sphincter. Demographic data and detailed clinical histories were recorded, including information about anal pain intensity and duration, bowel habits, and stool consistency (using the Bristol stool scale) (15) before treatment. Patients were examined in the Sims position. The anal verge was inspected to confirm the presence of the anal fissure and to determine its location. When tolerated, digitorectal examination (DRE) to evaluate the anal sphincter tone and anoscopy were performed. Eligible patients received three boxes of Levorag® Emulgel (THD, SpA, Coreggio, RE, Italy), a topical ointment containing a Hibiscus plant extract called myoxinol with a botox-like effect, and carboxymethyl glucan, a yeast polysaccharide with immune-stimulating properties, for use in the conservative treatment of anal fissures. Each box contained twenty 3.5 ml single-dose tubes. Patients were instructed to apply the ointment twice a day (every 12 h) for 30 days using the tip of their finger. Stool softeners were administered in case of constipation. The efficacy of the treatment was evaluated using the REALISE score, a new validated scoring system that rates VAS for pain, NSAID use, pain duration, bleeding, and quality of life (QoL) (16). The score was calculated during the first clinical evaluation, at day 10 and 20 by a telephone interview (17, 18), and at day 30 by an outpatient evaluation. Side effects were recorded. The degree of re-epithelization (healing) was evaluated and scored as follows: 0 = anal fissure still present, 1 = superficial fissure, 2 = partial re-epithelization, 3 = complete re-epithelization. Patient satisfaction was rated on a scale of 0 (failure) to 5 (excellent).

Statistical analysis

Continuous parameters were reported as median and interquartile ranges. Categorical variables were recorded as numbers and percentages. Comparisons of categorical variables were performed by the Chi-square and Fisher's Exact test, where appropriate. Comparisons between groups were made by the Mann-Whitney U test. A p value < 0.05 was considered statistically significant. Statistical analysis was carried out using RStudio (R version 4.0.3 (2020-10-10) Copyright (C) 2020 The R Foundation for Statistical Computing).

Results

Forty patients (median age 46 years, IQR 29–57, 70% women) with acute (22, 55%) or chronic (18, 45%) anal fissures entered the study after giving an oral informed consent.

Thirty-six patients (12 males, median age 52 years, IQR 28–57, and 24 females, median age 45 years, IQR 29–56) completed both telephone interviews and a proctological evaluation at day 30. Four out of forty patients (10%) who did not complete the follow-up, underwent internal anal sphincterotomy (1 patient) and calcium antagonist-based ointments 10 days after the first consultation (3 patients). Previous pregnancies were reported by 14 women (58%) (Table 1). Four patients (11%) had an anterior anal fissure. digital rectal examination (DRE) was not tolerated at the first consultation by 10 patients (28%). The median anal pain score according to the visual analogue scale (VAS) was 7 (IQR 4.7–8) at baseline, and decreased to 3 (IQR 1–5, $p < 0.005$) 10 days later and to 1 (IQR 0–3.2, $p = 0.05$) after 20 days. At the 30-day proctological examination, 22 patients (61%) were pain free (median VAS of 0, IQR 0–1.2, $p < 0.05$). Pain duration after defecation measured according to the REALISE score, showed a significant decrease after 10 days, from a median value of 2 (IQR 1–4) to 1 (IQR 1–1.2) ($p < 0.005$). This score did not change after 20 and 30 days (median value 1, IQR 1–1, $p = 0.23$). With regard

TABLE 1 Demographic characteristics of patients included in the study.

	$n = 36$
Gender	
- M	12 (33%)
- F	24 (67%)
Pregnancy	
- 0	10 42%
- 1	25%
- 2	7 29%
- 3	1 4%
Type of fissure	
- Acute	22 (61%)
- Chronic	14 (39%)

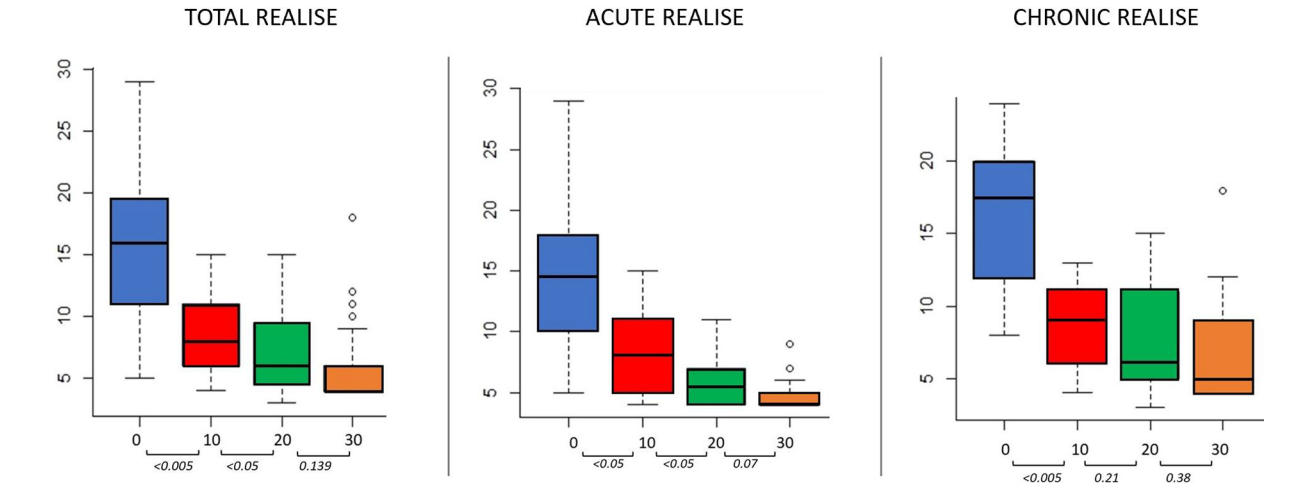

FIGURE 1
REALISE score at the baseline, 10–20 and 30 days from the start of treatment.

to bowel habits at the first evaluation, 8 patients (22%) had stool type 2 according to the Bristol stool scale, while 24 (67%) and 4 (11%) patients had type 3 and 6, respectively. The median value of the REALISE score at the first clinical evaluation was 15 (IQR 11–19.25) with a significant reduction at 10 days to 8 (IQR 6–11, $p < 0.005$). At 20 days, a median value of 6 (IQR 4.75–6.25, $p < 0.05$) was recorded. Between 20 and 30 days after the onset of treatment, the score decreased to 4 (IQR 4–6, $p = 0.139$) (Figure 1). At day 30, complete fissure healing was achieved in 30 patients (80%). One patient still had a chronic anal fissure at 30 days follow-up. Partial healing with complete symptoms remission was recorded in 5 patients. The healing rate was 82% and 78% in patients with acute and chronic anal fissures, respectively. At the last consultation, satisfaction was scored as 5 (extremely satisfied) by 25 patients, 4 (satisfied) by 7 patients, 3 (moderately satisfied) by 2 patients, 2 (not satisfied) by 1 patient and 1 (completely not satisfied) by the last one. Eight patients complained of pruritus ani during the first examination, with complete relief 20 days after. No other adverse events were recorded. All domains of the REALISE score are reported in Table 2.

TABLE 2 RALISE domains at the baseline, 10-20 and 30 days from the start of treatment.

	First evaluation	10 days	20 days	30 days
VAS	7 (4.75–8)	3 (1–5)	1 (0–3.25)	0 (0–1.25)
		$p < 0.005$	$p = 0.05$	$p < 0.05$
Pain duration	2 (1–4)	1 (1–1.25)	1 (1–1)	1 (1–1)
		$p < 0.005$	$p = 0.239$	$p = 0.239$
NSAID use				
- Never	25 (69.5%)	33 (92%)	34 (94%)	34 (94%)
- Rarely	6 (16.5%)	3 (8%)	1 (3%)	1 (3%)
- Sometimes	2 (5.5%)	0	1 (3%)	0 (3%)
- Often	2 (5.5%)	0	0	1
- Alwalys	1 (3%)	0	0	0
		$p < 0.005$	$p = 0.05$	$p < 0.05$
Bleeding				
- Never	14 (39%)	28 (78%)	32 (89%)	31 (86%)
- Rarely	11 (31%)	8 (22%)	4 (11%)	4 (11%)
- Sometimes	6 (16.5%)	0	0	0
- Often	3 (8%)	0	0	1 (3%)
- Alwalys	2 (5.5%)	0	0	0
		$p < 0.005$	$p = 0.21$	$p = 0.54$
QoL				
- No impact	4 (11%)	10 (28%)	21 (58%)	26 (72.5%)
- Slightly	5 (14.5%)	13 (36%)	11 (31%)	6 (16.5%)
- Moderately	8 (22%)	12 (33%)	4 (11%)	3 (8%)
- Considerably	16 (44.5%)	1 (3%)	0	1 (3%)
- Severely	3 (8%)	0	0	0
		$p < 0.005$	$p < 0.005$	$p = 0.64$
REALISE	15 (11–19.25)	8 (6–11)	6 (4.75–9.25)	4 (4–6)
		$p < 0.005$	$p < 0.05$	$p = 0.139$

Discussion

Non-operative management is the first-line approach for treating anal fissures, as it can provide relief the associated anal spasm with pain decreases and healing of the fissure in about 60 to 80% of the cases (19).

A recent survey among gastrointestinal surgeons in the Netherlands reported that initial treatment consists of conservative measures including administration of fibers/laxatives and topical ointments (20).

In the past few decades, several topical ointments have been proposed as non-invasive treatments for anal fissures. Currently, the Association of Coloproctologists of Great Britain and Ireland recommends diltiazem as first-line treatment for chronic anal fissures (21) with a healing rate of 52.3% after 8 weeks, because of its lower side effect (22), despite the use of topical nitrate has showed a higher healing rate (63.6%). However, in a recent randomized clinical trial on patients affected by chronic anal fissures, glyceryl trinitrate ointment resulted less effective than tocopherol acetate in the reduction of anal pain and in term of healing and recurrence rate 16 weeks after finishing the treatment (23).

Botulinum toxin can also be used as conservative treatment being more effective than nitrates and calcium channel blockers even if but the local injection is painful and its effect is temporary (7).

In this study, the administration of Levorag® Emulgel, a topical ointment with natural anti-inflammatory agents, botox-like effect, and immune-stimulating properties, resulted in complete healing in 80% of patients with acute or chronic anal fissures. These results are in agreement with data published by Digennaro et al. (11) who reported an efficacy of 89.4% in acute and 62.8% in chronic anal fissures in their prospective multicenter observational trial on 265 patients.

Nordholm-Cartensen et al. (24) reported a healing rate of 52% in a randomized clinical trial of patients with chronic anal fissures, although the number of patients in the Levorag group (26 patients) was smaller than the estimated sample size and the study's power was only 70%. Furthermore, the RCT did not provide a clear definition of "fissure healing."

A preliminary study by Giordano et al. (25) on the use of Levorag in patients with chronic anal fissures, reported a healing rate of 84% with over 85% of bleeding control after 40 days of treatment. Our study confirms these results, but the Levorag ointment was administered for only 30 days. In addition, our data showed a significant reduction of pain after 10 days of treatment (7 vs. 3 on the median VAS), with a slow but progressive pain reduction in the follow-up. Furthermore, the introduction of a validated score to assess the severity of the fissure, makes the evaluation of our results more objective and measurable.

In our analysis, the healing rate was higher than other medical treatments using topical ointments, however the small sample size and the inclusion of acute anal fissures may limit the reliability of the study. Other limitations of this study are the lack of a control group and the use of only the Bristol scale to evaluate bowel habit.

In conclusion the use of Levorag® Emulgel may represent a safe and effective non-invasive first line treatment in patients affected by acute or chronic anal fissure. Multicenter prospective randomized studies with long-term follow-up are expected to confirm our results.

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 Comitato Etico Indipendente Azienda Ospedaliero-Universitaria consorziale Policlinico. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GT, AD, MR and AP, all contributed equally to this study in terms of contributions to the conception and design of the research project; acquisition, analysis, and interpretation of data for the study; drafting and revising the project critically; final approval of the version to be published. DFA and CG contributed equally to this study Drafting the work and revising it critically for important intellectual content. MDF and GM: Substantial contributions to the conception and design of the study; acquisition, analysis, and interpretation of data for the work; Final approval of the version to be published. 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.

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Analgesic effect of subcutaneous injection of different concentrations of methylene blue after hemorrhoidectomy: A retrospective study

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Objective: Subcutaneous injection of methylene blue around the anus may help reduce postoperative pain. However, the concentration of methylene blue is still controversial. Therefore, Our study aims to investigate the efficacy and safety of different methylene blue injected concentrations subcutaneously in pain treatment after hemorrhoidectomy.

Methods: A total of 180 consecutive patients with grade III or IV hemorrhoids from March 2020 to December 2021 were reviewed. All patients underwent hemorrhoidectomy under spinal anesthesia and were divided into three groups. Group A received subcutaneous injection of 0.1% methylene blue after hemorrhoidectomy, group B received subcutaneous injection of 0.2% methylene blue, and Group C did not received subcutaneous injection of methylene blue. The primary outcome measures were the visual analog scale (VAS) pain score on postoperative days 1, 2, 3, 7, 14, and total analgesic consumption within 14 days. Secondary outcomes were complications after hemorrhoidectomy, including acute urinary retention, secondary bleeding, perianal incision edema, and perianal skin infection, and the Wexner scores used to assess the level of anal incontinence at one and three months after surgery.

Results: There was no significant difference among three groups in sex, age, course of the disease, hemorrhoid grade and the number of incisions, and there was no significant difference in the volume of methylene blue injected between group A and group B. The VAS pain score and total analgesics consumption within 14 days in group A and group B were significantly lower than those in group C, but the differences between group A and group B were not statistically significant. The Wexner scores of group B were significantly higher than those of group A and group C one month after the operation, but the differences between group A and group C were not statistically significant. In addition, the Wexner score among three groups decreased to zero at three months after operation. There was no significant difference in the incidence of other complications among three groups.

Conclusion: The perianal injection of 0.1% methylene blue and 0.2% methylene blue have a similar analgesic effect in pain treatment after hemorrhoidectomy, but 0.1% methylene blue has higher safety.

KEYWORDS

subcutaneous injection, methylene blue, different concentrations, postoperative pain, hemorrhoidectomy

Introduction

Hemorrhoids are one of the most common anorectal diseases. According to the results of an epidemiological survey on common anorectal diseases of urban residents conducted in China from 2013 to 2014, the adults who reported having anorectal diseases accounted for 51.14% of the total survey population, and the incidence rate of hemorrhoids among anorectal diseases was the highest (50.28%) (1) Hemorrhoidectomy is generally advocated for patients with grade III or IV hemorrhoids (2). However, postoperative incision pain is very common and becomes an important reason for patients to refuse surgery (3). Postoperative pain reduces patients' acceptance and satisfaction with surgery, affecting wound healing and increasing hospitalization time and expenses.

In clinical practice, oral or intravenous opioids, nonsteroidal anti-inflammatory drugs, and other multimodal analgesia are often used to treat pain after hemorrhoidectomy (4), but many patients still feel obvious pain after surgery (5). Methylene blue can prevent nerve conduction and has strong analgesic, anti-inflammatory, and neurophilic properties (6). In recent years, methylene blue has been used to treat post-hemorrhoidectomy pain (7), postherpetic neuralgia (8), intractable anal pruritus (9), and other diseases. However, the concentration of methylene blue is still not uniform (6–9). There have been few reports on the effects of different concentrations of methylene blue on hemorrhoidectomy pain. Therefore, this retrospective study aimed to evaluate the efficacy and safety of subcutaneous injection of methylene blue at different concentrations for pain treatment after hemorrhoidectomy.

Materials and methods

Participants

This was a single-center retrospective study. We followed the retrospective observational study design. The ethics committee approved this study at the Affiliated Hospital of Southwest Medical University. We reviewed consecutive patients who underwent hemorrhoidectomy under spinal anesthesia. The same surgical team performed surgery from March 2020 to December 2021, and data from the electronic medical record system and prescription records were collected. The inclusion criteria were 18–65 years old, diagnosed with mixed hemorrhoids, grade III/IV hemorrhoids (Goligher's classification), and underwent hemorrhoidectomy under spinal anesthesia. The exclusion criteria included the following: concurrent additional anorectal diseases (e.g., perianal abscess, anal fistula, anal incontinence); a history of cardiac insufficiency; hepatic insufficiency; renal insufficiency; diabetes mellitus; coagulation disorders; peptic ulcer disease; incomplete perioperative clinical data.

Methods

We reviewed a total of 180 patients who underwent hemorrhoidectomy under spinal anesthesia. The operations were performed by colorectal surgeons with senior professional titles according to standard techniques described by Milligan and Morgan (10). After the hemorrhoidectomy, 0.1% or 0.2% methylene blue was injected subcutaneously with a skin test needle at the edge of the perianal incision in Group A($n = 60$) and Group B ($n = 60$), while Group C ($n = 60$) did not received subcutaneous injection of methylene blue. Group A received 0.1% methylene blue subcutaneously (1% methylene blue 1 ml + 0.1% ropivacaine 4 ml + 0.9% saline 5 ml) and group B received 0.2% methylene blue subcutaneously (1% methylene blue 2 ml + 0.1% ropivacaine 4 ml + 0.9% saline 4 ml). The total volume of injection was not more than 10 ml. Methylene blue was injected from the distal end of the incision to the level of the dentate line (**Figure 1A**). Methylene blue was injected with a 26-gauge needle from the distal end of the wound into the level of the dentate line. The injection site includes the cutaneous margins of the wound and the bed of the wound. The injection depth should not be too deep or too shallow to prevent the drug from entering the muscle or penetrating the skin. The standard was that the skin in the injection area was blue (**Figure 1B**). After injection of methylene blue, massage the injection site thoroughly so that the medication is evenly distributed under the skin. Postoperative management included stool control for 24 h, intravenous drip of antibiotics (cefuroxime) to prevent infection, clean anus with warm water sitz bath, and change of dressing after defecation. When the patient has constipation symptoms, oral laxatives (lactulose oral liquid) would be used to reduce incision pain during defecation. When the pain of the patient was intolerable, the oral analgesic nimesulide dispersible tablets (0.1 g/tablet) were given and the dose was recorded.

Data collection

We extracted sex, age, course of the disease, hemorrhoid grade, the number of incisions, and the volume of methylene blue injected, the visual analog scale (VAS) pain score, complications and the Wexner incontinence scores (Wexner scores). Operationrelated variables from the electronic medical records' system and analgesics consumption information from the prescription monitoring program were collected. The primary outcome measures were the visual analog scale (VAS) pain score on postoperative days 1, 2, 3, 7, 14, and total analgesic consumption within 14 days. The VAS evaluates the intensity of pain from 0 (no pain) to 10 (very severe pain). Secondary outcomes were complications after hemorrhoidectomy, including acute urinary retention, secondary bleeding, perianal incision edema, perianal skin infection, and the Wexner scores used to assess the level of anal incontinence at 1 and 3 months after surgery. Two independent researchers analyzed all data.

Statistical analysis

SPSS22.0 statistical software was used to process the data. The enumeration data are presented as counts (%), and the chi-square

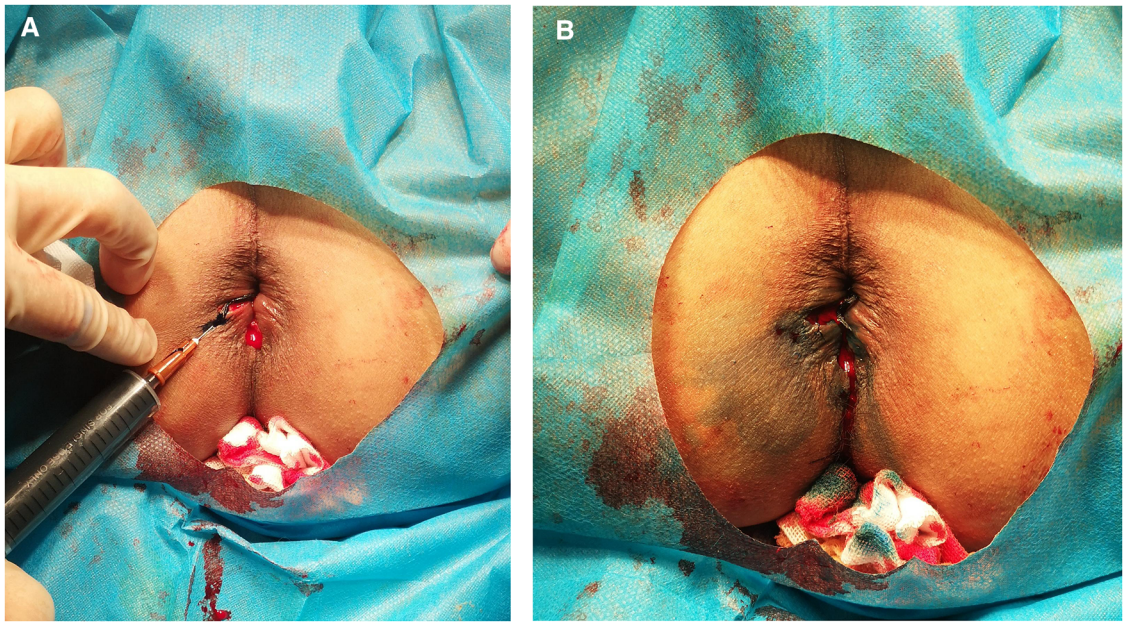

FIGURE 1
The technique of methylene blue injection. (A) Injecting from the distal end of the incision to the dentate line. (B) Incision after injection.

test or Fisher's exact test was used to compare differences and calculate *p*-values. The measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$). The data of three groups were compared by one-way ANOVA. When there was a significant difference among the four groups, the Bonferroni test was used for pairwise comparisons. The difference was considered significant when $P < 0.05$.

Results

There was no significant difference among three groups in sex, age, course of the disease, hemorrhoid grade and the number of incisions, and there was no significant difference in the volume of methylene blue injected between group A and group B, as shown in Table 1.

The VAS pain score on postoperative days 1, 2, 3, 7, and 14 and the total consumption of analgesics within 14 days in group A and group B were significantly lower than those in group C, but the differences between group A and group B were not statistically significant, as shown in Table 2. There was no significant difference in complications among three groups, including urinary retention, secondary bleeding, perianal incision edema, and skin infection. The Wexner scores of group B were significantly higher than those of group A and group C one month after the operation, but the differences between group A and group C were not statistically significant. In addition, the Wexner score among three groups decreased to zero at three months after operation, as shown in Table 3.

TABLE 1 Comparison of patient demographics and clinical aspects among three groups.

Group	Group A	Group B	Group C	*P*-value
Mean age (years)	42.85 ± 11.75	41.81 ± 10.89	38.51 ± 11.11	0.096
Female/male	25/35	27/33	24/36	0.853
Courses of disease (years)	3.90 ± 3.27	4.15 ± 2.46	4.91 ± 2.90	0.138
Hemorrhoids grades (III/IV)	51/9	53/7	50/10	0.730
The number of incisions	2.96 ± 0.90	3.00 ± 0.73	2.98 ± 0.92	0.976
The volume of methylene blue injected(ml)	4.60 ± 1.01	5.43 ± 7.93	/	0.145

Mean age, courses of disease, the number of incisions, and the volume of methylene blue injected are presented as the mean ± standard deviation.

Discussion

Although stapled hemorrhoidopexy (11) and Doppler-guided hemorrhoid artery ligation (HAL) (12) can be used to treat hemorrhoids, several systematic reviews have compared the treatment effects of stapled hemorrhoidopexy, HAL, and hemorrhoidectomy. The results show that compared with hemorrhoidectomy, stapled hemorrhoidopexy has more short-term benefits, such as less pain, faster recovery, shorter hospital stay, shorter time of returning to normal activities, and higher patient's satisfaction, but the incidence of postoperative prolapse and the re-intervention rate of prolapse are higher in patients undergoing stapled hemorrhoidopexy (13, 14). Although HAL has less bleeding after operation, the number of patients requiring r-emergency surgical intervention is significantly

TABLE 2 Comparison of postoperative visual analog scale (VAS) for pain and total analgesic consumption over 14 days among three groups.

Group	Group A	Group B	Group C	*P* value	*P* AvsB	*P* AvsC	*P* BvsC
VAS (1d)	4.01 ± 0.98	3.86 ± 0.98	4.48 ± 0.65	0.001	1.000	0.013	0.001
VAS (2d)	3.10 ± 0.81	3.06 ± 0.82	3.50 ± 0.96	0.011	1.000	0.038	0.021
VAS (3d)	2.63 ± 0.75	2.51 ± 0.87	3.05 ± 0.83	0.001	1.000	0.018	0.001
VAS (7d)	2.10 ± 1.00	1.90 ± 0.75	2.51 ± 0.92	0.001	0.677	0.037	0.001
VAS (14d)	0.96 ± 0.75	0.95 ± 0.87	1.40 ± 0.80	0.003	1.000	0.012	0.008
Total analgesic consumption within 14 days (g)	0.69 ± 0.19	0.65 ± 0.20	0.78 ± 0.17	0.001	0.695	0.031	0.001

Postoperative visual analog scale (VAS) for pain and total analgesic consumption over 7 days are presented as the mean ± standard deviation.

TABLE 3 Comparison of acute urinary retention, secondary hemorrhage, perianal incision edema, perianal skin infection, the Wexner score at one and three months after the operation among three groups.

Group	Group A	Group B	Group C	*P* value	*P* A vs B	*P* A vs C	*P* B vs C
Acute urinary retention	6 (10.00%)	5 (8.33%)	6 (10.00%)	0.937	/	/	/
Secondary hemorrhage	0 (0%)	0 (0%)	0 (0%)	/	/	/	/
Perianal incision edema	12 (20.00%)	11 (18.33%)	9 (15.00%)	0.766	/	/	/
Perianal skin infection	0 (0%)	0 (0%)	0 (0%)	/	/	/	/
The Wexner score at one month after the operation	0.35 ± 0.57	0.70 ± 0.80	0.10 ± 0.30	<0.001	0.005	0.071	<0.001
The Wexner score at three months after the operation	0	0	0	/	/	/	/

Acute urinary retention, secondary hemorrhage, perianal incision edema,and perianal skin infection are presented as N (percentage). The Wexner score at one month after the operation is presented as the mean ± standard deviation.

reduced, and the recovery is faster, but the recurrence rate is high (15). Therefore, although hemorrhoidectomy has some disadvantages, such as long postoperative pain, pain period, and recovery period, the treatment effect of this method is clear, and the long-term success rate is high. It is still the preferred surgical treatment and "gold standard operation" for patients with grade III-IV hemorrhoids (16, 17). The pain after hemorrhoidectomy is related to many factors, such as spasm of the anal sphincter and puborectal muscle, delayed wound healing, acute local inflammatory reaction caused by tissue trauma, surgical technique, stool type, and subjective perception of patients (18–20). The unsatisfactory analgesia effect after a hemorrhoid operation limits the activity ability and self-care ability of patients, reduces their quality of life (21), prolongs the hospitalization time, increases the demand for opioid analgesia (22), and may increase myocardial ischemia, arrhythmia, thromboembolism, urinary retention and intestinal obstruction (23). Therefore, it is essential to minimize the pain after hemorrhoidectomy.

In the clinic, multimodal analgesia methods are often used to treat incision pain after hemorrhoid surgery, including opioid analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), metronidazole, flavonoids, laxatives, local anesthetics, botulinum toxin, and local calcium channel blockers (24, 25). However, despite the standard pain management, some patients still have problems in postoperative pain control (22).

Methylene blue is a water-soluble thiazine dye used to treat various conditions, which has been found to have unique analgesic property through temporary disruption of anal sensory nerve terminals of patients. Methylene blue has been used to treat intractable pruritus around the anus (9) and pain after hemorrhoid surgery (7). There is a latency period of 4–6 h for methylene blue to exert its analgesic effect after subcutaneous injection. Because methylene blue destroys the nerve myelin sheath during this period, the patient can feel burning pain. Therefore, in this study, we prepared methylene blue and ropivacaine in a certain proportion and used the nerve block effect of ropivacaine to cover the latency period of methylene blue so that the early burning pain of the patient after subcutaneous injection of methylene blue can be greatly reduced. Because methylene blue destroys the nerve myelin sheath, it has a long term analgesic effect, which may also cause anal sensation incontinence, perianal necrosis and other risks when used in high concentrations. However, the concentration of methylene blue for perianal injection is still controversial, and some researchers use concentrations are in the range of 0.2%–0.5% (7, 26–29), but there are also reports of higher concentration (30).

This study shows that the VAS pain score and total analgesics consumption within 14 days in group A and group B were significantly lower than those in group C, but the differences between group A and group B were not statistically significant, indicating that 0.1% and 0.2% methylene blue perianal injection have the same analgesic effect in the treatment of post-hemorrhoidectomy pain. There was no significant difference in complications among three groups, including urinary retention, secondary bleeding, perianal incision edema, and skin infection. At one month after the operation, the Wexner scores of group B were significantly higher than those of group A and group C, but the differences between group A and group C were not statistically significant, while the Wexner score among three

groups decreased to zero at three months after operation. This indicates that 0.1% or 0.2% methylene blue subcutaneous injection after hemorrhoidectomy has little effect on anal function, and it is temporary and reversible. In addition, 0.1% methylene blue subcutaneous injection can not only effectively relieve pain, but also has less impact on anal function, with a lower risk of anal incontinence and higher safety. At the same time, subcutaneous injection of methylene blue around the perianal incision after surgery also conforms to the concept of preemptive analgesia.

However, there are still several limitations to be considered in the current study. First of all, this was a retrospective study with a small sample size and a short follow-up period of only 3 months. We should continue to expand the sample size and conduct long-term follow-up analysis of patients. More data are required to reduce the difference. In addition, more large-scale prospective randomized controlled trials should be carried out in the future to provide higher level of evidence.

Conclusions

This study demonstrates that perianal subcutaneous injection of 0.1% and 0.2% methylene blue has comparable analgesic efficacy in treating post-hemorrhoidectomy pain, but 0.1% methylene blue is safer.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

QL and YL performed the collection of clinical patients and wrote the article. YL performed ethical supervision and the initial data analysis. JL and QL were responsible for the technical operation of the surgery and the revision of the article. All authors contributed to the article and approved the submitted version.

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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.

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Associations of advanced age with comorbidity, stage and primary subsite as contributors to mortality from colorectal cancer

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Background: Although survival from colorectal cancer (CRC) has improved substantially in recent decades, people with advanced age still have a high likelihood of mortality from this disease. Nonetheless, few studies have investigated how cancer stage, subsite and comorbidities contribute collectively to poor prognosis of older people with CRC. Here, we decided to explore the association of age with mortality measures and how other variables influenced this association.

Methods: Using linkage of several administrative datasets, we investigated the risk of death among CRC cases during 2003–2014. Different models were used to explore the association of age with mortality measures and how other variables influenced this association.

Results: Our results indicated that people diagnosed at a young age and with lower comorbidity had a lower likelihood of all-cause and CRC-specific mortality. Aging had a greater association with mortality in early-stage CRC, and in rectal cancer, compared that seen with advanced-stage CRC and right colon cancer, respectively. Meanwhile, people with different levels of comorbidity were not significantly different in terms of their increased likelihood of mortality with advanced age. We also found that while most comorbidities were associated with all-cause mortality, only dementia [SHR = 1.43 (1.24–1.64)], Peptic ulcer disease [SHR = 1.12 (1.02–1.24)], kidney disease [SHR = 1.11 (1.04–1.20)] and liver disease [SHR = 1.65 (1.38–1.98)] were risk factors for CRC-specific mortality.

Conclusion: This study showed that the positive association of advanced age with mortality in CRC depended on stage and subsite of the disease. We also found only a limited number of comorbidities to be associated with CRC-specific mortality. These novel findings implicate the need for more attention on factors that cause poor prognosis in older people.

KEYWORDS

advanced age, mortality, comorbidity, cancer stage, colorectal cancer

1. Background

CRC is the second leading cause of cancer death in Australia, despite increases in 5-year relative survival in recent decades which now approximates 70% (1). Older age is still associated with higher case fatality, however, with 5-year survival now close to 60% in those who were aged 80 years or more at diagnosis. The number of older CRC patients is increasing markedly with increased population sizes in the older age brackets in Australia, along with their age-related comorbidity (2, 3).

Older age is found to be associated with poorer CRC outcomes, irrespective of the statistical methodology (i.e., all-cause/cancer-specific or short-term/long-term mortality) (4–6). This is so despite the fact that older people are often diagnosed at an earlier CRC stage than younger people (3, 7), with potential influences from increased comorbidity and frailty. While many studies reported lower survival among older patients, the literature is fairly sparse on the respective quantitative contributions of comorbidities, diagnostic stage, and cancer subsite in combination. We found only one study that had studied the impact of age on the CRC mortality by cancer stage (8).

Comorbidities are well-established predictors of CRC survival, but little evidence exists on the contribution made by specific comorbidities to CRC mortality. One study found that only some comorbidities impacted on CRC-specific mortality (5), although most comorbidities were associated with all-cause mortality (5, 9).

This study focusses on how stage, subsite and comorbidity influence the association of age with mortality in CRC patients. We also examine the association of individual comorbidities with CRC-specific and all-cause mortality.

2. Materials and methods

2.1. Study population and variables

People with colorectal cancer (C18-C20, ICD-10, International Classification of Disease) recorded by South Australian Cancer Registry (SACR) between January 1st, 2004–December 31st, 2013 were enrolled for this study. Pathology laboratories and health care centers in South Australia are mandated to notify SACR as a State-government registry of any malignancies diagnosed in their facilities (10). Through linkage with Deaths and Marriages (BDM) and the National Death Index (NDI) data, follow-up death data were obtained for the period up to December 31, 2014. Vital status and cause of death information were provided by the SACR using ICD-10 codes with a unique identification number for each patient. The minimum follow-up time in the study was 370 days. The underlying cause of death was derived from the death certificate issued by a certified medical practitioner and was based on the World Health Organization's rules for attribution of cause of death (10). This included death from CRC (disease specific) when recorded and verified by the SACR (C18–C20). Otherwise, death was classified as attributed to "another cause" (i.e., non-CRC) cause of death. The combination of the two indicated all-cause mortality. Socioeconomic status was categorized from most to least disadvantaged (Q1 to Q5) based on Index of Relative Socio-economic Disadvantage (11).

Cases with missing data on date of diagnosis and those whose diagnosis was changed (e.g., anal canal cancer) were excluded from the study (242 cases). The stage of CRC was provided by the South Australia Clinical Cancer Registry using Australian Clinico-Pathological Staging (ACPS), which is an extension of Duke staging (12). Where stage was unknown on the registry we categorized cases as advanced stage where so indicated by hospital admission records {i.e., stage C for metastasis to regional lymph nodes and stage D for more distant metastases (C77–C79) (13)}. Comorbidity burden was measured by Charlson comorbidity index (CCI) (14), using morbidities recorded in hospital inpatient data that were present on admission (15, 16). Treatment data were extracted from multiple sources and defined as binary variables (receipt of a treatment or not). The datasets that were used in this study and the linkage process is shown in Figure 1.

2.2. Statistical analysis

Survival from CRC-specific and all-cause mortality at one, two, five and ten years by age group was estimated by Kaplan-Meier analysis. All-cause mortality was also used as the outcome in Cox proportional hazards regression for multiple independent variables. We also used a competing risk model to investigate associations of different variables, including age, stage, comorbidity and treatment with CRC-specific mortality (17). This model accounted for deaths from non-CRC competing deaths, with results expressed as sub-distribution hazard ratios (SHRs). Time was estimated by days from CRC diagnosis date to the date of death or end of follow-up, whichever occurred first. The model was first adjusted by the variable described apart from treatment, and then with inclusion of treatment types. The purpose was to infer the influence of treatment on associations of age, comorbidity and stage with mortality. In all models, where testing for proportionality and, if this requirement not to be met, time-varying covariates were included (18–20). The models outcome were reported by Hazard ratio and SHR with a 95% confidence interval. *P*-values of $<5\%$ were considered as a statistically significant result.

The models estimated mortality by comorbidity status (CCI $=0$, CCI $=1$, 2 and CCI >2), stage (stage A, B, C, D and unknown) and subsites (right and left colon, rectum) to explore whether variations in associations with mortality were indicated across these variables (by comparing the range of confidence intervals). In order to test if associations of age with mortality varied by subsite, stage and the level of comorbidity, interaction terms were tested. Among interaction term analyses for stage, stages A and B were combined due to small numbers of deaths.

Associations of individual comorbidities selected from the CCI index with CRC-specific mortality and all-cause mortality

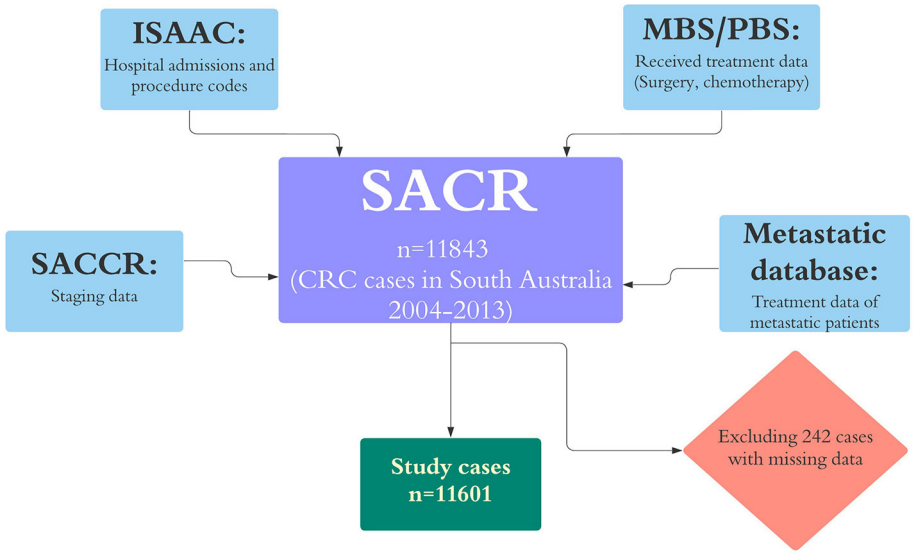

FIGURE 1
Datasets that were linked to SACR for this study and excluded cases. ISAAC, the Integrated South Australian Activity Collection; MBS, the Medicare Benefits Schedule; PBS, the Pharmaceutical Benefits Scheme; RAH, the Royal Adelaide Hospital; ARC, the Adelaide Radiotherapy Centre; and SACR, the South Australian Cancer Registry.

was also measured to assess whether these comorbidities showed different associations.

3. Results

3.1. CRC survivals based on age groups

Among the 11,601 CRC cases, 6233 (53.7%) were alive at the date censoring of December 31, 2014, 3,863 (33.3%) had experienced a CRC-specific death, and 1,505 (12.9%) had died of another cause. Table 1 shows descriptive features of the cases and their survival status at the end of the study period. Patients of older age, higher comorbidity, and advanced stage accounted for a high proportion of deaths.

Table 2 shows the all-cause and CRC-specific survival functions by age group using Kaplan-Meier analyses. A comparison of the two survivor functions shows that CRC-specific survival was often close to all-cause survival for younger ages, and short follow-up intervals. However, for a 10-year interval, the difference between the two types of survival increases, especially for people older than 80 years. For example, for those aged 80+ years, the CRC-specific survival at 10 years was 0.41 (0.34–0.48) compared to 0.07 (0.04–0.10) for all-cause survival. Comparison of survival estimates and confidence intervals indicated that people younger than 70 years had similar CRC-specific survival within the study period. Meanwhile, people older than 70 years had lower survivals compared to younger age groups which was more evident after 5–10 years. Supplementary Figure S1 shows the Kaplan-Meier curves for all-cause and CRC-specific survivals. We can observe that the CRC-specific curves specially for cases older than 70 experience a plateau within the 5–10-year interval, however, this pattern is not seen for all-cause curves.

3.2. Association of age and other clinicodemographic variable with mortality

The association of all-cause and CRC-specific mortality with study variables was measured (Table 3). Cancer stage was the strongest predictor of both all-cause and CRC-specific mortality (stage D all-cause mortality at HR = 12.33, 95% CI = 9.76–15.56, and CRC-specific mortality: SHR = 30.95, 95% CI = 20.23–47.35). Younger age was significantly associated with lower all-cause and CRC-specific mortality than those aged 80 years or over. This association was stronger for all-cause mortality than CRC-specific mortality (e.g., for the 71–80 age group, HR = 0.57, 95% CI = 0.53–0.61, and the SHR = 0.79, 95% CI = 0.72–0.88). The association of comorbidity was stronger with all-cause mortality than CRC-specific mortality (HR = 2.08, 95% CI = 1.94–2.24 vs. SHR = 1.20, 95% CI = 1.09–1.32). People with CCI > 2 had poorer all-cause mortality than people with CCI = 1, 2 (HR = 2.08, 95% CI = 1.94–2.24 vs. HR = 1.37, 95% CI = 1.29–1.46). Site of the cancer was not significantly associated with all-cause mortality, however, left colon and rectal cancers were significantly associated with higher CRC-specific mortality compared with right colon cancer.

3.3. Mortality measures after inclusion of treatments

Recipients of chemotherapy and surgery had significantly lower mortalities. Radiotherapy was also associated with lower mortality, but it wasn't statistically significant. There was not a great difference between the models after adjustment for treatment modalities (neither for all-cause nor CRC-specific mortality). However, the associations for age and comorbidity became weaker after addition

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TABLE 1 Characteristic of CRC cases and death outcomes by December 31, 2014: South Australia, 2004–2013 diagnoses.

Variable		Total (%)	All-cause death (%)	CRC-specific death (%)
Age group (years)	≤50	922 (7.9)	306 (5.7)	271 (7.2)
	51–60	1,741 (15.0)	624 (11.6)	566 (14.6)
	61–70	2,859 (24.6)	1,041 (19.4)	842 (21.8)
	71–80	3,495 (29.8)	1,647 (30.7)	1,130 (29.3)
	>80	2,620 (22.6)	1,750 (32.6)	1,054 (27.3)
CCI	0	6,107 (52.6)	2,224 (41.4)	1,823 (47.2)
	1, 2	3,560 (30.7)	1,803 (33.6)	1,262 (32.7)
	>2	1,934 (16.7)	1,341 (25.0)	778 (20.1)
Socioeconomic quintile*	Q1	2,885 (24.9)	1,397 (26.0)	1,022 (26.5)
	Q2	2,592 (22.3)	1,196 (22.3)	874 (22.6)
	Q3	2,215 (19.1)	1,027 (19.1)	699 (18.1)
	Q4	2,191 (18.9)	1,003 (18.7)	733 (19.0)
	Q5	1,716 (14.8)	744 (13.9)	534 (13.8)
Remoteness	Major cities	8,991 (77.5)	4,166 (77.6)	2,950 (76.4)
	Regional areas	2,270 (19.6)	1,027 (19.1)	780 (20.2)
	Remote areas	340 (2.9)	175 (3.3)	133 (3.4)
Primary subsite	Right colon	4,634 (39.9)	2,159 (40.2)	1,469 (38.0)
	Left colon	3,171 (27.3)	1,479 (27.6)	1,076 (27.9)
	Rectum	3,796 (32.7)	1,730 (32.2)	1,318 (34.1)
Sex*	Male	6,276 (54.9)	2,915 (54.6)	2,059 (5.6)
	Female	5,163 (45.1)	2,427 (45.4)	1,779 (46.4)
Stage	A	1,113 (9.6)	234 (4.4)	72 (1.9)
	B	1,947 (16.8)	648 (12.1)	323 (8.4)
	C	2,928 (25.2)	1,247 (23.2)	919 (23.8)
	D	2,475 (21.3)	1,990 (37.1)	1,800 (46.6)
	Unknown	3,138 (27.1)	1,249 (23.3)	749 (19.4)
Tumor differentiation (grade)	Well	581 (5.0)	113 (3.3)	113 (2.9)
	Moderate	7,629 (65.8)	3,086 (57.5)	2,036 (52.7)
	Poor/undifferentiated	2,153 (18.6)	1,233 (23.0)	983 (25.5)
	Unknown	1,238 (10.7)	869 (16.2)	731 (18.9)
Diagnostic period	2004–2008	5,861 (50.5)	3,315 (61.7)	2,287 (59.2)
	2009–2013	5,740 (49.5)	1,496 (38.2)	1,576 (40.8)

*12 and 162 cases had missing data in administrative datasets for socioeconomic status and sex respectively.

of treatment modalities to the models (Table 3). Associations left colon and rectal cancer with CRC-specific mortality was no longer significant after adjusting for treatments.

3.4. How stage, subsite and comorbidity affect the association of age with mortality

3.4.1. Stage

Younger age was associated with lower all-cause and CRC-specific mortality for all stages compared with >80 years as the reference (Supplementary Table S1). However, in all-cause mortality, these associations were stronger for earlier stages (A, B) than advanced stages (C, D); as people between 51 and 80 were less likely to experience all-cause mortality in comparison to the 80+ age group when they had earlier stages (e.g., for the 70–79 age group: for stage A, B 95% CI = 0.25–0.36 vs. for stage C 95% CI = 0.60–0.83). This difference was not observed for CRC-specific mortality.

The interaction term analysis between age group and stage showed that the association of age with all-cause mortality is significantly dependent on the stage of the disease, with people under 80 years having a higher risk of dying relative to older

TABLE 2 Kaplan-Meier analyses for all-cause and CRC-specific survival by age groups: South Australia, 2004–2013 diagnoses, date of censoring: 31 December 2014.

Variable		Survival (95% CI)			
Age groups (mean follow-up)		1 year	2 years	5 years	10 years
≤50 years	AC	0.89 (0.87–0.91)	0.78 (0.75–0.81)	0.64 (0.60–0.67)	0.44 (0.35–0.52)
(1,364.0 days)	CS	0.90 (0.88–0.92)	0.80 (0.77–0.83)	0.67 (0.63–0.70)	0.48 (0.38–0.57)
51–60 years	AC	0.87 (0.86–0.89)	0.78 (0.76–0.80)	0.63 (0.61–0.66)	0.40 (0.34–0.45)
(1,403.5 days)	CS	0.88 (0.87–0.90)	0.80 (0.78–0.82)	0.66 (0.63–0.67)	0.44 (0.38–0.49)
61–70 years	AC	0.87 (0.86–0.88)	0.79 (0.77–0.80)	0.62 (0.60–0.64)	0.39 (0.35–0.44)
(1,382.4 days)	CS	0.89 (0.88–0.90)	0.81 (0.80–0.83)	0.67 (0.65–0.69)	0.51 (0.46–0.55)
71–80 years	AC	0.80 (0.79–0.82)	0.71 (0.69–0.72)	0.52 (0.50–0.54)	0.25 (0.21–0.30)
(1,283.3 days)	CS	0.84 (0.83–0.85)	0.76 (0.74–0.77)	0.64 (0.62–0.66)	0.47 (0.42–0.53)
>80 years	AC	0.64 (0.62–0.65)	0.52 (0.50–0.53)	0.30 (0.28–0.33)	0.07 (0.04–0.10)
(868.5 days)	CS	0.71 (0.69–0.73)	0.62 (0.60–0.64)	0.51 (0.49–0.54)	0.41 (0.34–0.48)

AC, All-cause survival; CS, CRC-specific survival.

TABLE 3 Associations of age, comorbidity status (CCI), stage (ACPS), grade, primary subsite, and treatment variables with all-cause (HR) and CRC-specific (SHR) mortality (multivariable regression): South Australia, 2004–2013 diagnose, date of censoring December 31, 2014*.

Variable		All-cause mortality		CRC-specific mortality	
(Reference)		HR (95% CI)[+]	HR (95% CI)[‡]	SHR (95% CI) [†]	SHR (95% CI)[‡]
Age group	≤50	**0.33 (0.29–0.37)**	**0.34 (0.30–0.39)**	**0.54 (0.47–0.62)**	**0.53 (0.45–0.61)**
(80<)	51–60	**0.41 (0.37–0.45)**	**0.44 (0.39–0.48)**	**0.74 (0.66–0.83)**	**0.74 (0.65–0.84)**
	61–70	**0.43 (0.40–0.46)**	**0.47 (0.43–0.51)**	**0.72 (0.65–0.80)**	**0.73 (0.65–0.82)**
	71–80	**0.57 (0.53–0.61)**	**0.61 (0.57–0.66)**	**0.79 (0.72–0.87)**	**0.80 (0.72–0.88)**
CCI	CCI = 1, 2	**1.37 (1.29–1.46)**	**1.35 (1.27–1.44)**	**1.11 (1.04–1.20)**	**1.10 (1.02–1.18)**
(CCI = 0)	CCI > 2	**2.08 (1.94–2.24)**	**1.99 (1.85–2.14)**	**1.20 (1.09–1.32)**	**1.15 (1.05–1.27)**
Stage	B	**1.87 (1.45–2.41)**	**2.05 (1.59–2.65)**	**3.01 (1.93–4.71)**	**3.21 (2.07–4.99)**
(stage A)	C	**3.21 (2.53–4.07)**	**3.99 (3.12–5.09)**	**7.36 (4.52–10.60)**	**8.76 (5.71–13.44)**
	D	**12.33 (9.76–15.56)**	**13.26(10.43–16.85)**	**30.95 (20.23–47.35)**	**34.23 (22.34–52.44)**
	Unknown	**1.77 (1.39–2.26)**	**1.47 (1.15–1.87)**	**3.38 (2.18–5.23)**	**2.80 (1.82–4.31)**
Primary site	Left colon	1.01 (0.91–1.11)	1.04 (0.97–1.11)	**1.11 (1.02–1.21)**	1.05 (0.96–1.14)
(right colon)	Rectum	0.91 (0.83–1.01)	0.96 (0.89–1.03)	**1.18 (1.09–1.27)**	0.98 (0.90–1.08)
Surgery (non-receipt)		–	**0.48 (0.44–0.52)**	–	**0.52 (0.47–0.57)**
Chemotherapy (non-receipt)		–	**0.73 (0.67–0.81)**	–	**0.63 (0.56–0.70)**
Radiotherapy (non-receipt)		–	0.93 (0.83–1.04)	–	0.90 (0.80–1.02)

*Significant results are shown in bold, [†]adjusted for age, CCI, stage, primary subsite, grade, socioeconomic and remoteness status, diagnostic period, sex, [‡] addition of treatments in addition to previous adjustments. Time varying covariates for stage, grade, surgery, chemotherapy, and radiotherapy, HR, Hazard ratio; SHR, Sub-hazard ratio; CI, confidence interval; CCI, Charlson comorbidity index.

people when they have stages C and D (Supplementary Table S2). This correlation is also observed to a lesser extent for CRC-specific mortality. This shows that aging has a greater influence on the association of early-stage CRC with mortality than advanced-stage CRC.

3.4.2. Subsite

Younger age was associated with lower all-cause and CRC-specific mortality in both colon and rectal cancer (Supplementary Table S3). This significant associations were not different across different site (i.e., right, left colon and rectum).

Supplementary Table S4 shows that the association of age group with mortality measures (especially CRC-specific) was "statistically significantly" different by subsite, with people with rectal cancer and younger than 80 years being less likely to have both all-cause and CRC-specific mortality (compared to the reference group) than patients with right colon cancer [e.g., for age group 71–80 and rectal cancer SHR = 0.69 (0.55–0.086)]. No difference of association of age with mortality was observed between right and left colon.

3.4.3. Comorbidity

Supplementary Table S5 indicates that younger age was significantly associated with lower all-cause mortality regardless of the CCI status. For CRC- specific mortality, the significance of the associations only existed for those with CCI $\leq$ 2, and those with CCI $>$ 2 had no significant association of age with CRC-specific mortality.

Interaction terms indicated that the association between age group and both mortality measures did not vary to a "statistically significant" extent with level of comorbidity, except for all-cause mortality in 71–80 year when those older than 80 are significantly more likely to experience all-cause mortality when they have CCI $>$ 2 (Supplementary Table S6).

3.5. Specific comorbidities

Figure 2 indicates associations of individual comorbidities in CCI with all-cause and CRC-specific mortality. All the listed comorbidities except for connective tissue disease (HR = 0.93, 95% CI = 0.75–1.14) were associated with all-cause mortality. Dementia, diabetes, Peptic ulcer disease, chronic kidney disease, and liver diseases were the only comorbidities, however, that were associated with CRC-specific mortality.

4. Discussion

Several studies have already shown advanced age and comorbidity to be associated with all-cause and CRC-specific mortality (21, 22). It's previously found that age and primary subsite are associated with stage of CRC. It is therefore relevant to consider the influences of these factors on associations of age with survival. Kaplan-Meier analyses indicated that the CRC-specific survival was quantitatively close to survival from all causes in the first 5 years after CRC diagnosis. However, within 5 to 10 years after diagnosis the difference of the two survivals tends to increase especially among older age groups. This shows that most cases die due to CRC in the first years of the diagnosis, but non-CRC mortality is more likely to happen after the first years of CRC diagnosis.

Our results were consistent with those from earlier studies indicating that age and comorbidity were stronger determinants of all-cause than CRC-specific mortality (5, 8, 23). An earlier study found patients with the comorbidities were more likely to die of circulatory diseases and other cancers than of CRC (24). In total, these findings underscore the importance of addressing chronic comorbidity in CRC care, particularly among older patients. Studies of CRC mortality for different subsites have conflicting results based on the methodology and stage of the cancer (25–27). Our results showed no difference of overall survival based on the subsite of CRC. CRC-specific mortality was higher for left colon and rectal cancer before adjusting for treatment, which indicates difference in this mortality mostly stems from different treatment pattern based on subsite.

Addition of treatment modalities to our predictive models slightly weakened the associations of age and comorbidity with mortality. Associations of stage with mortality however experienced an increase in significance. The data indicated that treatment modalities were potential confounders of associations of stage with mortality. Surgery had the strongest association with mortality measures compared with chemotherapy and radiotherapy.

The strength of associations of age with CRC mortality measures reduced with increasingly advanced stage and for unknown stage. That is, for advanced stages, the association of younger age with better prognosis was weaker. An earlier study found the association of advanced age with all-cause mortality to be stronger for stage I and II than stage III, although an equivalent gradient was not observed for CRC-specific survival (8). The weaker association of age with mortality for advanced stages may reflect the higher mortality experienced by younger people with advanced stage, which acted to increase likelihood of death to a level more akin to that seen in older people. As a result, there was a clearer aging effect on mortality for early-stage than late-stage patients.

The association of age with mortality also differed by cancer subsite, being stronger for rectal than right colon cancer. In other words, the association of advanced age with increased likelihood of mortality appeared greater for rectal than right colon cancers. A possible reason could be differences in treatment, in that rectal cancer patients have more chemotherapy, both adjuvant and neoadjuvant, and often were treated by radiotherapy. Such treatments are more likely to cause toxicity in older patients, leading to poorer survival in these people (28–30).

We are not aware of studies that previously investigated variations in associations of age with mortality across different levels of comorbidity. Our analyses indicated that older people were more likely to experience CRC-specific death, and deaths from all causes of death, irrespective of comorbidity status except for all-cause mortality in those older than 70. In other words, effects of aging on mortality appeared to be largely unchanged irrespective of comorbidity level which means advanced age is almost as a great contributor to mortality for people with no comorbidity that it is for those with higher levels of comorbidity. However, in case of inclusion of factors that are confounders of comorbidity (e.g., performance status, treatment intensity or frailty), we might have found more significant difference in association of age with mortality across different comorbidity levels.

Other studies have shown that most individual comorbidities are associated with increased all-cause mortality in CRC patients (9, 31). Unlike all-cause mortality, however, we found few specific comorbidities to be associated with CRC-specific mortality. Kidney disease was associated with increased CRC-specific mortality as found by other researchers (5). We also found peptic ulcer disease and dementia to be associated with CRC-specific mortality, which were more novel findings. Patients with kidney, liver and gastric diseases generally are given reduced doses of chemotherapy which may predispose to an increased likelihood of CRC-specific mortality (32, 33). The association of peptic ulcer disease increased CRC-specific mortality is more difficult to explain, especially as this disease is commonly controlled by diet and medications. In this study, however, the cases were hospitalized and potentially of greater severity with increased gastrointestinal bleeding (15). People with previous cancers were less likely to have CRC-specific mortality. The reasons are uncertain but might include increased likelihood of attributions of deaths to other cancers.

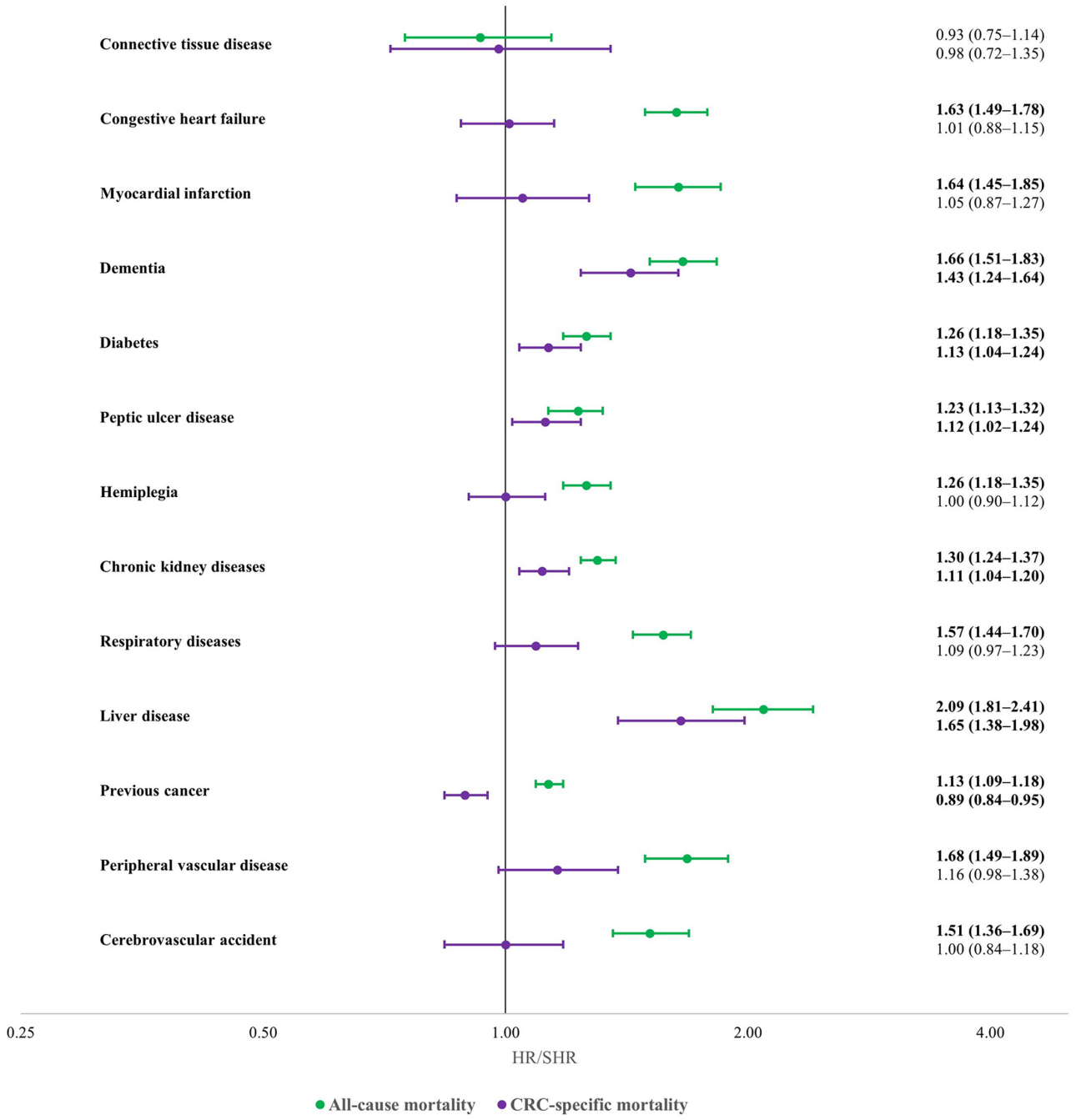

FIGURE 2
Associations of specific comorbidities with all-cause (green) and CRC-specific (purple) mortality in CRC cases (multivariable regression): South Australia, 2004–2013 diagnose, date of censoring December 31, 2014 adjusted for age, stage, primary subsite, grade, socioeconomic and remoteness status, diagnostic period, sex. Statistically significant results are shown with bold font. All-cause mortality outcomes are reported as hazard ratio (HR), and CRC-specific mortality outcomes are reported as sub-distribution hazard ratio (SHR).

Another potential explanation is that these people might have received several chemotherapy treatments for both their cancers. Evidence already has been reported that people with complications of chemotherapy (e.g., hematological and gastric toxicities) are less likely to have a CRC-death, with most dying of other causes (24).

4.1. Implications and further research

It is evident from registry data reported by the Australian Institute of Health and Welfare that survival of CRC patient declines precipitously from the age of 80 years (1). It will be important in future research to explore reasons, including the

potential for lower referral rates to multidisciplinary teams and lower participation in clinical trials.

We found that associations of age with mortality is not significantly influenced by the level of comorbidity. This means that younger people of any comorbidity status had equally a better prognosis than their counterparts older than 79. These results showed that the poor prognosis of older people which is believed to be partly due to comorbidities in this population (34), similarly exists for people without comorbidities. The relationship may be complicated, however, and further research is needed to explore causes other than comorbidity for the poorer prognosis of older CRC patients (e.g., frailty). Another possible explanation for poorer outcomes in old patients is variations in treatment complications, such as toxicities (e.g., neurologic, hematological etc.), perforations, and infections. We lacked the range and quality of data to explore these possibilities.

Even though rectal cancer has lower all-cause mortality, the cancer-specific mortality is significantly higher in our analysis. Some studies have reported that unlike colon cancer, rectal cancer mortality has an increasing trend in some countries including Australia, Canada and the United States and needs to be further investigated (35, 36). It is also shown that even though older people are experiencing higher mortality and the number of CRC deaths is going to rise because of the growing incidence rates; age groups younger than 50 are the only ones with an increasing projection of CRC mortality and more studies are needed in this area (37, 38).

Unlike all-cause mortality, only some comorbidities appear to change the CRC-specific mortality of patients. These comorbidities may affect treatment options and could include lowering doses of chemotherapy or delaying surgery. Studies are needed into mechanisms whereby co-existing conditions can alter the CRC-specific mortality such as by interacting with the pathogenesis of the disease or treatment.

Our results showed the groups in population that are more vulnerable to aging. Those with early stage are more likely to experience mortality as they age compared with their counterparts with advanced stage. Likewise, aging has a greater influence on rectal cancer mortality than colon cancer. This shows that more emphasis should be placed on early detection of CRC in these groups. Conversely, mortality likelihood of younger people with advanced stage or colon cancer is significantly closer to their older counterparts when being compared to those with early stage or rectal cancer respectively, which indicates the necessity of finding better treatment strategies for these groups.

4.2. Strengths and limitations

A strength of this study was long-term follow-up through linkages to the BDM registry. This would have minimized the chance of under-detection of deaths. The study also achieved broad coverage of South Australian CRC population. Many analyses in this study, including the subgroup analyses by subsite and comorbidity status, and analyses of individual comorbidities, were novel and pointed to factors that may predispose to poorer prognosis in older CRC patients. These factors need to inform strategic priorities for reducing CRC mortality.

A limitation of the study is that the data used for this research were not originally collected for research purposes which caused some patients to have different follow-up times based on the time of diagnosis and a proportion of the cases had unknown stages. Some important variables could also improve our results such as frailty indices or treatment type and intensity. Obtaining health administrative data in Australia requires extensive scrutiny of applications through research and ethics committees which is time-consuming and causes delays in reporting results. However, the main focus of this study (i.e., the correlation of age and comorbidity with CRC mortality) may not have been unduly affected by this lack of recency. CCI which was the measuring tool for comorbidity level which has limitations such as not having all main comorbidities (16, 39), but it provides a general score which was generally shown to be associated with mortality (39, 40).

5. Conclusion

This study confirms that advanced age and comorbidities are associated with all-cause and CRC-specific mortality. They are more likely, however, to increase the probability of all-cause mortality than CRC-specific mortality. Treatments were negatively associated with mortality measures, and they also moderated the association of advanced age, comorbidity and subsite with mortality. The positive association of mortality with age was observed to be mediated by stage and subsite. However, level of comorbidity was not found to significantly alter the association of age with mortality. We found only a limited number of comorbidities to be associated with CRC-specific mortality. This is a novel finding that requires confirmation in independent studies. Increased attention should be given to studies into the factors responsible for poorer prognosis of older patients with colorectal cancer, including studies of customized design and data collection to obtain the best possible evidence.

Data availability statement

The raw data supporting the conclusions of this article are protected by the AIHW and cannot be made readily available. Any queries can be directed to the corresponding author(s).

Ethics statement

The studies involving human participants were reviewed and approved by SA Health (HREC/16/SAH/6/AM04) and University of South Australia (EO2016/4/317). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

KG drafted the manuscript and performed statistical analysis. EB supervised the statistical methodology and study design. AV helped the study in terms of therapeutical methods for CRC and review of the literature. DR and his team obtained the study data and he supervised the whole project. All authors contributed to the article and approved the submitted version.

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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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1101771/full#supplementary-material

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Rectal prolapse as the initial presentation of rectal cancer—A case report

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Herein we report the case of a 63-year-old female tourist who presented to our Emergency Department with complete rectal prolapse. She had complained of diarrhea with traces of blood and mucus and had experienced fatigue after hiking. After the initial evaluation, it became clear that prolapse bares a large rectal tumor as a leading point. The prolapse was reduced under general anesthesia, along with a tumor biopsy. Further workup confirmed locally advanced adenocarcinoma of the rectum, which was treated with neoadjuvant chemoradiation followed by curative surgery in another hospital after repatriation. Rectal prolapse affects people of all ages, but it is more common in older adults, particularly women. Treatment options vary depending on the severity of the prolapse and can range from conservative measures to surgical interventions. This case report highlights the importance of early recognition and appropriate management of rectal prolapse in the emergency setting and the possibility of an underlying malignancy.

KEYWORDS

rectal prolapse, rectal cancer, emergency department (ED), anemia, case report

1. Introduction

Rectal prolapse or procidentia is a circumferential, full-thickness protrusion of the rectum through the anus. When irreducible and painful, it is classified as incarcerated (1). Delayed or unsuccessful reduction leads to strangulation, ischemia, bowel necrosis, perforation, and sepsis. Both conditions represent a complicated form of rectal prolapse mandating appropriate urgent treatment (2, 3).

Rectal prolapse is a rare condition that most commonly affects older adults, particularly women. The exact cause of rectal prolapse is unknown, but it has been associated with various factors, including chronic constipation, elongated rectosigmoid junction, weakened pelvic floor, and repetitive straining at defecation. Underlying bowel tumorous growth is a rare cause of prolapse but can occur even in children (4–6). A rising number of authors in the last decade published rectal or sigmoid adenocarcinoma cases leading to the presentation as a rectal prolapse (7–19).

Herein we report a 63-year-old female patient with the emergency presentation of incarcerated rectal prolapse caused by a locally advanced rectal tumor. The case is written in accordance with the CARE checklist (20).

2. Case description

A 63-year-old slim and fit female tourist arrived at the Emergency Department (ED) with complete rectal prolapse. A few days before, the patient had diarrhea with traces of blood and mucus. She recently noticed fatigue associated with intense hiking. After having the last stool in the mountains, a "massive prolapse" through the anus occurred. Ambulance Emergency Service transferred her to our hospital's ED. Until now, she didn't have any problems related to bowel habits and, therefore, never had an endoscopic workup. She took regular medication for hypertension.

A clinical examination revealed a complete rectal prolapse with a bulky exulcerated tumor occupying the posterior and right rectal wall, 8 cm × 10 cm in size (**Supplementary Figure S1**). The abdomen was soft and non-tender. The patient did not develop yet signs or symptoms of intestinal obstruction. There were no signs of hemodynamic instability. Her general condition was unimpaired, apart from the pale appearance of her skin.

3. Diagnostic assessment

Initial laboratory findings showed elevated white blood cell (WBC) count (26.8×10^9/L; reference range 3.4–9.7), with predominant neutrophilia (87% of granulocytes; reference range 44%–72%), and almost normal C-reactive protein (CRP) level (6.4 mg/L; reference range 0–3). The complete blood count showed severe hypochromic microcytic anemia. Red blood cell (RBC) count was 3.41×10^{12}/L (reference 4.34–5.72), hematocrit (HCT) was 21% (reference 41.5–53), hemoglobin (Hb) level was 62 g/L (reference 138–175), mean corpuscular volume (MCV) was 61.5 fl (reference 83–97.2), mean corpuscular hemoglobin (MCH) was 18.1 pg (reference 27.4–33.9), mean corpuscular hemoglobin concentration (MCHC) was 294 g/L (reference 320–345), with increased red cell distribution width (RDW) (18%; reference 9–15), and elevated platelets (PLT) count (528×10^9/L; reference 158–424).

Since the patient was a foreign citizen, after explaining therapeutic options, a decision was made to reduce the prolapse and perform a tumor biopsy to complete the work-up after repatriation. Under general anesthesia, tumor samples were taken for biopsy, and the prolapse was easily reduced since the anal sphincter appeared significantly weakened. After the reduction, a further digit rectal examination was performed to assess the tumor's position and size. It was located on the posterior and right rectal wall, reaching almost the anal sphincter, albeit not infiltrating the sphincter itself.

The patient was kept in our department for three days, receiving three units of erythrocyte concentrate. Upon dismission, her laboratory findings showed improvement: WBC count dropped to 10.4×10^9/L, whereas RBC increased to 4.47×10^{12}/L, Hg to 93 g/L, and HCT to 31.8%. Besides, specific tumor markers showed elevated carcinoembryonic antigen (CEA) with 4.9 ng/ml (normal < 4.3 ng/L), while the value of CA 19–9 marker was within normal limits (17.6 U/ml); reference value <39. The histopathology report confirmed that prolapsed rectal tumor was adenocarcinoma (**Supplementary Figure S2**). We emailed the pathology report to the patient and continued the correspondence, learning that she completed a workup followed by neoadjuvant chemoradiotherapy and abdominoperineal resection.

4. Discussion

The association between rectal prolapse and bowel tumorous growth is poorly represented in the literature. There is only one study, retrospective in design, published in 1995, convincingly demonstrating that the patients suffering from chronic rectal prolapse have a 4.2-fold higher relative risk for colorectal cancer than the representative cohort without rectal prolapse. The authors advocated routine screening for cancer using endoscopy, though no plausible explanation of the increased risk was offered (21). Most of the subsequent authors seconded their proposal for endoscopic surveillance based solely on sporadic case reports (7–11, 15–18). Speculation is that chronic straining, mechanical irritation of mucosa, and obstipation might increase the colorectal cancer risk in patients with chronic rectal prolapse. In favor of the claim that increased intraabdominal pressure precipitates prolapse of the rectal tumor, stands the case of a pregnant patient developing incarceration and strangulation of prolapsed rectum-bearing tumor amid delivery (12). Weakened or absent sphincter tone is certainly contributing factor, as demonstrated in a prolapse of rectal tumor years after Hartmann's procedure for fecal incontinence after obstetric sphincter injury (13).

A somewhat opposing opinion is offered by Akyuz et al., who don't find common ground for the etiology of rectal prolapse and the formation of malignancy, which is the process occurring independently, not assisted (18). The etiology is separate, although a new onset of rectal prolapse might indicate cancer due to bowel semi-obstruction and the patient's efforts in prolonged and vigorous straining (17, 18). This is especially true for younger patients, males, and for acute onset of prolapse—therefore, emergency presentation or atypical patient background are red flags that should urge the clinician to expand the diagnostic umbrella even more. It was true in our case, where the relatively healthy, physically active patient with the new onset of prolapse presented in the emergency setting.

In their comprehensive guideline on anorectal emergencies, the World Society of Emergency Surgery (WSES) and American Association for the Surgery of Trauma (AAST), issued in 2021, under the chapter on complicated rectal prolapse, authoritatively advise performing an urgent contrast abdominopelvic computed tomography scan in all patients except for those with hemodynamic instability (1). The intention is to detect complications such as bowel necrosis or perforation and not to miss the possibility of underlying bowel malignancy. The recommendation is based on low-quality evidence (level 2C—outcomes studies), focusing more on detecting complications of rectal incarceration than having a stronghold in available case reports of synchronous malignant tumors in prolapse. Nevertheless, detecting both complications and possible cancer is of utmost importance in deciding upon the best treatment for the patient (conservative vs. surgical) and tailoring

the appropriate surgical approach (abdominal, perineal, laparoscopic vs. open).

There is a consensus that colorectal tumors can act as a leading point in the telescoping of the bowel in adults, being the cause of intussusception (22). The exact mechanism could be applied to sigmoid/rectal tumors that act as a leading point for invagination and subsequent tumor prolapse outside the anal canal. However, this remains ungrounded because more bowel tumors would present with rectal prolapse, and the published data do not support it. Namely, there are only a handful of published cases of rectal prolapse-containing cancer, with the first dating back to 2004 (8). It is possible that the condition was underreported because, in the last decade, there has been an increasing number of reports on this particular issue (8–19). We have researched published literature through PubMed using the keywords "rectal prolapse" and "rectal adenocarcinoma or cancer," which yielded 75 articles. A detailed study of the articles and their references found only nine relevant cases of rectal cancer with rectal prolapse (8, 10, 12–17, 19), where two more reported prolapses of sigmoid cancer (9, 18).

Existing literature on rectal prolapse has focused chiefly on its diagnosis, treatment, and associated risk factors, with little attention paid to the possible association between rectal prolapse and colorectal cancer. In this case, the main challenge was identifying the rectal prolapse containing cancer in the emergency setting and resolving the imminent danger of rectal strangulation. The acute situation was translated to elective, allowing time to complete the work-up and repatriate our patient. This case report adds to the existing literature on rectal prolapse. It highlights the importance of early recognition and appropriate rectal prolapse management, especially with emergency presentation.

Clinicians, teachers, and researchers should be aware of the potential association between rectal prolapse and rectal cancer and consider this possibility when evaluating patients with rectal prolapse. Early diagnosis and prompt management can improve patient outcomes. Further research may be necessary to understand the relationship between rectal prolapse and rectal cancer and to develop more effective diagnostic and treatment strategies. Overall, it is crucial to maintain a high level of clinical suspicion for rectal cancer in patients with rectal prolapse to provide timely and appropriate care.

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.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JM and OJ conceived the presented idea. OJ and VŽ wrote the manuscript draft. NL prepared the figures. JM, LM, and RK shaped and edited the manuscript. All authors contributed to the article and approved the submitted version.

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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.

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Multivisceral transplantation of pelvic organs in rats

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Background: Multivisceral transplantation of pelvic organs would be a potential treatment for severe pelvic floor dysfunction with fecal and urinary incontinence, extensive perineal trauma, or congenital disorders. Here, we describe the microsurgical technique of multivisceral transplantation of pelvic organs, including the pelvic floor, in rats.
Donor operation: We performed a perineal (including the genitalia, anus, muscles, and ligaments) and abdominal incision. The dissection progressed near the pelvic ring, dividing ligaments, muscles, external iliac vessels, and pudendal nerves, allowing pelvic floor mobilization. The aorta and vena cava were isolated distally, preserving the internal iliac and gonadal vessels. The graft containing the skin, muscles, ligaments, bladder, ureter, rectum, anus and vagina, uterus and ovarian (female), or penile, testis and its ducts (male) was removed *en bloc*, flushed, and cold-stored.
Recipient operation: The infrarenal aorta and vena cava were isolated and donor/recipient aorta-aorta and cava-cava end-to-side microanastomoses were performed. After pelvic floor and viscera removal, we performed microanastomoses between the donor and the recipient ureter, and the rectum and pudenda nerves. The pelvic floor was repositioned in its original position (orthotopic model) or the abdominal wall (heterotopic model). We sacrificed the animals 2 h after surgery.
Results: We performed seven orthotopic and four heterotopic transplantations. One animal from the orthotopic model and one from the heterotopic model died because of technical failure. Six orthotopic and three heterotopic recipients survived up to 2 h after transplantation.
Conclusion: The microsurgical technique for pelvic floor transplantation in rats is feasible, achieving an early survival rate of 81.82%.

KEYWORDS

pelvic floor disorders, fecal incontinence, urinary incontinence, intestinal transplantation, tissue transplantation, anal canal, gender reassignment, dysphoria

1. Introduction

Multivisceral transplantation of pelvic organs would be a potential treatment for complex pelvic fecal and urinary incontinence. This condition is also called "dual incontinence" (DI) and remains a critical complication of pelvic floor dysfunction. The prevalence rate in the general population ranges between 5.3% and 9.4%, and in women, it increases to 20%–30% (1–5). Patients with complex DI frequently experience feelings of

shame, social isolation, silent desperation, and serious impairment in their quality of life (1–5). Furthermore, there is no effective treatment for severe DI (6–9). Another potential indication for multivisceral transplantation of pelvic organs would be complex perineal defects secondary to congenital disorders or those caused by extensive trauma or burn.

Vascularized composite tissue allotransplantation—covering the face, members (arm, leg, hand, etc.), trachea, and anorectal segment, among others—is a recent advancement in the field of transplantation. This innovation aims to improve the quality of life and individual function, rather than mere survival, defining a new trend for the treatment of many system dysfunctions (10–13).

We hypothesize that pelvic floor transplantation covering the skin, pelvic muscular complex, urethra, bladder, ureter, genitalia (vagina or penile), anorectal segment, neurovascular pedicle, and secondary genital organs is a potential treatment for severe DI and complex perineal congenital disorders or injuries following extensive trauma. We have already observed in another study that the surgical technique for pelvic floor transplantation in cadavers is feasible (14). In this report, we describe the surgical technique and anatomic details of pelvic floor transplantation in rats, aiming at translational research.

2. Method

2.1 Animal and anesthesia procedures

Twenty-two Lewis rats weighing 250–300 g were used as donors and recipients in 11 pelvic floor transplantations. All procedures were approved by the research ethics committee of the University of São Paulo School of Medicine and the anesthesia was performed intraperitoneally using ketamine (30 mg/kg) and xylazine (10 ml/kg).

2.2 Surgical procedure

2.2.1 Donor operation

A combined perineal and abdominal incision was performed (**Figures 1A,B**). The dissection progressed externally between the pelvic floor and the structures of the legs, abdominal wall, and gluteus and internally near the pelvic ring bone, preserving the perineal muscles, anorectal segment, and genitourinary organs of male (**Figure 1C**) and female (**Figure 1D**) donors. The division of the pubis makes this dissection easier and facilitates the identification of the vascular and pudendal nerves. The entire pelvic floor was mobilized to inside the abdomen. The genital organs, urinary bladder, and rectum were mobilized by performing the abdominal incision. The abdominal aorta and vena cava were isolated up to the renal vessels and down to the iliac bifurcation, preserving the internal iliac vessels, including the rectal vessels (**Figure 2A**). The pudendal nerves and vessels were identified and divided far from the pelvis (**Figure 2B**). The aorta and vena cava were sectioned near the renal vessels to preserve the gonadal vessels. The rectum was sectioned 3 cm before the anus and the ureters were sectioned 2 cm proximally from the bladder. Finally, we removed the graft *en bloc*, containing the skin, muscular complex, ligaments, bladder, ureter, rectum, anus and vagina, uterus and ovarian in female (**Figure 3A**) or penile, and testis and its ducts in male (**Figure 3B**) and placed it in a recipient containing a cold lactate Ringer solution. Immediately after, a catheter was inserted in the aorta to flush the graft with the Ringer solution. Afterward, the back-table procedures were performed.

2.2.2 Recipient operation

We performed the same donor's anesthesia and abdominal incision and isolated a segment of 2 cm of the infrarenal aorta and vena cava for the anastomoses. We positioned the graft in the abdomen and performed end-to-side aorta-aorta and cava-cava microanastomoses using a 10.0 nylon suture. We removed the vascular clamps from the recipient's aorta and vena cava, allowing graft reperfusion. After that, we performed a similar perineal incision as that of the donor, and the internal iliac vessels were divided near the external vessels. We divided the pudendal nerves far from the sacrum, removed the native pelvic floor tissues, and performed end-to-end continuous anastomosis between the donor and the recipient rectum (7.0 polypropylene) and the pudendal nerves (10.0 nylon). For the ureter anastomosis, we used a polyethylene stent with a minimum ID of 0.5 mm inserted in both (donor and recipient) ureter ends and secured with two 7/0 silk ligatures. The pelvic floor was positioned in its original position (orthotopic) or in the lower part of the abdominal incision (heterotopic) and fixed by stitches between pelvic floor ligaments, muscles, and skin, completing the operation (**Figure 4**). We sacrificed the animals 2 h after surgery and removed the graft for histological analysis. The tissues were stained with hematoxylin and eosin for ischemia/reperfusion injury graduation.

3. Results

We performed a total of 11 consecutive pelvic floor transplantations in rats. Seven recipients were transplanted using the orthotopic model, whereas four were done with the heterotopic model. The reproductive organs were maintained in the graft, so the vascular pedicle included the gonadal vessels for their vascularization. Consequently, a long venous and arterial pedicle including the renal vessels was required. The donor/recipient size match is very important (4). Donor/recipient weight should be the same or the donor's weight should be slightly smaller to prevent compartmental syndrome. Furthermore, in this technique, we access the axis of the vascular (internal iliac vessels) and neuronal (pudendal nerves) pedicles, which allows larger vessels for anastomosis and provides higher chances of regeneration and functional reconstitution. The mean time for the donor's operation was 62.54 ± 11.45 min. For the recipient's operation, it was 108.14 ± 16.32 min for the orthotopic model and 68 ± 10.89 min for the heterotopic one. All grafts achieved normal color and good arterial pulse after reperfusion,

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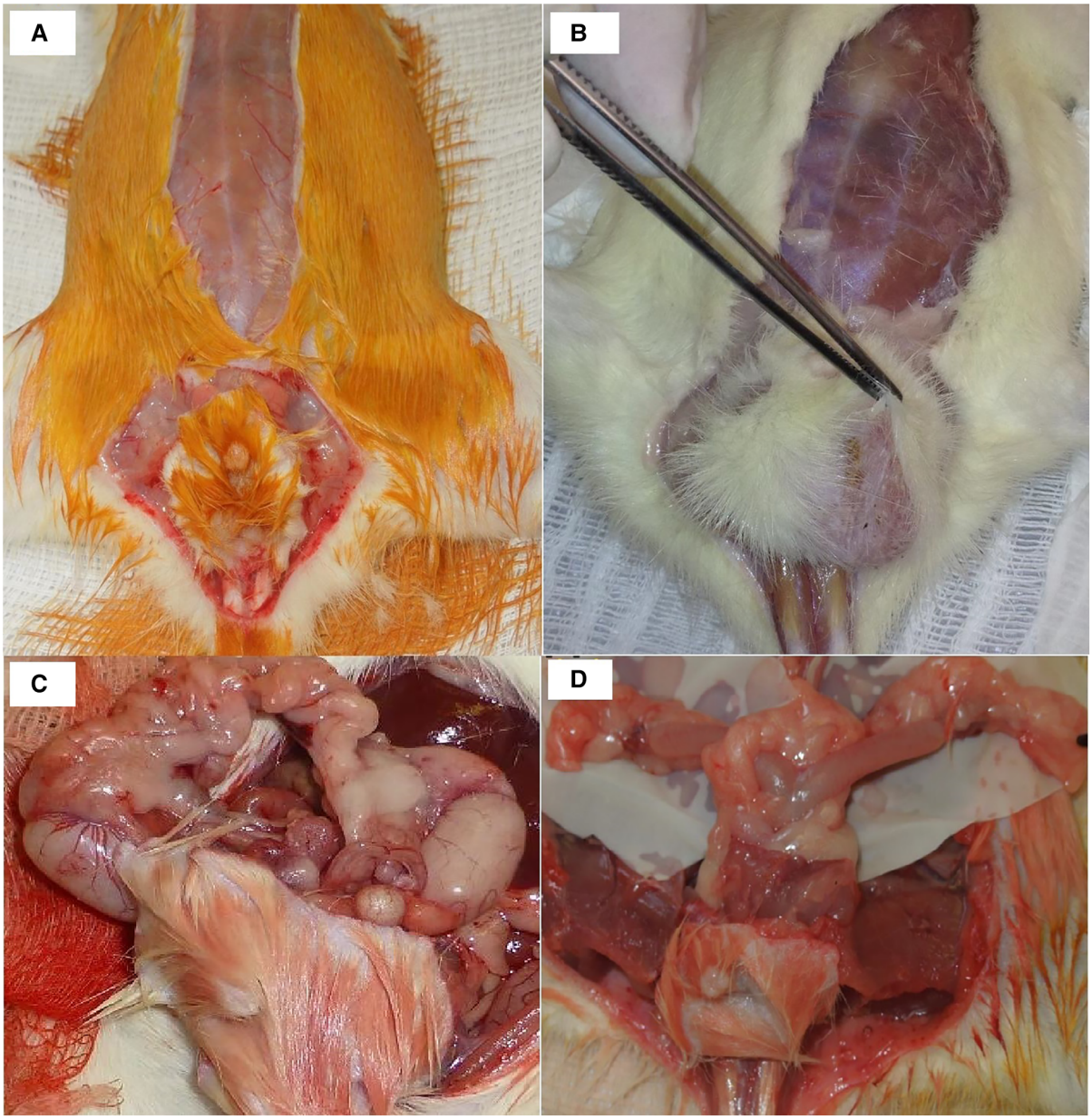

FIGURE 1
Incision details in male (A) and female (B) donors. Graft dissection in male (C) and female (D) rats.

and nine animals survived up to 2 h after the surgical procedure (experiment endpoint), with six in the orthotopic group and three in the heterotopic group. Two animals died before this period, one because of bleeding from perineal dissection (orthotopic fashion) and the other because of bleeding from arterial microanastomosis (heterotopic fashion). The histology assessment of the present investigation (normal = 0, mild = I, moderate = II, and severe = III) was based on the anorectal transplantation histological classification that searched for ischemic/reperfusion injury (mainly inflammatory cell infiltration and edema) in all organs of the composite tissue transplanted (15, 16). In the current research, ischemia/reperfusion injury was graded 0 in five grafts and 1 in four grafts. The small amount of lesion in the present investigation was probably due to the short period of cold ischemia. All animals that survived during the heterotopic model procedure recovered from anesthesia until the experiment endpoint, probably because of the shorter surgical time. In the orthotopic model, the three animals with the shortest surgical time also fully recovered from anesthesia. The heterotopic model of pelvic floor transplantation was conceptualized to develop a two-step technique in which the graft is implanted heterotopically first and then, after 2 days, another surgery is performed to remove the recipient's pelvic organs and to place the graft in orthotopic position. We believe that this two-step technique may improve the survival rate of patients undergoing this complex procedure.

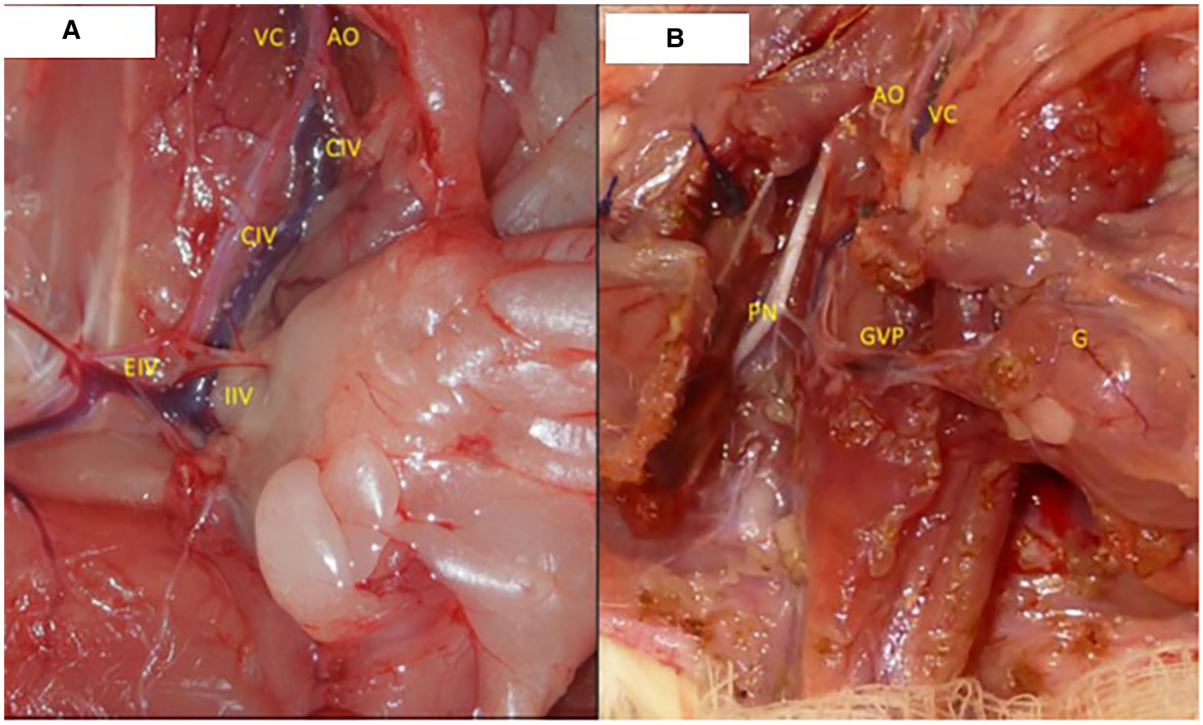

FIGURE 2
(**A**) Vascular dissection details: AO, aorta; VC, vena cava; IIV, internal iliac vessels; EIV, external iliac vessels; CIV, common iliac vessels. (**B**) Pedicle vessels from the final dissection and the source of the pudendal nerves: AO, aorta; VC, vena cava; NP, pudendal nerves; GVP, graft vascular pedicle; G, graft.

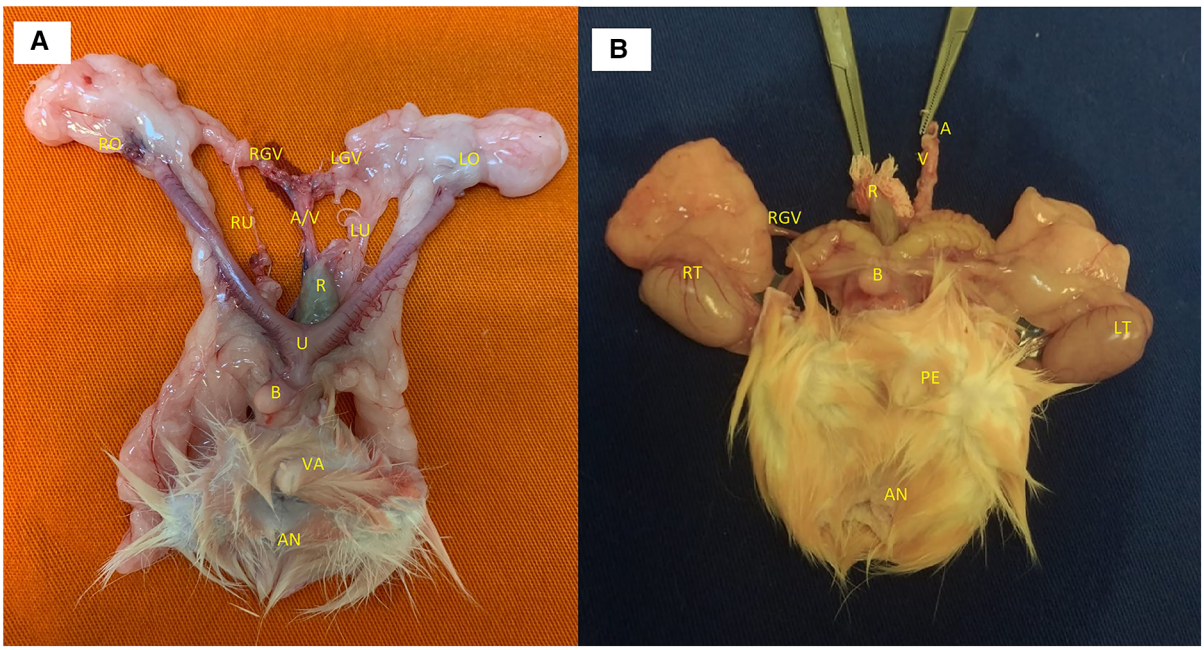

FIGURE 3
(**A**) female graft: RO, right ovary; LO, left ovary; RGV, right gonadal vessels; LGV, left gonadal vessels; A/V, aorta and vena Cava; RU, right ureter; LU, left ureter; R, rectum; U, uterus; B, bladder; VA, vagina; AN, anus. (**B**) Male graft: RT, right testicle; LT, left testicle; RGV, right gonadal vessels; R, rectum; A, aorta; V, vena cava; B, bladder; PE, penis; AN, anus.

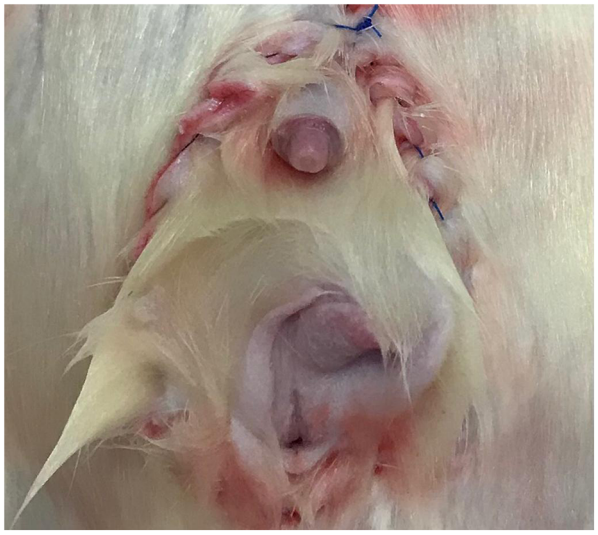

FIGURE 4
The final appearance of pelvic floor transplantation in a male subject.

4. Discussion

Our group and others have investigated anorectal transplantation as a potential solution for severe fecal incontinence. The initial results of this procedure in rats, swine, and canines are promising, showing a convenient functional recovery of this composite graft transplantation. Thus, these experiments suggest that anorectal transplantation would be a promising solution for severe fecal incontinence and permanent colostomy (15–24).

The necessity of anatomic studies for our research in anorectal transplantation inspired us to develop pelvic floor transplantation. During pelvic floor dissection in cadavers and rats, we observed that the pelvic floor is a complex system working like a singular organ. They share the same vascular and neuronal pedicles that control the musculature, which promotes both urinary and fecal continence as well as sexual reproductive functions. Thus, we formulated the hypothesis that the entire structure could be transplanted as a composite graft.

Araki et al. suggest that the anastomosis of pudendal vessels by super-microsurgery would be important for the recovery of pudendal function after anal transplantation, affecting all pelvic organs (22, 23). Nevertheless, in a recent series of anorectal transplantations in rats, we observed adequate anorectal recovery without pudendal vessel anastomosis (16). Furthermore, we could observe satisfactory anal function in a heterotopic model of anal autotransplantation (19), suggesting a profound influence of intrinsic bowel innervation on the rat's anorectal function. These thought-provoking results demand further research studies for easy elucidation.

Many patients would benefit from this procedure, including those with complex perineal trauma and congenital pelvic deformation. We are currently designing new models to expand the indications of this composite graft, mainly for trauma. Another possible indication would be for sexual gender reassignment for patients with gender identity disorder (dysphoria). Gender reassignment surgeries have been indicated for these patients; however, these procedures create artificial organs and may cause intricate complications (25, 26). Pelvic floor transplantation research may explore new possibilities depending on the demand for the inclusion of cross-gender pelvic floor transplantation with the reproductive organs for dysphoria or inclusion in the graft of parts of the pelvic bone framework, gluteus, abdominal wall, and limbs, with their respective vascular and nervous pedicles, for complex trauma or congenital disorders.

Currently, we are designing in our laboratory new experiments to observe the long-term survival rates of rats in pelvic floor transplantation as well as the function of the graft. This is a highly complex procedure that requires high microsurgical skills and intensive peri- and postoperative care, including hemodynamic and biochemical monitoring, respiratory support, administration of antibiotics, fluid infusion, and potential blood transfusion.

The possibility of the genitalia and adnexa transfer in the present procedure may increase the bioethical and metaphysical concerns of patients; nevertheless, these anxieties would be similar to those that exist in gender reassignment surgeries, which are already well accepted as a current therapeutic option for gender identity disorder (25, 26). Furthermore, additional refined, basic, and preclinic translational research of this procedure and an intense and reflective community debate about this medical advancement would be necessary to prepare society for this innovation, mainly pertaining to the donation of these composite tissues by the deceased. Another concern would be the high amount of immunogenic tissues present in this graft like skin, which would importantly require permanent immunosuppression after transplantation. The current procedure the current procedure would request similar immunosuppression used for the face, arms, and lower-extremity transplantation (10, 12, 13), which also enclose high immunogenic graft and need treatment for rejection by specific immunosuppressive induction therapy and maintenance immunosuppression, mainly with tacrolimus.

Pelvic floor transplantation may be a relevant option for severe pelvic floor dysfunction caused by extensive trauma or complex congenital disorders. This procedure is feasible in rats and opens the door for meaningful ethical, biotechnological, anatomical, and surgical debate.

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.

Ethics statement

The animal study was reviewed and approved by Comissão de Ética em Uso Animal da Faculdade de Medicina da Universidade de São Paulo (CEUA-FMUSP). It was aproved by the Ethical Committe for experimental animals from our institution, number: 1291/2019.

Author contributions

FG made the hypothesis. FG and JA conducted the experiment and looked after the management aspects. AF, CL, DW, EC, LN, MT, EM, and WA were responsible for providing technical support, participation in the experiments, article writing, and review and submission. LD'A oversaw the whole project in his capacity as the head of the department. All authors contributed to the article and approved the submitted version.

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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

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Evaluation of thromboembolic event, basic coagulation parameters, and associated factors in patients with colorectal cancer: a multicenter study

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Background: Patients with colorectal cancer are at an increased risk of hemostatic disturbances, and recent studies have shown that coagulation disorders could be the first sign of malignancy. Although coagulopathy is a significant cause of cancer-related death and disability, it is usually underestimated, and there has been no recent scientific evidence regarding the exact burden and its specific determinants. Moreover, the public health importance of the risk of coagulopathy among patients with colorectal polyps has not been addressed.

Materials and methods: An institution-based comparative cross-sectional study was conducted on a total of 500 study participants (250 colorectal cancer patients, 150 colorectal polyp patients, and 100 controls) from January to December 2022. Venous blood was collected for basic coagulation and platelet analysis. Descriptive statistics and non-parametric tests (Kruskal–Wallis and Dunn–Bonferroni pairwise comparisons) were used to compare study parameters among the groups. The test results were expressed as medians and interquartile ranges. Binary logistic regressions were fitted, and statistical significance was declared at a *p*-value of less than 0.05, with 95% CI.

Results: The prevalence of coagulopathy among colorectal cancer patients was 198 (79.2%; 95% CI: 73.86, 83.64), while the prevalence was 76 (50.7%; 95% CI: 45.66, 54.34) among colorectal polyp patients. From the final model, age between 61 and 70 (AOR = 3.13: 95% CI: 1.03, 6.94), age > 70 years (AOR = 2.73: 95% CI: 1.08, 4.71), hypertension (AOR = 6.8: 95% CI: 1.07, 14.1), larger tumor size (AOR = 3.31: 95% CI: 1.11, 6.74), metastatic cancer (AOR = 5.8: 95% CI:

1.1, 14.7), and BMI ≥30 kg/m^2 (AOR = 3.8: 95% CI: 2.3, 4.8) were positively associated with coagulopathy.

Conclusion: This study showed that coagulopathy is a major public health concern among patients with colorectal cancer. Therefore, existing oncology care efforts should be strengthened to prevent coagulopathy among patients with colorectal cancer. Moreover, patients with colorectal polyps should receive more attention.

KEYWORDS

coagulopathy, thromboembolic event, basic coagulation profiles, colorectal cancer, Ethiopia

1 Introduction

Colorectal cancer (CRC) is a significant cause of morbidity and mortality worldwide, and it is especially on the rise in sub-Saharan African countries (1). Worldwide, approximately 35 million people die due to non-communicable diseases like cancer, of which approximately 80% of deaths occur in developing countries (2, 3). CRC, which comprises approximately 10.2% of gastrointestinal (GI) cancers, is relatively prevalent with lethal groups of malignancy arising from the inner lining of the colon or rectum (4). Globally, GI cancers account for one in four cancer cases and one in three cancer deaths, and in recent times, although the overall prevalence of GI cancer has decreased, CRC incidence has increased globally, including in formerly low-incidence regions (5). According to WHO, CRC is the third most commonly diagnosed cancer in men and the second in women, and the lifetime risk of developing CRC is also high, estimated to be 1 in 23 (4.3%) for men and 1 in 25 (4.0%) for women (6). In the United States, CRC is the third leading cause of cancer-related deaths and the second most common cause of cancer-related deaths. In 2022, it was estimated to cause approximately 52,580 deaths, and in younger people, deaths from CRC have increased by 1% per year since 2008 (7, 8). CRC is one of the most common causes of morbidity and mortality in developing countries, and its occurrence is higher than that in other European, American, and Chinese countries (9, 10). In Africa, mortality from CRC has increased over time (3) due to the increased prevalence of risk factors such as growth and aging of the population, sedentary lifestyle, lack of modern treatment system, late presentation, increased comorbid illness, and poor awareness (11, 12).

Acute and chronic cancer-related complications that arise either as an initial malignancy manifestation or due to its progression are often the main cause of cancer-related mortality and hospital admission. These complications influence the prognosis and timing of cancer diagnosis, as well as the timing and receipt of treatment outcomes (13).

Cancer patients are usually associated with an increased risk of hemostatic disturbances and thromboembolic events (6, 14) and recent studies have shown that coagulation disorders could be the first sign of malignancy, and coagulation and fibrinolysis indicators are deranged in the blood-supplying tumors and peripheral blood of cancer patients, suggesting that cancer can directly affect the coagulation and fibrinolytic systems (15). Among CRC patients, clinical and subclinical changes in the coagulation and fibrinolysis systems, thrombotic disease, and disseminated intravascular coagulation are particularly common (16). Since it was first identified in the early 19th century by Professor Armand Trousseau [Trousseau's syndrome (TS)] (17), thromboembolic events have become an important public health burden for cancer patients and are associated with a complicated surgery, hospitalizations, and systemic therapies (18). Among patients with CRC, thromboembolic complications are becoming the second leading cause of death by interrupting or delaying essential cancer treatments, often with increased healthcare resource utilization (19, 20).

Recent international studies have reported that multiple risk factors, including patient-related (advanced age, race, sex, comorbidities, obesity, and history of thrombosis), cancer-related (primary tumor site, disease stage/grade, cancer histology type, and duration since initial diagnosis), and cancer treatment-related (chemotherapy, radiotherapy, surgery, anti-angiogenic agents, hormonal therapy, and transfusions) factors are associated with an increased risk of developing coagulopathy (21, 22). The overall prevalence and mortality rates of CRC are higher in men due to a number of biological and gender-related behavioral factors like high consumption of red and processed meat, high rate of alcohol consumption, smoking, higher risk of visceral obesity, and the protective role of estrogen hormone in women; however, women were found to have more aggressive forms of the cancer (23). To avoid cancer-related complications, such as coagulopathy, minimize mortality, and enhance patient quality of life, it is critical to recognize and manage risk factors early. In Ethiopia, despite the increased incidence and prevalence of CRC and its complications, the relatively high incidence of CRC mortality, and the high rate of delay to diagnosis, CRC receives a relatively low public health priority due to low public awareness, scarce financial resources, weak healthcare systems, a shortage of oncologists, and an already overburdened economy (24). Evidence also indicated

that the Ethiopian public lacks a comprehensive understanding of CRC and its risk factors, warning signs and symptoms, and early and late complications (25).

However, data on the prevalence and determinants of coagulopathy among patients with CRC in Ethiopia are limited. Moreover, documented data about the prevalence and associated factors of coagulopathy among CRC patients are important to understand the disease burden, identify high-risk groups, and develop effective preventive strategies. From this perspective, this study aimed to assess the prevalence of thromboembolic events and the prevalence and determinants of coagulopathy among adult CRC patients visiting the oncology units of public referral hospitals in Addis Ababa, Ethiopia.

2 Materials and methods

2.1 Study design, setting, and period

An institution-based comparative cross-sectional study was conducted from January to December 2022 at oncology centers in referral hospitals of Addis Ababa, Ethiopia, namely, Tikur Anbessa Specialized Hospital, Zewditu Memorial Hospital, and St. Paul Specialized Hospital. Currently, these hospitals provide basic cancer diagnosis, follow-up, chronic care, chemo/radiotherapy, surgery, and other services to almost all Ethiopian clients.

2.2 Study participants, sample size, and sampling techniques

The study was conducted with 500 participants. In this study, all adult participants (≥18 years old) of both sexes were included. The study participants were divided into three groups: Group I comprised 250 histopathologically confirmed CRC patients, diagnosed and on chronic follow-up; CRC patients who were admitted for anticancer treatment (chemotherapy/surgery); and CRC patients admitted due to any cancer-related complication management but who did not receive any type of anticancer treatment at the selected hospitals during the data collection period. To analyze and compare the evaluated basic coagulation parameters, in addition to CRC patients, our study also recruited 150 histopathologically confirmed (colonoscopy or flexible sigmoidoscopy) colorectal polyp (CRP) patients who visited the selected hospitals or were on chronic follow-ups, and who did not receive any type of treatment during the data collection period as group II and 100 apparently healthy volunteers as the third group (group III), which included apparently healthy adults who visited the selected study areas for any reason (clinical and administrative staff members, patient attendants) during the study period. For all healthy controls, after screening (detailed medical record review and physical examination) for any acute febrile illness and chronic disease, including known cancer, CT scan imaging was performed for any lesion. Finally, individuals who fulfilled the selection criteria and had no lesions were included (sex and age range matched).

2.3 Inclusion and exclusion criteria

All adult CRC and CRP patients whose age was older than 18 years and visiting the selected hospitals during the study period (from January 2022 to December 2022) were included in the study.

Starting from 1 January 2022, all consecutive patients (CRC and CRP) were evaluated on the first day of diagnosis and/or hospitalization, and those fulfilling the eligibility criteria were included. Study participants on chronic anticoagulation therapy, those with a history of thromboembolic events in the past 3 months, and pregnant women were excluded from the study for all groups.

2.4 Data collection procedures

2.4.1 Sociodemographic and clinical data collection

To collect baseline information on study participants' sociodemographic characteristics and related information, an interviewer-based pretested and structured questionnaire was used. Clinical and histopathological data [medical conditions/comorbidities, HIV/AIDS status, primary tumor location (colon, rectal), tumor size, sites of metastases, risk factors for coagulopathy, and BMI] were abstracted from the patient's medical chart by medical record review using a structured checklist with a physical examination. The tools were prepared by reviewing many similar international studies with some modifications in the local context, but most were developed by researchers after consulting oncologists and hematologists. The questionnaire was first prepared in English and then translated into Amharic, and the final tool was prepared in English after retranslating the Amharic version for consistency purposes. Pretests were performed on 5% of the total sample size, and modifications were made accordingly.

2.4.2 Blood sample collection and laboratory analysis procedure

Before surgery or any other treatment modality, the study participants were well-informed and made aware of the aim of the study. After obtaining written informed consent, blood samples and responses to the questionnaires were collected by qualified laboratory personnel following standard operating procedures (SOPs). A total of 500 fasting blood samples (250 CRC patients, 150 CRP patients, and 100 controls) with a volume of approximately 8 ml were collected and dispensed into a test tube containing 0.3 ml of 3.2% trisodium citrate, and platelet-poor plasma (PPP) was obtained after centrifugation at 1,500 *g* for 15 min. Then, using PPP, basic coagulation parameters PT (prothrombin time), APTT (activated partial thromboplastin clotting time), and INR (international normalized ratio) were analyzed using a HUMACLOT DUE PLUS coagulation analyzer (Wiesbaden, Germany). During the analysis, the analyzer read the clotting time of APTT and displayed the result in seconds, and the time taken for clot formation (in seconds) was recorded for the PT measurement. The INR was calculated and displayed from the PT output. For platelet count, approximately 3 ml of whole blood was

analyzed using the SYSMEX K-21N automated hematology analyzer (Sysmex Corporation, Kobe, Japan). All laboratory analyses were conducted following SOPs and the manufacturers' recommendations. All laboratory analyses were conducted on the same day as blood sample collection.

2.4.3 Thromboembolic and bleeding events

The study participants (CRC and CRP patients) were also assessed for the development of thromboembolic and bleeding events. For all included CRC patients, contrast-enhanced CT was performed, and a diagnosis of a thromboembolic event was made based on the description by the original reporting radiologist. We also included patients with CRC who developed all types of thromboembolic events detected by CT or additional imaging tests within 1 month of admission. Upon reviewing the medical records of patients with CRC on chronic follow-up, radiologic imaging was repeated if the imaging was performed before a month. The same imaging procedure was performed for the CRP patient groups.

Bleeding events were assessed according to the International Society on Thrombosis and Hemostasis definitions of major bleeding and clinically relevant non-major bleeding.

2.4.4 Operational definitions

Coagulopathy was considered an abnormality in one of the basic coagulation parameters assessed: prolonged PT and/or APTT values, thrombocytopenia, abnormally high PT/international normalized ratio (INR), or APTT.

Normal time for PT: The normal time for PT was considered between 10 and 14 s.

Normal time for APTT: The normal APTT time was considered 24–36 s.

Abnormal high INR: The normal INR was considered 0.8–1.2.

Normal platelet count: Platelet count between 150,000 and 400,000/μl.

2.5 Data processing and statistical analysis

Before analysis, the data were checked for completeness and internal consistency, coded and entered into Epidata version 4.6, and analyzed using STATA software version 16. Descriptive statistics, such as percentages, mean, median, IQR, and standard deviations, were used to present the sociodemographic and clinical characteristics of the study participants. Non-parametric Kruskal–Wallis tests followed by Dunn–Bonferroni pairwise comparison tests were used to compare the median (IQR) values of the different serum parameters between the case and control groups. Binary logistic regression analysis was used to examine independent variables associated with coagulopathy. Bivariate logistic regression was used to rank the relative importance of each independent variable with the outcome variables using odds ratios. Variables with a p-value of less than 0.25 in the bivariate analysis were chosen for multiple logistic regression analysis. Finally, AOR with 95% confidence intervals (CIs) was used, and p-values less than 0.05 were used to determine statistically significant factors.

2.6 Data quality assurance

Before actual data collection, training and discussion with the data collectors, laboratory technicians, and supervisors were undertaken regarding the content of the questionnaires, data collection techniques, and measurement procedures. Before data collection, a pretest was performed on 5% of the sample size to determine the effectiveness and consistency of the questionnaire under the direct supervision of an oncologist, after the supervisors and principal investigator checked them daily for accuracy, consistency, and completeness. Blood samples were collected using aseptic techniques and standard operating procedures. The kit was free of contamination and checked for consistency. All laboratory procedures were handled by professional laboratory technologists, and the results were checked daily for completeness by an immediate supervisor.

This cross-sectional study was appraised according to the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) (Appendix A) (26).

3 Results

3.1 Sociodemographic characteristics of study participants

A total of 500 adult participants participated in this study with a 100% response rate. The study participants were in three groups: 250 CRC patients, 150 CRP patients, and 100 healthy controls. The median ages of the CRC patients, CRP patients, and control groups were 42.5, 57.0, and 50.0 years, respectively. In the study, only 4 (1.6%), 1 (0.7%), and 1 (1.0%) of study participants had a family history of CRC for the respective CRC, CRP, and control groups (Table 1).

3.2 Histological, pathological, and clinical characteristics of study participants

Out of the 250 CRC patients, more than half (148, 59.2%) had a tumor located in the colon. Histopathological examination showed that adenocarcinoma (199, 79.6%) and mucinous adenocarcinoma (34, 13.6%) were the common histologic types, and 116 (46.4%) and 47 (18.8%) were moderately and poorly differentiated, respectively. Among the 150 CRP patients who participated, 122 (81.3%) had only one polyp, and histological examination revealed that the neoplastic histological type was dominant (103, 68.6.3%), of which 50 (48.5%) were tubulovillous adenomas and 32 (31.1%) were tubular adenomas (Table 2).

3.3 Basic coagulation and platelet profiles of study participants

In this study, compared to apparently healthy and CRP patients, PT, INR, and APTT were prolonged in most CRC patients, of whom 190 (76%), 178 (71.2%), and 107 (42.8%) had prolonged PT,

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TABLE 1 Sociodemographic characteristics of study participants at the referral hospitals of Addis Ababa, Ethiopia, 2022.

Variables	Categories	CRC (N = 250) N (%)	CRP (N = 150) N (%)	Control group (N = 100) N (%)
Age (years)	≤50 51–60 61–70 >71	149 (59.6) 39 (15.6) 42 (16.8) 20 (8.0)	21 (14.0) 30 (20.0) 41 (27.4) 58 (38.6)	31 (23.0) 26 (26.0) 37 (37.0) 6 (6.0)
Gender	Male Female	157 (62.8) 93 (37.2)	97 (64.7) 53 (35.3)	59 (59.0) 41 (41.0)
Residence	Urban Rural	98 (39.2) 152 (60.8)	68 (45.3) 82 (54.7)	60 (60.0) 40 (40.0)
Marital status	Single Married Widowed	90 (36.0) 145 (58.0) 15 (6.0)	30 (60.0) 13 (26.0) 7 (14.0)	17 (17.0) 73 (73.0) 10 (10.0)
Educational status	Illiterate Primary school Secondary school College/University	33 (13.2) 62 (24.8) 41 (16.4) 114 (45.6)	28 (18.7) 30 (20.0) 30 (20.0) 50 (33.3)	7 (7.0) 7 (7.0) 10 (10.0) 76 (76.0)
Religion	Orthodox Protestant Muslim Other	92 (37.0) 85 (34.0) 70 (28.0) 3 (1.2)	81 (54.0) 33 (22.0) 35 (23.3) 1 (0.7)	46 (46.0) 29 (29.0) 25 (25.0) 0 (0.0)
Alcohol consumption	Yes no	17 (6.8) 233 (93.2)	14 (9.3) 136 (90.7)	7 (7.0) 93 (93.0)
Smoking	Yes no	18 (7.2) 232 (92.8)	7 (4.7) 143 (95.3)	2 (2.0) 98 (98.0)
Family history of colorectal cancer	Yes No Unspecified	4 (1.6) 102 (40.8) 144 (57.6)	1 (0.7) 50 (33.3) 99 (66.0)	1 (1.0) 50 (50.0) 49 (49.0)
Family history of colorectal polyp	Yes No Unspecified	2 (0.8) 52 (20.8) 196 (78.4)	1 (0.7) 50 (33.3) 99 (66.0)	1 (0.01.0) 50 (50.0) 49 (49.0)
Family history of bleeding	Yes No Unspecified	2 (0.8) 52 (20.8) 196 (78.4)	1 (0.7) 50 (33.3) 99 (66.0)	1 (0.01) 50 (50.0) 49 (49.0)
Physical exercise habits	Never Once a week 2–3 times a week 4–6 times a week	153 (61.2) 78 (31.2) 14 (5.6) 5 (2.0)	81 (54.0) 22 (14.7) 36 (24.0) 11 (7.3)	59 (59.0) 22 (22.0) 13 (13.0) 6 (6.0)
Body mass index (kg/m^2)	Underweight (<18.5) Normal weight (18.5–24.9) Overweight (25–29.9) Obese (≥30)	80 (32.0) 130 (52.0) 34 (13.6) 6 (2.4)	10 (6.7) 92 (61.3) 41 (27.3) 7 (4.7)	5 (5.0) 64 (64.0) 24 (24.0) 7 (7.0)
Hypertension	Yes No	19 (7.6) 231 (92.4)	14 (9.3) 136 (90.7)	6 (6.0) 94 (94.0)
Diabetes mellitus	Yes No	2 (0.8) 248 (99.2)	0 (0.0) 150 (100.0)	1 (1.0) 99 (99.0)
Cardiac disease	Yes No	2 (0.8) 248 (99.2)	0 (0.0) 150 (100.0)	1 (1.0) 99 (99.0)
HIV/AIDS	Yes No	13 (5.2) 237 (94.8)	17 (11.3) 133 (88.6)	23 (23.0) 77 (77.0)

CRC, colorectal cancer; CRP, colorectal polyp.

TABLE 2 Histological, pathological, and clinical characteristics of study participants at referral hospitals of Addis Ababa, Ethiopia, 2022.

Variables	Categories	CRC N = 250 N (%)	CRP N = 150 N (%)
Primary tumor site	Colon Rectum	148 (59.2) 102 (40.8)	108 (72.0) 42 (28.0)
Tumor histopathology	Adenocarcinoma Mucinous adenocarcinoma Signet ring cell adenocarcinoma Unspecified	199 (79.6) 34 (13.6) 12 (4.8) 5 (2.0)	NA
Tumor grade	Well differentiated Moderately differentiated Poorly differentiated Undifferentiated	54 (21.6) 116 (46.4) 47 (18.8) 33 (13.2)	NA
Tumor size (cm)	0–2 2–5 5–10 ≥10	28 (11.2) 136 (54.4) 77 (30.8) 9 (3.6)	NA
Distant metastasis	Yes No	124 (49.6) 126 (50.4)	NA
Lymph node involvement	Node negative Node positive Node unknown	59 (23.6) 175 (70.0) 16 (6.4)	NA
Lymph vascular invasion	Yes No Unspecified	6 (2.4) 152 (60.8) 92 (36.8)	NA
CEA level	Not elevated (≤5 ng/ml) Elevated (>5 ng/ml) Unspecified	110 (44.0) 131 (52.4) 9 (3.6)	NA
Duration since diagnosed (years)	<1.5 years 1.5–3 years >3 years	150 (60.0) 62 (24.8) 38 (15.2)	72 (48.0) 41 (27.3) 37 (24.7)

CRC, colorectal cancer; CRP, colorectal polyp; CEA, carcinoembryonic antigen; NA, not applicable.

INR, and APTT, respectively, and 65 (26%) CRC patients had thrombocytopenia (Table 3).

3.4 Commutative prevalence of coagulopathy among study participants

In this study, the overall prevalence of coagulopathy among CRC patients was 198 (79.2%; 95% CI: 73.86, 83.64), of whom 190 (76.0%) showed prolonged PT, 178 (71.2%) showed prolonged APPT, and 65 (26.0%) showed thrombocytopenia. Furthermore, the total prevalence of coagulopathy among CRP patients was 76 (50.7%; 95% CI: 45.66, 54.34). From them, the prevalence of prolonged PT was 40.7% (61/150), and 8.0% (12/150) had thrombocytopenia (Table 3).

3.5 Comparison of basic coagulation and platelet parameters among study groups

Non-parametric tests, Kruskal–Wallis followed by Dunn–Bonferroni pairwise comparison test, were used to compare the median and IQR values and the median and IQR differences in basic coagulation and platelet parameters between study groups. In the Kruskal–Wallis analysis, the median [IQR] PT, APTT, and INR showed statistically significant differences among the CRC, CRP, and healthy control groups ($p < 0.001$) (Table 4).

In multiple pairwise comparison analysis using Dunn–Bonferroni pairwise comparison, the median [IQR] values of PT showed a statistically significant difference across all study groups, while the median [IQR] values of INR and platelet count among CRC patients were significantly different compared to CRP and healthy controls ($p < 0.001$). The median [IQR] values of platelet count showed significant differences between the CRC and CRP patients ($p < 0.001$), but there was no significant difference between the CRP and healthy control groups ($p \geq 0.271$) (Table 4).

3.6 Prevalence of thromboembolic and hemorrhagic events among the study participants

In this study, the overall prevalence of thromboembolic events among CRC patients was 17 (6.8%), of which 9 (52.9%) were in the form of pulmonary embolism, followed by deep venous thrombosis (3, 17.6%), and most of the pulmonary embolisms were asymptomatic segmental (7/9, 77.8%). Thromboembolic events were also observed in the examined CRP patients, with a

TABLE 3 Basic coagulation profiles and platelet parameters of study participants at referral hospitals of Addis Ababa, Ethiopia, 2022.

Variable	Categories	CRC (N=250) N (%)	CRP (N=250) N (%)	Control groups (N=250) N (%)	Reference range
PT(sec.)	Range	9.9-27.2	9.5-17.9	9.8-14.4	10s–14s
	Normal	60(24.0)	89(59.3)	90(90.0)	
	Prolonged	190 (76.0)	61 (40.7)	10 (10.0)	
INR	Range	0.92-2.17	0.79-1.47	0.75-1.15	0.8–1.2
	Normal	72(28.8)	92(61.3)	90(90.0)	
	Prolonged	178 (71.2)	58 (38.7)	10(10.0)	
APTT(sec.)	Range	21.7-72.7	28.7-49.2	27.3-43.4	24s–36s
	Normal	143(57.2)	113(75.3)	93(93.0)	
	Prolonged	107 (42.8)	37 (24.7)	7 (7.0)	
PLT (×103/ µl)	Range	74-635	94–434	139-251	150-400*10^3/µl
	Low	65 (26.0)	12 (8.0)	1 (1.0)	
	Normal	180 (72.0)	138(92.0)	99 (99.0)	
	High	5(2.0)	0 (0.0)	0 (0.0)	

CRC, colorectal cancer; CRP, colorectal polyp; PT, prothrombin time; PTA, prothrombin time activity; INR, international normalized ratio; APTT, activated partial thromboplastin time; PLT, platelet count.

cumulative prevalence of 6 (4%), and the majority (4/6, 66.7) were in the form of pulmonary embolism. Bleeding events were observed in 2 (0.8%) CRC patients (Table 5).

3.7 Determinant factors associated with coagulopathy among colorectal cancer patients

In the bivariate logistic regression analysis, old age CRC patients, physical exercise, BMI, tumor size, hypertension, duration since CRC diagnosis, and cancer metastasis were crudely associated with coagulopathy. However, after statistical adjustments in the final model, physical exercise and duration since cancer diagnosis were not independent predictors of the outcome variable (Table 6).

The result of the multivariable logistic regression analysis showed that those CRC patients of age between 61 and 70 and greater than 70 years were 3.13 (AOR = 3.13: 95% CI: 1.03, 6.94) and 2.73 (AOR = 2.73, 95% CI: 1.08, 4.71) times more likely to have coagulopathy than younger age groups, respectively. CRC patients who had hypertension were 6.8 (AOR = 6.8; 95% CI: 1.07, 14.1)

TABLE 4 Comparative analysis of basic coagulation and platelet parameters (Kruskal–Wallis followed by post hoc analysis using Dunn–Bonferroni correction) of study participants at referral hospitals of Addis Ababa, Ethiopia, 2022.

Variable	CRC (N = 250) Median [IQR]	CRP (N = 150) Median [IQR]	Healthy controls (N = 100) Median [IQR]	p-value
PT (s)	15.4 [2.96]	13.5 [2.69]	13.1 [2.46]	<0.001*
INR	1.37 [0.28]	1.18 [0.25]	1.11 [0.24]	<0.001*
APTT (s)	35.91 [11.7]	33.7 [10.30]	29.4 [5.22]	<0.001*
Platelet count	309 [106]	237 [85]	227 [83]	<0.001*
Multiple pairwise comparisons using Dunn–Bonferroni correction				
Parameters	CRC vs. Healthy control	CRC vs. CRP	CRP vs. Healthy control	
PT (s)	<0.001*	<0.001*	<0.001*	
INR	<0.001*	<0.001*	0.301	
APTT (s)	<0.001*	0.111	<0.001*	
Platelet count	<0.001*	<0.001*	0.271	

CRC, colorectal cancer; CRP, colorectal polyp; PT, prothrombin time; PTA, prothrombin time activity; INR, international normalized ratio; APTT, activated partial thromboplastin time; PLT, platelet count; IQR, interquartile range; *p < 0.005.

TABLE 5 Detailed characterization of thromboembolic and hemorrhagic events among the study participants at referral hospitals of Addis Ababa, Ethiopia, 2022.

Variable	Type of thromboembolic event	Categories	CRC (n = 250) N (%)	CRP (n = 150) N (%)
Type of thromboembolic event	Pulmonary embolism	Asymptomatic, segmental	7 (2.8)	4 (2.7)
		Symptomatic, segmental	2 (0.8)	0 (0.0)
		Heavily symptomatic and/or bilateral	1 (0.4)	0 (0.0)
	Deep venous thrombosis + pulmonary embolism	Asymptomatic, segmental	1 (0.4)	1 (0.7)
		Heavily symptomatic	1 (0.4)	0 (0.0)
	Deep venous thrombosis		3 (1.2)	0 (0.0)
	Visceral thrombosis		2 (0.8)	1 (0.7)
	CVC-related thrombosis		0 (0.0)	0 (0.0)
Bleeding events (symptoms)	Major		1 (0.4)	0 (0.0)
	Minor		1 (0.4)	1 (0.7)

CRC, colorectal cancer; CRP, colorectal polyp; CVC, central venous catheter.

times more likely to develop coagulopathy than normotensive CRC patients. The likelihood of developing coagulopathy was 3.31 (AOR = 3.31: 95% CI: 1.11, 6.74) times higher in those CRC patients who have a larger tumor size (≥10) than in those with a smaller size. CRC patients who had metastatic cancer were 5.8 (AOR = 5.8; 95% CI: 1.1, 14.7) more likely to develop coagulopathy when compared to those patients who had no metastatic cancer. Finally, cancer patients with a BMI ≥30 kg/m^2 (obese patients) had 3.8 (AOR = 3.8: 95% CI: 2.3, 4.8) times higher odds of the likelihood of developing coagulopathy than those patients with lower BMI (Table 6).

4 Discussion

In the present study, thromboembolic events, basic coagulation parameters, and determinant factors associated with the likelihood of developing coagulopathy among CRC patients attending oncology centers in the public referral hospitals of Addis Ababa are reported. Recent evidence has reported that CRC patients are at an increased risk of hemostatic disturbance, causing significant morbidity, worsened quality of life, and poorer prognosis (27–29).

In this study, the overall prevalence of coagulopathy among CRC patients was 198 (79.2%), of whom 190 (76%), 178 (71.2%), and 107 (42.8%) had prolonged PT, INR, and APTT, respectively, while 65 (26%) CRC patients had thrombocytopenia. Comparative analysis also confirmed that the evaluated basic coagulation parameters were significantly higher in CRC patients than in CRP patients and healthy controls ($p < 0.001$). This result was in agreement with the findings reported in Guangzhou, China (27) and two other studies (30, 31) where PT, APTT, and INR were significantly elevated among CRC patients compared with healthy controls ($p < 0.05$). Zhang et al. (27) also discovered that among CRC patients, APTT increased gradually, and PT and APTT can have prognostic value and help predict mortality, as these values increased significantly in patients with advanced-stage CRC than those in an early stage (27). Studies have also revealed that APTT could be used as a reference index, and patients with elevated APTT, especially in the early stage, could have poor prognoses by causing decreases in blood coagulation function, which could lead to colorectal bleeding (32, 33). The extent of elevation of PT, APTT, and INR in this study was higher than that reported in other cancer patients, such as those with breast, multiple myeloma, and lung cancer (34, 35).

Hematologic disturbances among cancer patients are multifactorial, and the mechanisms are not fully understood (36). However, the interaction of cancer cells with the host's endothelial cells and cancer cell expression of different pro-coagulant molecules, including tissue factor, which has factor-activating properties and induces the formation of platelet microthrombi, are believed to play a role (37–39). Malignant tumor growth, weakened immunity, physical failure, and deranged liver function may also be responsible for elevated serum PT and APTT levels (36).

Patients with CRC are also known to have a substantially higher risk of thromboembolic and bleeding events (40, 41). In the present study, the overall prevalence of thromboembolic events was 17 (6.8%), of which most (9, 52.9%) were in the form of pulmonary embolism. The study result was higher than the results of studies conducted in America (4.1%) (41) and Italy (5.4%) (42) but was lower than a study conducted in the United States (8.4%) (43). A study by Khorana et al. also revealed that thromboembolic events are the main complication in cancer patients, causing death and significantly poorer survival (41). CRP patients were also found to have a risk of thromboembolic and bleeding events, with 6 (4%) patients having thromboembolic events, and bleeding events were observed in 2 (0.8%) CRP patients.

TABLE 6 Bivariable and multivariable logistic regression for factors associated with coagulopathy among colorectal cancer patients at referral hospitals of Addis Ababa, Ethiopia, 2022.

Factors	Coagulopathy		95% CI		*p*-value
	Yes, *N* (%)	No, *N* (%)	COR (95% CI)	AOR (95% CI)	
1. Age					
≤50	126	23	1	1	
51–60	31	8	3.71 (1.40, 9.82)	1.91 (1.11, 8.48)	0.74
61–70	29	13	3.61 (0.91, 12.35)	3.13 (1.03, 6.94)	0.001*
>70	12	8	0.96 (0.25, 3.40)	2.73 (1.08, 4.71)	0.001*
2. Hypertension					
Yes	63	118	11.7 (9.3, 21.8)	6.8 (1.07, 14.1)	0.03*
No	167	74	1	1	
3. Tumor size (cm)					
0–2	19	9	1	1	
2–5	120	16	1.25 (0.65, 2.55)	2.41 (0.59, 3.75)	0.41
5–10	52	25	1.32 (0.64, 3.56)	1.22 (0.81, 3.29)	0.53
≥10	7	2	3.14 (1.43, 6.34)	3.31 (1.11, 6.74)	0.03*
4. Metastasis					
Yes	111	13	15.1 (8.1, 23.6)	5.8 (1.1, 14.7)	.000*
No	87	39	1	1	
5. Body mass index (kg/m2)					
Underweight (<18.5)	68	12	3.1 (0.6, 27.1)	6.7 (0.9, 23.46)	0.098
Normal weight (18.5–24.9)	100	30	1	1	
Overweight (25–29.9)	25	9	4.9 (3.5, 11.4)	6.2 (1.5, 11.4)	.11
Obese (≥30)	5	1	11.5 (1.5, 21.9)	3.8 (2.3, 4.8)	.000*
6. Duration since diagnosed with CRC					
<1.5 years	128	22	1	1	
1.5–3 years	48	14	4.5 (4.7, 9.1)	3.5 (0.4, 9.6)	.22
>3 years	22	16	3.4 (2.4, 6.4)	8.6 (2.6, 16.2)	.11
7. Physical exercise (per week)					
Never	119	34	2.29 (1.2, 3.96)	3.05 (1.03, 4.05)	0.33
Once a week	70	8	7.1 (3.7, 10.4)	6.0 (2.5, 11.8)	0.098
2–3 times	6	8	1.8 (0.2, 16.6)	3.6 (0.2, 52.9)	0.779
4–6 times	3	2	1	1	

In the analysis of determinant factors that may increase the likelihood of developing coagulopathy among CRC patients, older CRC patients (>60 years) were three times more likely to have coagulopathy than younger age groups. Some studies have asserted that advanced age is a risk factor for coagulopathy and thromboembolism, and these risks further increase among patients with cancer (44). Coagulopathy among elderly cancer patients could be associated with aging of the vascular system, leading to decreased vessel wall integrity and microcirculation, endothelial dysfunction, reduced vascular tone, increased plasma levels of coagulation factors, and sedentary lifestyles, all of which increase the risk of coagulopathy and thromboembolism (45, 46).

Coagulopathy is mostly associated with chronic diseases; in this study, CRC patients with hypertension were significantly associated

with coagulopathy. The study participants with hypertension were nearly seven times more likely to develop coagulopathy than those without hypertension. Eleni et al. (2018) reported that hypertensive cancer patients could have exhaustion of the coagulation process, endothelial dysfunction, and chronic activation of the procoagulant pathways, and these patients may also take different medications, which might have an impact on the normal hemostasis process (47).

The likelihood of developing coagulopathy was 6.9 times higher in patients with CRC who had a larger tumor size (≥10 cm) than in those with a smaller tumor size. Similarly, CRC patients who had metastatic cancer were at risk for coagulopathy, as shown by its six times higher odds of association with coagulopathy when compared to patients who had no metastatic cancer. Elevated plasma levels of procoagulant and activated coagulation function have been shown to be associated with angiogenesis, tumor progression, metastasis, and reduced survival in patients with lung cancer (48), gastric cancer (49), renal cell carcinoma (50), and CRC (51). It is hypothesized that tumor cells and host production of procoagulants, fibrinolytic factors, local thrombin, and plasmin are important factors in tumor progression and metastases by enhancing sustained adherence of tumor cells to the vasculature of target organs, supporting vessel formation, and stimulating endothelial cell proliferation during tumor development (48, 49).

Finally, CRC patients with abnormal BMI, especially obesity, had almost four times higher odds of association with coagulopathy than those with a normal BMI. The association between abnormal BMI and coagulopathy, especially in cancer patients, may be related to chronic low-grade inflammation and endothelial dysfunction (52, 53). In addition, obese patients could have increased adipocytokine-mediated activity of coagulation factors, decreased activity of the fibrinolytic system, adipocyte release of tissue factor, increased production of leptin (54, 55) and adiponectin, and production of plasminogen activator inhibitor-1 from adipocytes, all of which result in coagulopathy (56).

5 Conclusion and recommendations

Among CRC patients, the burden of coagulopathy has remained a problem of public health importance. To the specific context of the study, older age, hypertension, larger tumor size, metastatic cancer, and obesity were positively associated with coagulopathy. Furthermore, thromboembolic and bleeding events are also significant burdens in patients with CRC. Regular screening is advised due to the growing prevalence of the disease and its complications, especially in those at higher risk, such as those with a personal history of CRC or certain types of polyps; a family history of the condition; a personal history of inflammatory bowel disease, ulcerative colitis, or Crohn's disease; a confirmed or suspected hereditary CRC syndrome; or a personal history of receiving radiation to the pelvic and abdomen.

The existing efforts in oncology care should be strengthened to prevent coagulopathy and other complications, and cancer care providers should invest in their efforts for early detection using different diagnostic modalities. Moreover, patients with CRPs should be given more emphasis.

6 Limitation of the study

Despite being the first in type, the robust methodology we used, and the important findings we reached, the study was not without limitations. The limitations include the small sample size, and due to the high cost of reagents and imaging tests, we have only included 250 colorectal patients and only PT, APTT, INR, and platelet count were measured to assess coagulation profile; the different assays that would help differentiate the exact cause of coagulopathy were not measured. In addition, we did not investigate the impact of the anticancer treatment on the measured parameters.

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.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Review Board of College of Health Sciences, Addis Ababa University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors of the study have made a significant contribution to the reported work, which includes the conception, supervision, study design, execution, acquisition of data, statistical analysis, and interpretation of the results, as well as drafting, revising, and critically reviewing the manuscript, and gave final approval of the version to be published. All authors have agreed to the journal to which the article has been submitted and to be accountable for all aspects of the work.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1143122/full#supplementary-material

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Appendiceal collision tumors: case reports, management and literature review

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Appendiceal tumors are incidentally detected in 0.5% cases of appendectomy for acute appendicitis and occur in approximately 1% of all appendectomies. Here, we report two cases of appendiceal collision tumors in two asymptomatic women. In both cases, imaging revealed right-lower-quadrant abdominal masses, which were laparoscopically resected. In both cases, histological examinations revealed an appendiceal collision tumor comprising a low-grade appendiceal mucinous neoplasm and well-differentiated neuroendocrine neoplasm (NEN). For complete oncological control, right hemicolectomy was performed in one patient for the aggressive behavior of NEN; however, histology revealed no metastasis. The other patient only underwent appendectomy. No further treatment was recommended. According to the latest guidelines, exact pathology needs to be defined. Proper management indicated by a multidisciplinary team is fundamental.

KEYWORDS

appendiceal tumors, collision tumor, low-grade appendiceal mucinous neoplasm, neuroendocrine neoplasm NEN, appendectomy

Introduction

Primary appendiceal tumors are rare entities in heterogeneous group of tumors, with an incidence of approximately 1.2 case per 100,000 people annually in the United States (1). They are most commonly found incidentally in a surgical specimen after appendectomy for acute appendicitis. However, their pathology and classification remain controversial. Hence, a new classification of these neoplasms was published in the World Health Organization (WHO) Classification of tumors, 5th edition, 2019 (2). Mucinous neoplasm and neuroendocrine neoplasm (NEN) are the most frequent benignant and malignant lesions (3).

When tumor components are composed by two adjacent, different but separate neoplasms from 2 different cellular lines, they are called collision tumor (3, 4). Appendiceal collision tumors are rare entities. Only 13 cases have been reported in the international literature to date. Here, we present two new cases comprising a low-grade appendix mucinous neoplasm (LAMN) and a well-differentiated NEN, which were managed differently.

Case presentation 1

A 49-year-old Caucasian woman with no significant medical history visited an ambulatory gynecology clinic for a routine check-up. Transvaginal ultrasonography revealed an oval mass with a mixed content measuring 74 mm × 44 mm in diameter, suggesting a dermoid cyst or an ovarian fibroma. Abdominal magnetic resonance imaging (MRI) also described a tumor close to the right ovarian gland (69 mm × 40 mm × 46 mm), with contrast enhancement in the arterial phase and clear margins afterward and a small nodulation inside (Figures 1A,B). Metastases or peritoneal deposits were not noted. Remarkably, Ca-125 and Ca 19-9 values were 10.7 and 42 U/ml (normal values: <35 and <37 U/ml), respectively. Thus, gynecologists performed laparoscopic surgery and found an appendiceal neoplasm intraoperatively. The surgery was completed with an appendectomy and a peritoneal biopsy performed by a general surgeon consultant. The specimen was removed through the umbilical port in an extraction bag, with no cystic lesion rupture. Intraoperative frozen sections indicated a LAMN. Macroscopically, the resected specimen showed an 8.5 cm-long appendix with a cystic neoformation measuring 8 cm × 5.5 cm × 5 cm, with mucinous content. At 1 cm proximal to the appendiceal cecal margin, another yellow node measuring 2.1 cm in diameter was detected. On histological examination, the bigger mass was described as a LAMN with acellular mucus confined to the wall (TNM Classification 8th edition 2016: pTis), whereas the smaller nodule was described as a NEN G1, characterized by mesenteric fat and visceral serous membrane involvement measuring 0.9 and 0.5 mm, respectively (Figure 1C). Perineural tumoral invasion without angiolymphatic invasion was observed. Immunohistochemical analysis revealed positivity for cromogranin A (Cg A) (Figure 1D) and synaptophysin, with a Ki-67 proliferation index of 0.4% (Figure 1E) (TNM Classification 8th edition 2016: pT2G1). Moreover, peritoneal biopsy was negative for tumor seeding. No complications occurred, and the patient was discharged on postoperative day (POD) 4. A multidisciplinary team analyzed the case and decided to perform segmental colectomy with lymph node dissection Finally, robot-assisted right hemicolectomy was performed. On POD 5, the patient was discharged after a regular postoperative course. Histologically, the specimen had no residual tumor and no nodal involvement (19 nodes). No adjuvant therapy was recommended. At 6 and 12 months follow-up, total body CT scan and assessment of serological markers showed no evidence of recurrence.

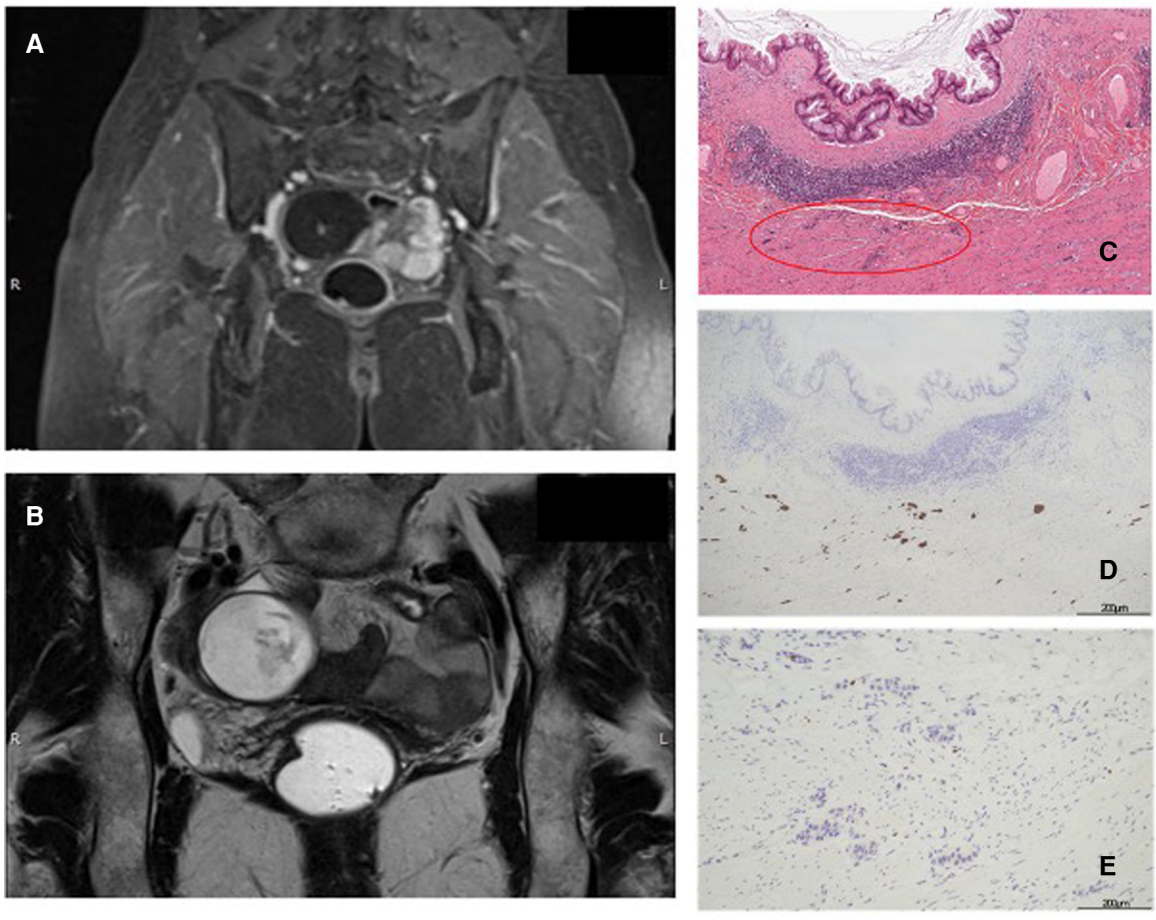

FIGURE 1
(A,B): Abdominal MR T1 and T2-weighted images. (C): LAMN and NEN (red circle), hematoxylin and eosin (H & E) staining 10×. (D): Immunohistochemistry positive for Cg A. (E): Immunohistochemistry for Ki-67: proliferation index of 0.4%.

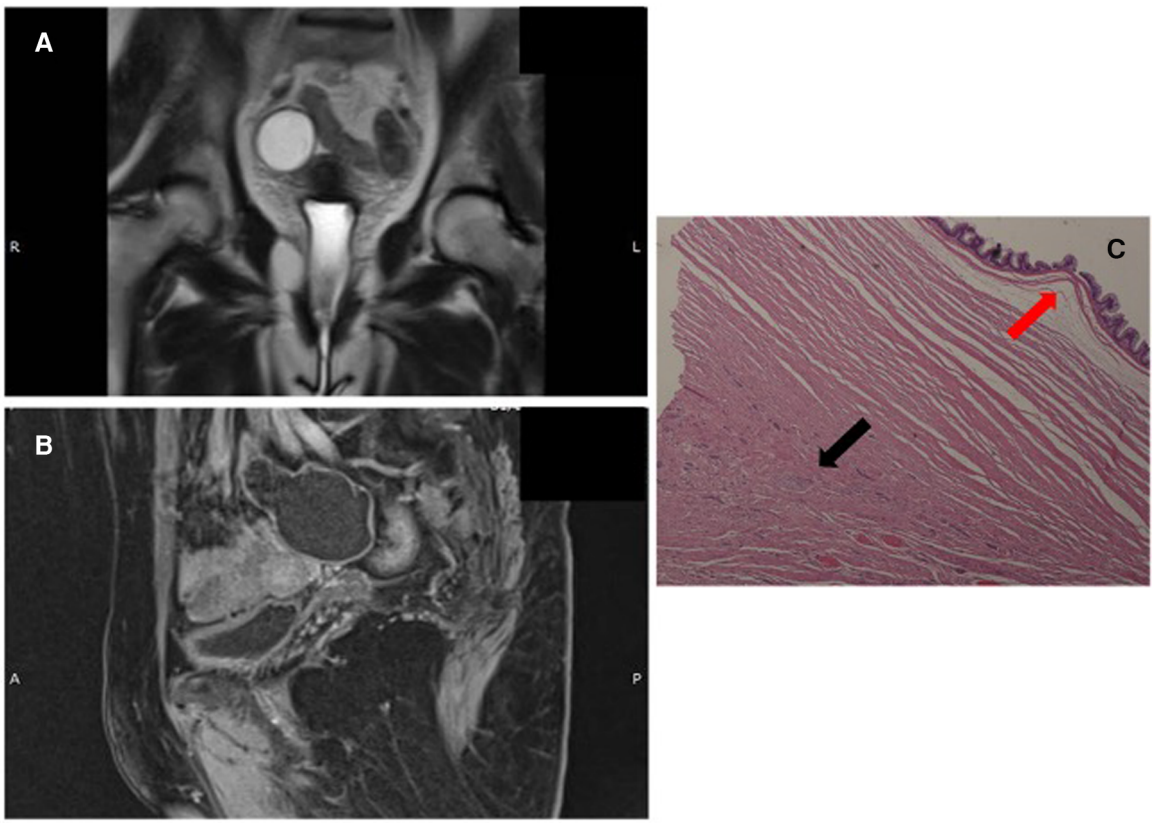

FIGURE 2
(A,B): abdominal MR T2- and T1-weighted images. (C): LAMN (red arrow) and NEN G1 (black arrow), (hematoxylin and eosin (H & E) staining).

Case presentation 2

A 59-year-old Caucasian asymptomatic woman underwent an abdominal ultrasound which revealed a right pelvic mass. Her Ca-125 value was 3.2 U/ml (normal value: < 35 U/ml). Abdominal MRI revealed a cystic oval mass [diameters 3.7 cm × 4.5 cm × 6.4 cm; hyperintense in T2-weighted images (Figure 2A) and hypointense in T1-weighted images Figure 2B)] in the right uterus space. Final radiological diagnosis was hydrosalpinx. Hence, the patient underwent laparoscopic surgical treatment. A general consultant surgeon performed appendectomy and appendiceal tumor (diameter 5 cm) with a smooth surface and stretched elastic consistency was found. No pelvic organ was involved. Subsequently, the patient demonstrated no complications, and on POD 2, she was discharged.

Gross morphology of the resected specimen showed a 9 cm-long cyst-like dilated appendix measuring 6 cm in diameter. The appendix was filled with thick mucus. Histologically (Figure 2C), the specimen appeared to be a LAMN with a fully thick mucus on the appendicular wall, but no peri-appendicular adipose tissue was involved (TNM Classification 8th edition 2016: pTis). A NEN G1 (9 mm × 7 mm) limited to the muscularis layer was identified in the proximal section of the appendix, with no serous and perivisceral fat invasion and no vascular or perineural neoplastic invasion. However, on immunohistochemical evaluation, Cg A and synaptophysin were positive. The Ki-67 proliferation index was 1% (TNM Classification 8th edition 2016: pT1G1). Additionally, the specimen had negative surgical margins. The multidisciplinary team did not recommend any adjuvant therapy. At 6 and 12 months follow-up, total body CT scan, abdominal ultrasound, and serological markers' assessment showed no evidence of recurrence.

Discussion

Appendiceal tumors are extremely rare entities, usually detected incidentally following an emergent appendectomy for acute appendicitis in approximately 1% (1) of cases and occurring in approximately 1%–2% of all appendectomies (5).

Incidental diagnosis of asymptomatic patients in the course of another examination is relatively common, as noted in the two cases described.

According to the 5th edition of the WHO classification (2), appendiceal tumors are classified into several histological types, such as serrated lesions and polyps, mucinous neoplasms, adenocarcinomas, goblet cell adenocarcinoma, and NEN.

The mucinous tumors of the appendix are categorized into serrated polyps, hyperplastic polyps, LAMNs, high-grade appendiceal mucinous neoplasms (HAMNs), and mucinous adenocarcinomas (2, 6). Mucinous neoplasms are characterized by a dilated appendix containing luminal mucin. High secretion

by these tumors can cause appendiceal rupture and tumoral cell dissemination in the peritoneal cavity. LAMNs are among the most common borderline neoplasms of the appendix, with an incidence of 0.3% in a recent series of appendectomy specimens (5). Histological examination show high-grade atypical glands with an infiltrative pattern extended through the muscularis mucosae. LAMNs comprise well-differentiated glands inside the muscularis mucosae, with dissecting mucin or epithelium and they do not exhibit infiltrative epithelial invasion of the appendiceal wall (2, 7–10).

Moreover, among the most common types of primary malignant lesion of the appendix are appendiceal NENs, with an incidence of approximately 0.15 per 100,000 people annually (11). The Ki-67 index determines the tumor grading according to the WHO and European Neuroendocrine Tumor Society classifications (2, 12). Generally, neuroendocrine tumors (NET) of the appendix are either G1 (more than 80%) (13) or G2 (14). These neoplasms appear as yellowish, well-demarcated nodules arising in any part of the appendix. Microscopically, they have uniform polygonal tumor cells frequently arranged in large nests (2).

Collision tumors results from the proliferation cellular lines. They are two distinct but adiacent neoplasms, retaining a transition between the two. Otherwise, a multidirectional differentiation of cells from a single tumor results in a combined neoplasm (3, 4).

The association between mucinous and neuroendocrine appendiceal tumors is an uncommon event with only few cases described (15). We found only 13 cases in 10 papers on PubMed research (**Tables 1A,B**). Our cases are appendiceal collision tumors, because both showed histologically distinct type of neoplastic cells with epithelial and neuroendocrine origin occurring in the same region the components, although

TABLE 1A Literature review.

Authors	M/F	Age	Signs and/or symptoms	US	CT	MRI	CEA	Others markers	Appendectomy	Minimally invasive surgery	Right hemicolectomy
Tan (15)	F	59	Yes	na	na	na	na	na	Yes	Yes	No
	M	52	No	No	Yes	No	H	na	Yes	Yes	No
Baena-del-Valle et al. (26)	F	49	No	No	Yes	No	na	na	Yes	No	na
	M	45	Yes	na	na	na	na	na	Yes	na	na
Dellaportas et al. (20)	F	57	Yes	Yes	Yes	No	na	Normal	Yes	Yes	Yes
Singh (16)	M	52	Yes	Yes	Yes	No	H	na	No	No	Yes
Rossi et al. (33)	F	35	Yes	Yes	No	No	na	na	Yes	No	Yes
Sholi (25)	F	23	Yes	No	Yes	No	na	na	Yes	Yes	Yes
Ekinci (34)	M	60	Yes	Yes	No	No	H	Normal	Yes	na	No (patient refused surgery)
Sugarbaker (32)	F	39	Yes	Yes	No	No	na	na	Yes	No	Yes
	M	32	Yes	No	Yes	No	na	na	Yes	No	Yes
Cafaro et al. (35)	F	35	Yes	Yes	No	No	No	No	Yes	No	No
Villa et al. (3)	F	31	Yes	Yes	Yes	Yes	na	na	Yes	Yes	Yes
Present serie	F	49	No	Yes	No	Yes	na	H	Yes	Yes	Yes
	F	59	No	Yes	No	Yes	No	Normal	Yes	Yes	No

TABLE 1B Literature review.

Authors	Pathology 1	Pathology 2	Ki-67%	FU months	Adjuvant therapy	Recurrence	Death
Tan (15)	Mucinous adenoma	NEN	na	60	No	No	No
	LAMN	NEN	na	3	No	No	No
Baena-del-Valle et al. (26)	LAMN	NEN	na	na	No	No	na
	LAMN	NEN	na	na	Yes	Yes	na
Dellaportas et al. (20)	Mucinous cystadenoma	NEN	na	12	No	No	No
Singh (16)	Adenoca	NEN	na	14	Yes	Yes	Yes
Rossi et al. (33)	Adenoca	NEN	na	65	Yes	No	No
Sholi (25)	LAMN	NEN	8	24	No	No	No
Ekinci (34)	LAMN	NEN	<1	6	No	No	No
Sugarbaker (32)	LAMN	NEN	na	60	Yes	Yes	No
	LAMN	NEN	5	12	Yes	No	No
Cafaro et al. (35)	LAMN	NEN	5	15	No	No	No
Villa et al. (3)	LAMN	NEN	<1	12	No	No	No
Present serie	LAMN	NEN	0.4	12	No	No	No
	LAMN	NEN	1	12	No	No	No

M, male; F, female; US, ultrasonography; CT, CT scan; MRI, magnetic resonance imaging; Adenoca, adenocarcinoma; CEA, carcinoembryonic antigen; LAMN, low-grade appendiceal mucinous neoplasm; NEN, neuroendocrine neoplasm; other markers, tumor markers generically reported in the papers; H, high; FU, follow-up (months) after surgery; na, not available.

intimately juxtaposed, are not intermixed and do not show transition, consistent with Singh NG et al.'s definition (16). The first case was of a LAMN containing acellular mucus confined to the wall; it was associated with a smaller NEN G1 nodule with mesenteric fat and visceral serous membrane involvement measuring 0.9 and 0.5 mm, respectively (**Figure 1C**). Perineural tumoral invasion without angiolymphatic invasion was also evident. In the second case, histological examination (**Figure 2C**) showed a LAMN with fully thick mucus on the appendicular wall; however, we did not observe the involvement of periappendicular adipose tissue associated with NEN G1, which was limited to the muscularis layer without serous, perivisceral, and vascular invasion. The mean age at diagnosis of patients with appendiceal collision tumors is 43 ± 12 years (23–60 years), with prevalence in women (8/5).

Clinical presentation is not specific and is characterized by a wide spectrum of findings and symptoms. Patients may have specific symptoms of clinical acute appendicitis or colorectal carcinoma syndrome or even nonspecific symptoms. The diagnosis is usually made incidentally in the course of another examination. Our patients did not report any symptoms, including NEN-related symptoms (weight loss, diarrhoea, or cutaneous flushing).

The role of tumor markers is still insufficiently defined. An elevated serum carcinoembryonic antigen (CEA) level was reported in 3 cases of the literature (15, 16, 34). In our study, only Case 1 had slightly elevated CA 19-9 levels.

Preoperative diagnosis of appendiceal collision tumor is often incidental because this entity has no special radiological or clinical features (17). An eventual preoperative biopsy generally detects only one histological component, and it may only identify a mixed histology in only one-third of cases (18). Incidental radiological findings of a pelvic mass could be the first evidence of the disease in asymptomatic patients. CT scan is the gold standard preoperative diagnostic imaging test; it shows a cystic mass of liquid density adjacent to the caecum and at a retrocecal location in most cases (19). Unfortunately, mass dimensions and radiological characteristics on CT scan and MRI in some cases cannot identify the origin of tumors, particularly if the origin is ovarian or appendicular (20). In both our cases, radiological findings were compatible with both origins, and the final evidence of an appendiceal disease was determined only during surgery.

Gold standard treatment is surgery for selected case. Laparoscopic approach appears to be a safe and feasible option for not advanced cases (15). Appendectomy alone is the treatment of choice when benign lesions, such as adenoma or LAMN with negative margins and NEN of <1 cm, are present (21–23). In adenocarcinoma or NEN of >2 cm with the involvement of the appendiceal base, segmental colectomy with lymph node dissection for tumor staging is indicated (5, 21, 25). Right hemicolectomy should also be considered in NEN of 1 cm–2 cm with serosal involvement, Ki-67 proliferative index of >2%, location at the base of the appendix, and angioinvasion or neuroinvasion (5, 12, 21–25).

Initially, we performed a laparoscopic appendectomy with peritoneum biopsy in one case. Through the laparoscopic exploration, a pseudomyxoma peritonei was excluded. Postoperative morbidity was not observed. The effect of two different histological components increases the complexity of therapeutic approach because it is not yet clear whether biological behavior depends on a larger or more aggressive component (17).

Histologic findings are relevant to the prognosis and treatment of patients, and the management of collision tumors is guided by component neoplasms (25). Generally, the more aggressive histological pattern determines the clinical evolution of the disease (26). Duffy et al. (27) suggested that the treatment should be more aggressive in a collision tumor with major neuroendocrine components and high grading. Therefore, in relation to the pathology, we performed a simple appendectomy in one case and a minimally invasive right hemicolectomy for the more aggressive behaviour of NEN in the other case.

The most important factor for improving the outcome is early and accurate diagnosis with adequate histopathological examination to confirm the presence of two components within the same neoplasm (28). Immunohistochemical tests are the cornerstone in identifying a large number of these tumors, from adenomas or adenocarcinomas with several neuroendocrine cells to classical neuroendocrine tumors with focal exocrine/epithelial elements (17).

Moreover, adjuvant chemotherapy for collision tumor has not been evaluated in prospective randomized trials. Adjuvant chemotherapy is not recommended for low-grade, well-differentiated mucinous tumors and should only be considered in cancers with invasive features such as lymphovascular or lymph node involvement (29). Prevention or delayed neuroendocrine syndrome is not supported by randomized evidence from the perioperative setting of pure G2 or G3 NENs (30). However, advanced appendiceal NEN treatment with somatostatin analogs (SSAs) as the first-line approach is associated with more prolonged progression-free survival; however, in patients with a progressive disease despite receiving treatment with SSAs, further therapeutic modalities may include temozolomide-based chemotherapy (30, 31).

In previous studies, recurrent disease was only found in 3 patients with metastasis at the first operation (16, 26, 32, 33).

Long-term surveillance and follow-up are necessary for both tumor types according to final pathological reports. However, there are no suggested guidelines for an optimal postoperative follow-up (15).

Conclusions

Appendiceal collision tumors are rare diseases; therefore, they continue to be challenging for physicians. Unfortunately, the small sample size of this study does not allow for definitive conclusions to be made. Considering the controversy relating to its definition, the limited diagnostic ability of biopsies, and the lack of awareness of this diagnosis within the scientific community, the disease remains underestimated. Currently, no

shared guidelines are available. Moreover, the definitive diagnosis can be achieved only after surgery because NEN could be overlooked during diagnosis because of its small dimension. Therefore, each patient must be managed case by case, and a multidisciplinary team, including gynecologists, surgeons, radiologist, oncologist and pathologists with expertise in NENs, is important for appropriate management of patients. This approach involves various health professionals from different organizations to provide utmost care and advanced treatment to patients based on latest available insights into the disease.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by APSS Santa Chiara Hospital Trento, Italy. The patients/participants provided their written informed consent to participate in this study.

Authors contribution

Conceptualization, GV; Data curation, EM, FA and GDP; Formal analysis, MF and NDL; Investigation, SM and MB; Validation, SV, EB, MB, LM and ST; Writing—review & editing, FC and AB. 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.

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Results of sclerotherapy and mucopexy with haemorrhoidal dearterialization in II and III degree haemorrhoids. A 4 years' single centre experience

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Introduction: Haemorrhoidal disease (HD) affects a considerable portion of the adult population. The aim of this study is to confirm the safety and efficacy of the treatments and to report the long-term outcomes of Sclerotherapy (ST) and Mucopexy and Haemorrhoidal Dearterialization (MHD) performed over the last 4 years in a single tertiary centre. The secondary outcome is to evaluate the usefulness of both techniques and to demonstrate how those can be associated as a bridge to surgery.

Materials and methods: Patients affected by second–third-degree haemorrhoids and undergoing ST or non-Doppler guided MHD between 2018 and 2021 were enrolled. Safety and efficacy, recurrence rate, Haemorrhoid Severity Score (HSS) and pain resulting from both techniques were evaluated.

Results: Out of 259 patients, 150 underwent ST. Further, 122 (81.3%) patients were male and 28 (18.7%) were female. The mean age was 50.8 (range 34–68) years. Most of the patients (103, 68.6%) were affected by second-degree HD, while 47 (31.4%) were affected by third-degree HD. The overall success rate was 83.3%. The median pre-operative HSS score was 3 (IQR 0–4, $p = 0.04$) and at 2 year the median HSS was 0 (IQR 0–1, $p = 0.03$). No intraoperative complications and no drug-related side effects occurred. The mean follow-up for ST was 2 years (range 1–4; SD $\pm$0.88). MHD was performed on 109 patients. In detail, 80 patients (73.4%) were male while 29 patients (26.6%) were female. The mean age in this group was 51.3 (range 31–69). Further, 72 patients (66.1%) were affected by third-degree HD and 37 (33.9%) by second-degree HD. The median HSS score was 9 (IQR 8–10, $p = 0.001$) preoperatively two years after treatment was 0 (IQR 0–1, $p = 0.004$). Major complications occurred in three patients (2.75%). The overall success rate was 93.5% (second degree 89.2% vs. third degree 95.8%). The mean follow-up for MHD was 2 years (range 1–4; SD $\pm$0.68).

Conclusions: The results confirm the usefulness of those techniques, which can be considered safe and easily repeatable procedures, with a low recurrence rate after 2 years of median follow-up.

KEYWORDS

haemorrhoidal disease, mucopexy and dearterialization, sclerotherapy, goligher classification, office-based procedures, surgical treatment

1. Introduction

Haemorrhoidal disease (HD) is one of the most common proctological diseases affecting the general population, from mid-teens onward, with considerable implications for the National Health Service (NHS) in terms of cost and surgeons' workload (1).

Despite various classifications having been proposed over the last 50 years, currently, Goligher's classification is still the most used, driving the diagnosis and representing the best therapeutic option for each patient (2). In the last two decades, several new techniques and devices have been proposed for HD treatments (3).

According to European guidelines (2), sclerotherapy (ST) can be recommended for first-, second- and third-degree HD when conservative treatment fails. A local intravenous injection of sclerosant agents induces sclerosis of the submucosal tissue with endothelial damage of the vessels and consequent suspension of the haemorrhoidal tissue (4).

Different sclerotherapy techniques with various sclerosant agents have been described in the literature. Nowadays, polidocanol is the most frequently used sclerosant agent because it is a non-ionic surfactant that targets endothelial cells (5).

The advantage of ST is the possibility to perform the procedure in an outpatient setting and to repeat the treatment "on demand". Furthermore, this technique could be adopted as a bridge to surgery, especially in high-risk patients.

An improved understanding of the pathogenesis of haemorrhoids and of the complications associated with excisional haemorrhoidectomy has led to the invention of new surgical procedures, including mucopexy with haemorrhoidal dearterialization (MHD), with or without Doppler, which can be used for second-, third- and, in certain cases, even for fourth-degree HD. This technique consists of interrupting the vascular supply and lifting the haemorrhoidal cushions. This technique has shown encouraging results in terms of postoperative pain, complications and long-term recurrence (6).

The aim of this study is to confirm the safety and efficacy of the treatments and to report the long-term outcomes of ST and MHD performed over the last 4 years in a single tertiary centre. The secondary outcome is to evaluate the usefulness of both techniques with different trends and results, and to demonstrate how those can be associated as a bridge to surgery.

2. Materials and methods

2.1. Patients

A retrospective study was designed to evaluate the safety, efficacy and long-term outcomes of sclerotherapy and mucopexy with non-Doppler guided haemorrhoidal dearterialization for symptomatic haemorrhoidal disease. The study was carried out in the Coloproctology Unit "Bari 2", Hospital University of Bari, between February 2018 and December 2021 (including the first wave of the Sars-Cov-2 pandemic, when there was a decrease in surgical activities (7, 8). All patients were not enrolled consecutively and all procedures were performed by the same experienced surgeon.

The inclusion criteria were: second- to third-degree symptomatic haemorrhoids, including previous HD with evidence of recurrence. For ST, the inclusion criteria also included patients on a waiting list for surgery, HD associated with severe anaemia requiring blood transfusion (as an emergency procedure), as well as HD in patients refusing surgery with American Society of Anesthesiologists scores of 3 and 4.

Pregnant women, patients younger than 18 years old, those affected by external haemorrhoidal thromboses or by other proctological diseases or IBD patients were excluded.

Information regarding family history, bowel habits, diet and previous intake of flavonoids was collected before the proctological evaluation, consisting of digitorectal examination and anoscopy. The guidelines on perioperative management of anticoagulant and antiplatelet agents were applied according to pharmaceutical anamnesis.

The severity of the condition was assessed through the administration of the Haemorrhoid Severity Score (HSS) (9) and the Visual Analog Scale (VAS from 0 to 10) for pain assessment.

All patients were asked to fill in a daily diary for the first 7 postoperative days and to report bleeding, pain, soiling, tenesmus, return to daily activity and satisfaction grade. Follow-up was scheduled at 1, 3, 6, 12, 24 and 48 months in the outpatient clinic.

Written informed consent was obtained from all patients.

2.2. Surgical techniques

- *Sclerotherapy*

Sclerosant foam (Atossisclerol 3% alias Polidocanol-Lauromacrogol 400 by Gloria Med Pharma) was administered according to a modified Blonde-Blanchard technique. Polidocanol foam is injected directly into the haemorrhoids at the 3, 7 and 11 o'clock positions and not into the submucosa, above the dentate line, with 2.5 ml of foam injected into each pile. The inclination of the needle in male patients should be tangential to the 11 o'clock position pile to avoid prostatic tissue. The foam was obtained as previously described (10).

The patients were treated in the Sims position with no anaesthesia. Walking for 20 min after the procedure was suggested before a pre-discharge check (**Figures 1A,B**).

- *Mucopexy and Haemorrhoidal Dearterialization with EndoRectal Operative Device*

Mucopexy with haemorrhoidal dearterialization was performed without Doppler, using the EndoRectal Operative Device (ERODe —Copyright © Sapi Med S.P.A.). Six longitudinal mucosal plications with 2–0 gauge, 5/8 Circle round-body needle, polygliactin sutures at 1, 3, 5, 7, 9 and 11 o'clock, not exceeding the dentate line, were performed, ligating arteries without a Doppler guide, with the patient in a modified lithotomy position and under spinal anaesthesia. In some cases, another plication was necessary because of excess mucosal prolapse or

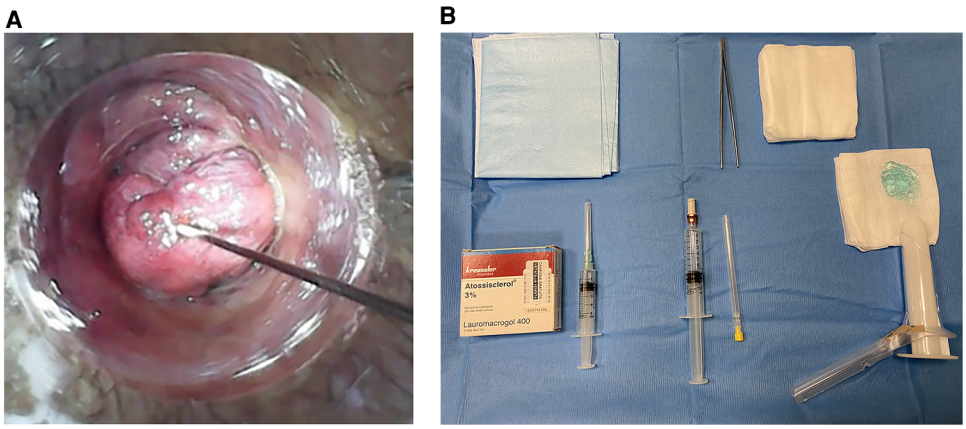

FIGURE 1
(A,B): sclerotherapy injection and materials.

haemorrhoidal tissue. The number of single plication steps was variable from sector to sector in proportion to the mucosal prolapse. The ERODe device consists of a conic retractor with an oval distal part, with a plate that allows for variation in the depth of the socket. This device allows for the homogenous and progressive dilation of the anal canal, with optimum ergonomics and dexterity (Figures 2A,B).

Discharge was scheduled on the first post-operative day (POD), with careful dietary and defaecation recommendations.

2.3. Statistical analysis

All the data were collected in an Office Excel® sheet. The chi-square test was used to compare categorical variables. Odds ratios (ORs) and 95% CI were calculated when required. The Mann–Whitney *U* test was used to compare continuous variables not normally distributed (presented as median, interquartile range (IQR) and range). Normality of variable distribution was determined using the D'Agostino–Pearson test. A p value < 0.05 was considered to be statistically significant. All tests were two-sided.

Data were analysed using R Studio (Version 1.1.419—© 2009–2018 RStudio, Inc).

3. Results

In total, 259 patients were enrolled in this study: 150 were recruited in the ST group and 109 patients in the MHD group.

3.1. Sclerotherapy

First, 150 symptomatic patients with second- and third-degree haemorrhoids underwent sclerotherapy treatment.

Further, 122 (81.3%) patients were male, 28 (18.7%) were female and their mean age was 50.8 (range 34–68) years. Most of the patients (103, 68.6%) were affected by second degree HD, while 47 (31.4%) were affected by third-degree HD. No intraoperative complications and no drug-related side effects occurred.

All patients resumed their normal daily activities the day after the procedure. The overall success rate was 83.3% after a single ST session (second degree 87.5% vs. third degree 73.9%) (Figure 3).

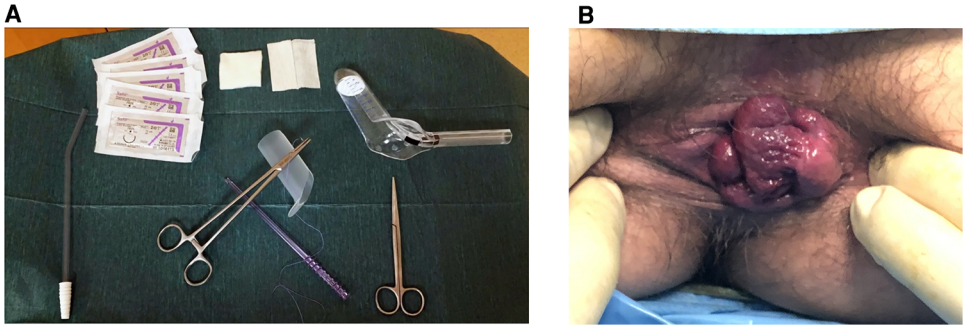

FIGURE 2
(A,B): mucopexy with haemorrhoidal dearterialization materials and pre-operative 3rd degree haemorrhoidal disease.

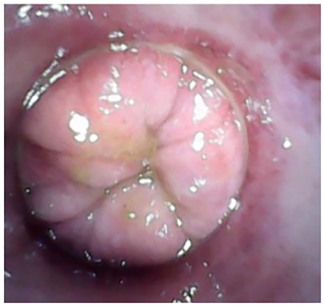

FIGURE 3
Follow-up after sclerotherapy (one month).

Recurrences in terms of bleeding occurred in 21 (31.5%) patients. A second ST session was performed for 11 patients (16.5%), and 10 patients required surgical treatment (Mucopexy and Dearterialization).

The median pre-operative HSS score was 3 (IQR 0–4, $p = 0.04$) and it did not improve after one week (median 3, IQR 0–4, $p = 0.04$), while it significantly improved after one month (median 2, IQR 0–3, $p = 0.01$) and at the one-year follow-up, with a median of 1 (IQR 0–1, $p = 0.01$). The effectiveness of ST was also confirmed after a follow-up of 2 years, with a median HSS of 0 (IQR 0–1, $p = 0.03$) (Figure 4). Eleven patients (16.5%) were affected by severe anaemia (in one case haemoglobin was less than 7gr/dl) and required blood transfusions, and, in these cases, ST was performed in an emergency setting.

VAS score pain was 0 in all patients after the procedure and during all follow-up sessions. The mean operative time was 3 (2–5; SD ± 1.03).

The Hospital University of Bari was a COVID-19 centre from March 2020, and proctological activity was stopped for one year. Only 15 ST treatments were performed for symptomatic HD disease (second and third degree): two cases were affected by severe anaemia, requiring a blood transfusion.

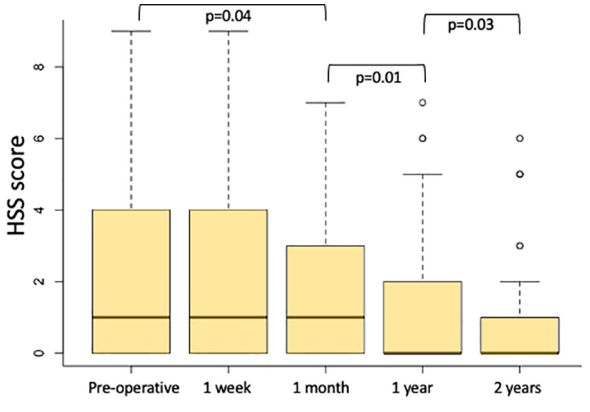

FIGURE 4
Haemorrhoids severity score (HSS) calculated preoperatively, one week, one month, one year and two years after ST.

TABLE 1 Patient's characteristics.

	Sclerotherapy	MHD
Patients	150	109
M	122 (81.3%)	80 (73.4%)
F	28 (18.7%)	29 (26.6%)
Age	50.8	51.3
Haemorrhoidal Disease Degree		
Second	103 (68.6%)	37 (33.9%)
Third	47 (31.4%)	72 (66.1%)
Overall Success Rate		
Second	87.5%	89.2%
Third	73.9%	95.8%
Recurrences	21 (31.5%)	7 (4.6%)
Haemorrhoid Severity Score (HSS)		
pre op	2.4	9
1 week	2.3	6
1 month	1.4	5
1 year	1	2
2 years	0	0
Mean Hospital stay (days)	0	1.1
Mean Operative Time (min)	3	40

The mean follow-up for ST was 2 years (range 1–4; DS ±0.88). Follow-up was regularly scheduled in an outpatient clinic with complete proctological examination.

All results can be appreciated in Table 1.

3.2. Mucopexy with haemorrhoidal dearterialization

In terms of patients, 109 underwent this surgical procedure. Further, 80 patients (73.4%) were male while 29 patients (26.6%) were female. The mean age in this group was 51.3 (range 31–69). Additionally, 72 patients (66.1%) were affected by third-degree HD and 37 (33.9%) by second-degree HD.

Fourteen patients (12.8%) had refractory HD, treated by previous surgical or outpatient procedures; eleven patients (10.1%) were also affected by anterior rectocele; and six patients (5.5%) had severe anaemia.

The mean hospital stay was 1.1 days (IQR 1–5), and the mean operative time was 40 min (IQR 34–52).

The median VAS pain score was 5 (IQR 3–8) on the 7th postoperative day (POD) and less than 2 after the first 10 days. In the first week after the procedure, bleeding occurred in 14 patients (15.2%), while tenesmus was reported by 66 patients (60.5%). At one month follow-up, bleeding was reported by three patients (2.75%) and tenesmus by two patients (2.1%) (Figure 5).

The median HSS score was 9 (IQR 8–10, $p = 0.001$) preoperatively and it significantly improved after one week (median value 6, IQR 5–6, $p = 0.002$), progressively decreased at one month (median value 5, IQR 3–6, $p = 0.001$) and after one year (median value 2, IQR 0–2, $p = 0.0001$). The HSS score also improved two years after treatment (median value 0, IQR 0–1, $p = 0.004$) (Figure 6).

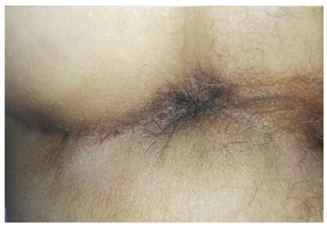

FIGURE 5
Follow-up after modified mucopexy with haemorrhoidal dearterialization (one year).

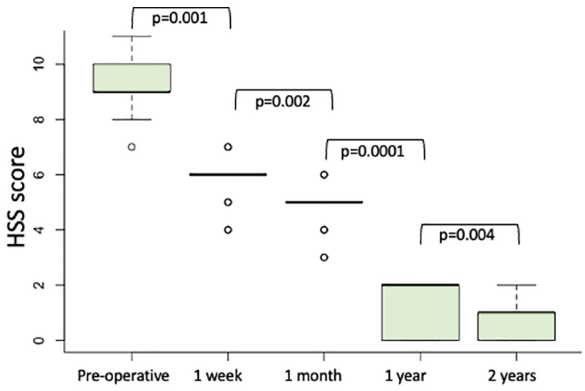

FIGURE 6
Haemorrhoids severity score (HSS) calculated preoperatively, one week, one month, one year and two years after modified mucopexy with haemorrhoidal dearterialization.

Major complications, consisting mainly of haemorrhage, occurred in three cases (2.7%), and these were treated with a blood transfusion in two cases and *via* surgical revision in one patient. Minor complications, including haemorrhoidal thrombosis, occurred in six (6.6%) patients, while abscess formation was observed in one patient. In this patient, the abscess was surgically drained in an outpatient setting. Recurrences were noted after 6 months in seven patients (4.6%). Three patients with a recurrent prolapse were treated *via* re-do surgery. Four patients reported persistent bleeding and they were treated with ST.

The overall success rate was 93.5% (second degree 89.2% vs. third degree 95.8%). The mean follow-up for MHD was 2 years (range 1–4; SD ±0.68). Follow-up was regularly scheduled in the outpatient clinic with a complete proctological examination.

All results can be appreciated in **Table 1**.

4. Discussion

The management of haemorrhoids has significantly changed in the last few decades. New insights into their pathophysiology have been described, and new mini-invasive surgical devices and procedures have been proposed (11).

Some of these procedures have been validated and included in national and international guidelines (2, 12).

A first step in the treatment of HD should include dietary changes (adequate water intake, high-fibre diet, laxatives such as bulking agents) and flavonoid intake. Patients with symptomatic HD should be informed of the pros and cons of all procedures, and patient shared decision making is crucial (2, 12).

Among the outpatient treatments, there are a few options that can be proposed to patients (13).

James Morgan described the use of Sclerotherapy for the first time in history of HD in 1869 (14).

The composition of the foam injected during ST has been a matter of debate. In 2000, Petrin reported good results with polidocanol 1% in 80 patients affected by second-degree HD (15).

The comparison between the transanal approach vs. endoscopic ST is still debated in the literature (16). Nevertheless, recent studies suggest better outcomes and comfort for patients treated with transanal ST rather than endoscopic ST (17).

In this study, we used the transanal approach, injecting Atossisclerol 3%, which has previously been demonstrated to be a safe, effective and repeatable conservative treatment for HD (4, 5, 18–21).

Furthermore, the modified Blonde-Blanchard technique adopted in this report reduces the risks of major complications, such as compartment syndrome, necrotising fasciitis, retroperitoneal sepsis, rectourethral fistula (22–25) and prostate injury, that can lead to prostatitis or prostatic abscess (26). The adopted technique with a tangential approach to the 11 o'clock pile is beneficial in that it avoids the prostatic tissue.

The results showed that after ST, pain is well-controlled, while tenesmus seems to be a frequent symptom until 7 POD (60.5%), which may be due to the oedema and hypertension in each of the haemorrhoidal piles. Furthermore, the reported patients demonstrated significant improvements in terms of bleeding in second-degree HD and also in terms of prolapse in third-degree HD.

Although Keng-Sheong reported "poor" long-term outcomes in terms of recurrence rate after ST (27), in this study, we reported a low recurrence rate after a period of at least 2 years.

The second group of patients was treated with a modified technique involving Mucopexy with Haemorrhoidal Dearterialization using the ERODe device without a Doppler guide. In the last decade, some studies have demonstrated the efficacy of haemorrhoidal artery ligation if associated with rectoanal repair or mucopexy for third-degree haemorrhoids (28, 29). On the other hand, Aigner et al. (30) recently cast some doubt on the usefulness of Doppler-guided haemorrhoidal artery ligation and reported that the Doppler proof was not beneficial for third-degree haemorrhoid treatment when compared to suture mucopexy alone.

This study demonstrates that the "suspensive" technique using the ERODe device without a Doppler guide is safe and repeatable for both prolapse and bleeding. In fact, plication lifts the haemorrhoidal and mucosal tissue, and artery ligation reduces bleeding. According to the Italian Society of Colorectal Surgery consensus statement, the use of MHD with or without Doppler is associated with a faster recovery, less postoperative pain and

good outcomes in eligible patients when compared to excisional procedures (12). A Doppler guide could be helpful to identify the haemorrhoidal arteries, but it is not mandatory and does not modify outcomes (1, 2, 12).

A recent multicentre study reported benefits from Doppler-guided MHD using a THD device with a 9.5% recurrence and 7% reoperation rate (29, 31, 32). Giuliani et al. reported that MHD is a safe and efficient technique, especially for third-degree HD (33).

The results of this work exposed a lower recurrence rate and shorter surgery duration in a smaller sample of recruited patients. Furthermore, MHD failure can be treated using ST in terms of bleeding resolution.

ST and MHD are two different procedures, not comparable in terms of application and surgical technique, but they may be associated. Eligibility criteria for each procedure can be combined in cases of recurrences in second-degree and third-degree HD and as a bridge to surgery or re-do surgery.

The statistical analysis demonstrates that there are no differences in terms of significance, reporting a good overall success rate for both procedures over the last 4 years.

This study has some limitations: it is a retrospective, single-centre study, based on the description of results of two treatments for HD, without any comparison to similar procedures, and the follow-up is not homogeneous. Patients were not selected consecutively representing a selection bias. This study presents real-world evidence from an experienced proctologic centre, accomplished according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (34).

5. Conclusions

The results of this study from an experienced proctologic centre confirm the usefulness of Sclerotherapy with Atossisclerol 3% and Mucopexy with Haemorrhoidal Dearterialization using ERODe device and demonstrate how they can be combined. Those techniques can be considered safe and easily repeatable procedures, with a low recurrence rate after 2 years of median follow-up.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: PL.; methodology: RL.; validation: AP. 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

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Does invasive acupuncture improve postoperative ileus after colorectal cancer surgery? A systematic review and meta-analysis

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Background: Postoperative ileus (POI) is one of the main complications after colorectal cancer (CRC) surgery, and there is still a lack of effective treatment. At present, the evidence for improvement of POI by invasive acupuncture (manual acupuncture and electroacupuncture, IA) is limited. This meta-analysis of randomized controlled trials (RCTs) aims to systematically review and evaluate the effect of IA in improving POI after CRC surgery.

Methods: This meta-analysis was reported according to PRISMA statement and AMSTAR guidelines. The retrieval time was from the inception to February 2023. The RCTs were screened by searching the databases (PubMed, Ovid, Embase, Cochrane Library, China National Knowledge Infrastructure, VIP Database, Sinomed Database, and WANFANG). Two independent investigators screened and extracted the data, assessed the risk of bias, and performed statistical analysis. The statistical analysis was carried out by RevMan5.3. The PROSPERO International Prospective Register of Systematic Reviews received this research for registration (CRD42023387700).

Results: Thirteen studies with 795 patients were included. In the primary outcome indicators: the IA group had shorter time to the first flauts [stand mean difference (SMD), −0.57; 95% CI, −0.73 to −0.41, $p < 0.00001$], shorter time to the first defecation [mean difference (MD), −4.92 h, 95% CI −8.10 to −1.74 h, $p = 0.002$] than the blank/sham stimulation (B/S) group. In the secondary outcome indicators: the IA group had shorter time to the first bowel motion (MD, −6.62 h, 95% CI −8.73 to −4.50 h, $p < 0.00001$), shorter length of hospital (SMD, −0.40, 95% CI −0.60 to −0.21, $p < 0.0001$) than the B/S group. In terms of the subgroup analysis: IA associated with enhanced recovery after surgery (ERAS) group had shorter time to the first flauts (MD, −6.41 h, 95% CI −9.34 to −3.49 h, $p < 0.0001$), shorter time to the first defacation (MD, −6.02 h, 95% CI −9.28 to −2.77 h, $p = 0.0003$) than ERAS group.

Conclusion: Invasive acupuncture (IA) after CRC surgery, acupuncture or electricacupuncture with a fixed number of times and duration at therapeutic acupoints, can promote the recovery of POI. IA combined with ERAS is better than simple ERAS in improving POI.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=387700, identifier CRD42023387700.

KEYWORDS

acupuncture therapy, meta-anlaysis, postoperative complications, surgical oncology, Traditional Chinese Medicine

1. Introduction

Postoperative ileus (POI) is one of the main postoperative complications of colorectal cancer (CRC) surgery, and recent research shows that its incidence rate is 13.5% (1). The recovery of POI usually takes 4 days, and the main clinical manifestations are delayed exhaust and defecation, abnormal bowel sounds, abdominal distention, nausea, and vomiting (2, 3). In addition, POI also extended the time and expenses for hospitalization (4). At present, basic treatments, such as fasting, nutritional support, maintaining water, electrolyte, and acid–base balance, are used to treat POI. Other therapies like drugs to promote gastrointestinal motility, chewing gum, and so on, are also used (5). However, the clinical efficacy of the existing treatment schemes is limited. Therefore, finding a new treatment to prevent POI has become an important issue so that patients with colorectal cancer can recover quickly during postoperative period (6).

Acupuncture is a non-drug, safe and inexpensive treatment. Some existing clinical studies show that acupuncture and related therapies can effectively improve the POI in surgical operations (7). However, external treatment were combined with invasive acupuncture (IA) in the intervention measures, such as moxibustion, acupoint application, and transcutaneous acupoint electrical stimulation (8). Therefore, we want to explore whether IA alone can improve POI after CRC surgery. And we include related randomized controlled trials (RCTs) for this meta-analysis so as to clarify its effect.

2. Materials and methods

2.1. Protocol and registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards were followed while reporting this study. Supplementary Table S2 contains the PRISMA checklist. This study was also followed the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions. PROSPERO International prospective register of systematic reviews was where the review procedure was registered (CRD42023387700).

2.2. Search strategy

The following databases were searched for this meta-analysis: PubMed, Ovid, Embase, Cochrane Library, China National Knowledge Infrastructure, VIP Database, Sinomed Database, and WANFANG Medical. It was reported in accordance with the PRISMA declaration and AMSTAR criteria. The search period spanned from beginning until February 2023. High-quality RCTs were gathered by two independent researchers. According to the search's approach, full-text search was carried out (Supplementary Table S3).

2.3. Eligibility criteria

Inclusion criteria include (1) Research type: RCTs on the preventive and therapeutic effects of IA (manual acupuncture and electroacupuncture) on POI after CRC surgery; Language is not limited. (2) Research objects: Patients with CRC undergoing IA during perioperative period; Age, gender and nationality are not limited. (3) Intervention measures: The acupuncture group received manual acupuncture (MA) or electroacupuncture (EA) during perioperative period; The blank/sham stimulation group(B/S) did not receive any treatment or stimulated non-meridian points.

Exclusion criteria include (1) Non-invasive acupuncture acupoint stimulation therapy, such as transcutaneous acupoint electrical stimulation, acupoint application, auricular point pressing beans, etc. (2) Intervention measures are IA combined with other Chinese medicine treatments, such as oral Chinese medicine decoction. (3) Non-colorectal cancer surgery patients or other intervention methods entered the research literature. (4) Literature with incomplete original text or ending index cannot be obtained. (5) Non-RCT, systematic review or comments, editorials, letters, meetings, and animal trials.

2.4. Outcome indicator

According to the effect of IA on preventing and treating POI, the main outcome indicators are: (1) Time to the first flauts; (2) Time to the first defecation; Secondary outcome indicators: (3) Time to the first bowel motion; and (4) Length of hospital.

2.5. Data extraction and quality assessment

According to the eligibility criteria above, two independent investigators preliminary screened through the title and abstract, and then the full text. The author's name, publishing years, size of the sample, intervention methods, outcome indicators, and other data were extracted from the final screened literature. In case of disagreement, any potential disagreement shall be submitted to the correspondent for arbitration.

According to the Cochrane systematic review handbook 5.1 and its suggested risk of bias assessment technique, the caliber of the included studies was assessed. Random sequence generation, allocation concealment, blinding of trial participants and staff, blinding of outcome assessors, inadequate outcome data, selective reporting, and other biases were all examined in the research. The bias assessment's findings were "low risk," "high risk," and "unclear." Two researchers independently completed the quality evaluation. Conflicts were resolved through mediation by the corresponding author.

2.6. Statistical analysis

Utilizing the program RevMan 5.3, statistical data analysis was carried out. The Standard mean difference (SMD) or Mean difference (MD) and its 95% CI are statistically described and the effect quantity is combined. Inter-study heterogeneity was assessed using chi-square test with a test level of $\alpha = 0.1$, and the degree of heterogeneity was observed based on I^2 values (9). The studies with clinical and methodological homogeneity were combined, and if $p \geq 0.1$ and $I^2 \leq 50\%$, the included studies had good homogeneity and were analyzed using a fixed-effects model for meta-analysis; if $p < 0.1$ and $I^2 > 50\%$, it was considered that there was significant heterogeneity among the included study literature, and subgroup analysis treatment or sensitivity analysis was needed to find the source of heterogeneity; if there was no significant clinical heterogeneity, the random-effects model was selected for merging; sensitivity analysis was performed when there were large weight items to check the stability of the results; if the heterogeneity was large, meta-analysis was not performed, and only descriptive analysis was performed. If the number of literatures was sufficient, funnel plots were used to determine whether there was publication bias (10).

3. Results

The GRADE evidence profiles and summary of findings table was shown in Table 1.

3.1. Literature search

A total of 350 relevant literatures were obtained from the search, 176 duplicates were excluded, 137 were eliminated based on title and abstract, and then 24 were excluded based on full text, resulting in the inclusion of 13 studies that met the study requirements, all in China, including one conducted in Hong Kong. There were 395 patients in the IA group and 400 patients in the B/S group, for a total of 795 patients. There of the included studies explicitly mentioned the use of open surgery, four explicitly mentioned the use of laparoscopic surgery, and the other studies described only part of the type of surgery; four studies used enhanced recovery after surgery (ERAS); nine studies used EA, four studies used MA; one study performed acupuncture 1 day before surgery; and the remaining studies were performed postoperatively. The literature screening process was shown in Figure 1. The basic characteristics of the included studies were shown in Tables 2, 3.

3.2. Quality assessment of included studies

(1) Random sequence generation: four papers used random number table method; two papers used computer software to generate random groupings; two papers used random zone grouping method; one paper used closed envelopes; two papers only mentioned random and did not describe the method of random sequence generation; one paper mentioned minimization; one paper did not mention random. (2) Allocation concealment: three papers used closed envelope allocation concealment; two papers mentioned allocation concealment without specific methods, and the rest did not mention allocation concealment. (3) Blinding of subjects and trial personnel: five papers mentioned blinding of subjects and investigators; one mentioned using single blinding, and the rest did not mention blinding. (4) Blinding of outcome assessors: five papers mentioned blinding of outcome index assessors, and the rest did not describe it. (5) Incomplete outcome data: one study mentioned the reason why some of the outcome indicators did not appear, but the proportion of missing outcome indicators was not enough to have a significant impact, and the rest of the studies had no missing data. (6) Selective reporting: three studies had access to the study protocol and eventually reported the expected outcome indicators, while the rest had incomplete information and it was difficult to determine whether there was a risk of selective reporting of outcomes. (7) Other bias: there was no evidence or information to determine whether there was other serious risk of bias in the included studies.

Of the 13 included publications, our quality assessment using the Cochrane Risk of Bias Assessment Tool showed that the overall quality of the total literature was moderate (Figure 2).

3.3. Primary outcome indicators

3.3.1. Time to the first flauts

All studies reported the effect of IA vs. B/S on the time to first flauts after CRC surgery, involving 632 patients, 316 in the IA group and 316 in the B/S group. Heterogeneity was detected ($p < 0.00001$, $I^2 = 88\%$) with significant heterogeneity, and sensitivity analysis was performed and three studies were excluded before heterogeneity was detected ($p = 0.53$, $I^2 = 0\%$) with no significant statistical heterogeneity, low sensitivity, and good stability. The fixed-effects model combined with effect size analysis was used, and the results showed that the time to the first flauts was significantly lower in the IA group than in the B/S group [stand mean difference (SMD), −0.57; 95% CI, −0.73 to −0.41, $p < 0.00001$], as shown in Figure 3A.

3.3.2. Time to the first defecation

Eight studies reported the effect of IA vs. B/S on the time to first defecation after CRC surgery: 380 patients were involved, 189 in the IA group and 191 in the B/S group. Heterogeneity was detected ($p = 0.02$, $I^2 = 58\%$) with significant heterogeneity, and sensitivity analysis was performed and one study was excluded before heterogeneity was detected ($p = 0.52$, $I^2 = 0\%$) with no significant statistical heterogeneity, low sensitivity, and good stability, and the fixed-effects model combined with effect size analysis was used, and the results showed that the time to the first defecation was significantly lower in the IA group than in the B/S group [mean difference (MD), −4.92 h, 95% CI −8.10 to −1.74 h, $p = 0.002$], as shown in Figure 3B.

3.4. Secondary outcome indicators

3.4.1. Time to the first bowel motion

Nine studies reported the effect of IA vs. B/S on the first bowel motion after CRC surgery: 405 patients were involved, 200 in the IA and 205 in the B/S group. Heterogeneity was detected ($p < 0.00001$, $I^2 = 80\%$) with significant heterogeneity, and sensitivity analysis was performed and two studies were excluded before heterogeneity was

TABLE 1 GRADE evidence profiles and summary of findings table.

Outcome (studies)	No. of participants		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence	Anticipated absolute effects (95% CI)
	IA	B/S							
Time to first flauts (13 RCTs)	316	316	Serious	Not serious	Not serious	Not serious	None	⨁⨁⨁◯ Moderate	SMD −0.57 lower (−0.73 lower to −0.41 lower)
Time to first defecation (hours; eight RCTs)	189	191	Serious	Not serious	Not serious	Not serious	None	⨁⨁⨁⨁ High	MD −4.92 lower (−8.10 lower to −1.74 lower)
Time to first bowel motion (hours; nine RCTs)	200	205	Very serious	Not serious	Not serious	Not serious	None	⨁⨁◯◯ Low	MD −6.62 lower (−8.73 lower to −4.50 lower)
Length to hospital (seven RCTs)	214	215	Not serious	Not serious	Not serious	Not serious	None	⨁⨁⨁⨁ High	SMD −0.40 lower (−0.60 lower to −0.21 lower)
ERAS subgroup time to first flauts (hours; four RCTs)	141	142	Serious	Not serious	Not serious	Not serious	None	⨁⨁⨁◯ Moderate	MD −6.41 lower (−9.34 lower to −3.49 lower)
ERAS subgroup time to first defecation (hours; four RCTs)	141	142	Serious	Not serious	Not serious	Not serious	None	⨁⨁⨁◯ Moderate	MD −6.02 lower (−9.28 lower to −2.77 lower)

IA, invasive acupuncture; B/S, the blank/sham stimulation; SMD, stand mean difference; and MD, mean difference.

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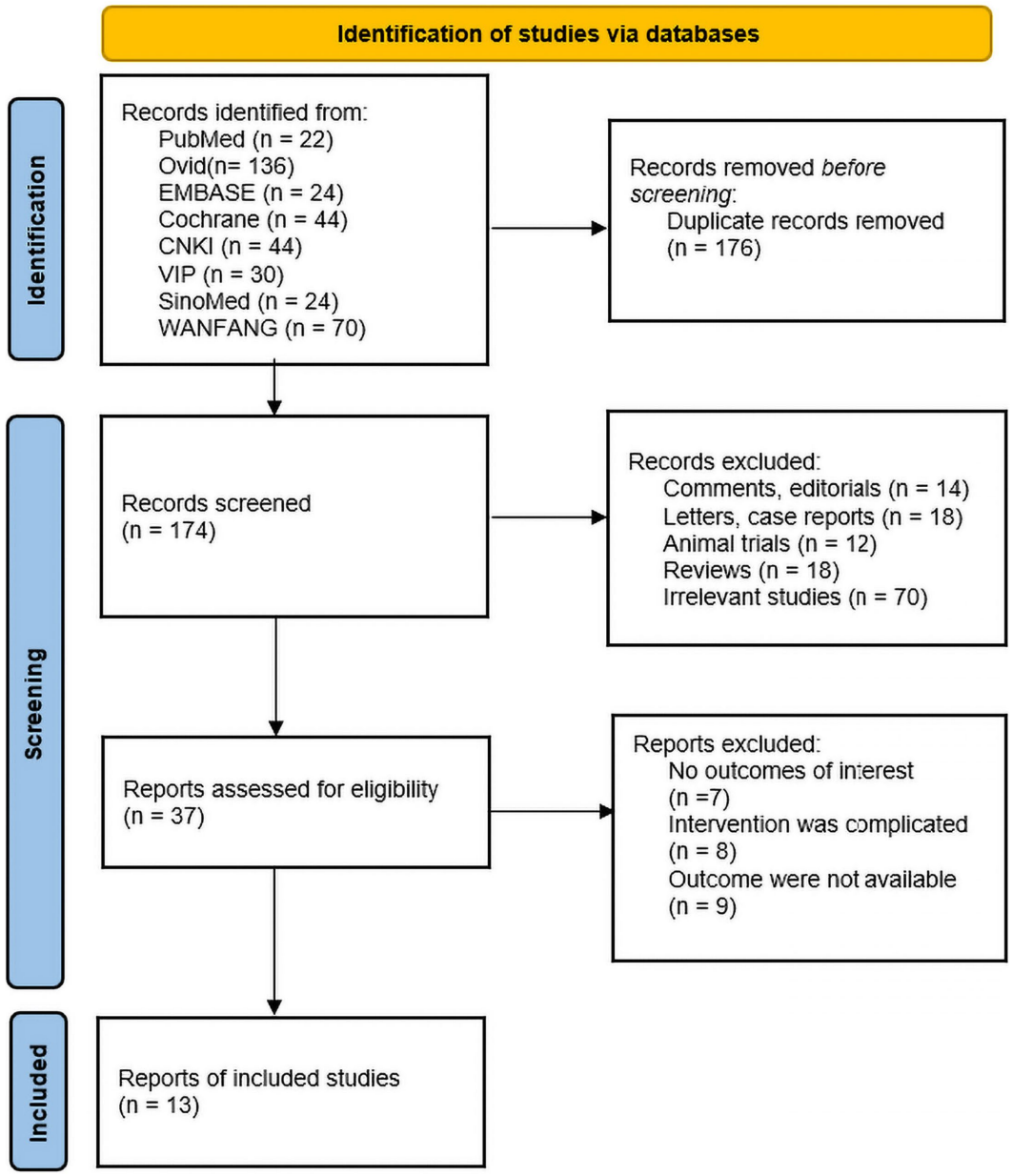

FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

detected ($p = 0.76$, $I^2 = 0\%$) with no significant statistical heterogeneity, low sensitivity, and good stability, using fixed-effects model combined with effect size analysis, the results showed that the time to the first bowel motion in the IA group was significantly lower than that of the B/S group (MD, −6.62 h, 95% CI −8.73 to −4.50 h, $p < 0.00001$), as shown in Figure 3C.

3.4.2. Length of hospital

Seven studies reported the effect of IA vs. B/S on the number of days in hospital: 429 patients were involved, 214 in the IA and 215 in the B/S group. Heterogeneity was detected ($p < 0.06$, $I^2 = 50\%$) with significant heterogeneity, and sensitivity analysis was performed and one study were excluded before heterogeneity was detected ($p = 0.55$, $I^2 = 0\%$) with no significant statistical heterogeneity, low sensitivity, and good stability, using fixed-effects model combined with effect size analysis, and the results showed that length of hospital was significantly lower in the IA group than in the B/S group (SMD, −0.40, 95% CI −0.60 to −0.21, $p < 0.0001$), as shown in Figure 3D.

3.5. Subgroup analysis results

Four studies reported the effect of IA combined with ERAS group on the time to the first flauts: 283 patients were involved, 141 in the IA combined with ERAS group and 142 in the ERAS group. Heterogeneity was detected ($p = 0.72$, $I^2 = 0\%$), with no significant statistical heterogeneity, low sensitivity, and good stability, using the fixed-effects model combined with effect size analysis, which showed that the time

TABLE 2 Study characteristics.

Authors, year	Surgery	Cancer type	Intervention	Patients	Sample size		Outcome
					T	C	
Yang et al. (11)	Laparoscopic surgery	CRC	EA	Adult	35	35	①②④
Wang et al. (12)	Laparoscopic radical surgery	CRC	MA	Adult	30	30	①②③④
Liu et al. (13)	Laparoscopic surgery	CRC	MA	Adult	33	35	①②③④
Cai et al. (14)	Radical surgery	CRC	MA	The aged	32	31	①②
Wang et al. (15)	Usual surgery	RC	EA	Adult	20	20	①②③
Li et al. (16)	Radical surgery	CRC	EA	Adult	42	40	①②③④
Mai et al. (17)	Open surgery	CRC	EA	Adult	20	20	①②③
Xiao et al. (18)	Radical surgery	CC	MA	The aged	30	30	①②④
Si et al. (19)	Radical surgery	CC	EA	Adult	25	25	①③
Zhang et al. (20)	Open surgery	CRC	EA	Adult	19	20	①②③④
Ng et al. (21)	Laparoscopic surgery	CRC	EA	Adult	55	55	①③④
Meng et al. (22)	Open surgery	CC	EA	Adult	35	40	①③
Niu et al. (23)	Radical surgery	CC	EA	Adult	19	19	①

CRC, colorectal cancer; RC, rectal cancer; CC, colon cancer; MA, manual acupuncture; and EA, electroacupuncture; ①: Time to first flatus; ②: Time to first defaecation; ③: Time to first bowel motion; and ④: Length of postperative hospital stay.

TABLE 3 Details of POI interventions.

Author, years	EA or MA procedures	Control interventions	Acupoints
Yang et al. (11)	Postoperative day 2–6/time of discharge; 30 min, once a day; United ERAS	ERAS	Bil (ST36, ST25)
Wang et al. (12)	Postoperative day 1–5; 30 min, once a day	Routine treatment	Bil (ST36, ST25, and PC6); RN6, RN10, RN12, and RN13
Liu et al. (13)	Postoperative day 1–4; 30 min, once a day; United ERAS	ERAS	Bil (ST36, ST37, LI4, and PC6)
Cai et al. (14)	Attached within 2 h after surgery and lasted for 3 days, pressure every 8 h; United ERAS	ERAS	Uk (TF4, CO4, CO6, CO7, CO17, ST36, ST37, ST25, and PC6)
Wang et al. (15)	Postoperative day 1–10; 20 min, once a day	Routine treatment	Bil (LI9, ST39, and ST25); RN12
Li et al. (16)	Once postoperative 6 h, postoperative day 1 to time of ending ileus; 30 min, twice a day; United ERAS	ERAS	Uk (ST36, PC6)
Mai et al. (17)	Preoperative 30 min/1 day; 30 min, once	Routine treatment	R (ST36, ST37, ST39, ST25, and PC6); RN12
Xiao et al. (18)	Postoperative day 1–14; 30 min, twice a day	Routine treatment	Bil (LU5, LU7, LI4, SJ6, ST36, and SP6)
Si et al. (19)	Postoperative 24 h to time of ending ileus; 20 min, once a day	Routine treatment	Bil (ST36, ST37, ST25, SP6, and LI4)
Zhang et al. (20)	Once postoperative 30 min, postoperative day 1–4; 30 min, once a day	Sham acupuncture	Bil (ST36)
Ng et al. (21)	Postoperative day 1–4/time of ending ileus; 20 min, once a day	Sham acupuncture	Uk (ST36, SP6, LI4, and SJ6)
Meng et al. (22)	Postoperative day 1–6/time of ending ileus; 20 min, once a day	Routine treatment	Uk (SJ6, GB34, ST36, and ST37)
Niu et al. (23)	From postoperative day 1, 15 min, twice a day	Routine treatment	Uk (ST36, ST37, and PC6)

Bil, bilateral; R, right; Uk (unknown), it was not clear whether it was unilateral or bilateral; ERAS, enhanced recovery after surgery; ST25,Tianshu acupoint, ST36, Zusanli acupoint; ST37, Shangjuxu acupoint; ST39, Xiajuxu acupoint; RN6, Qihai acupoint; RN10, Xiawan acupoint; RN12, Zhongwan acupoint; RN13, Shangwan acupoint; LI4, Hegu acupoint; LI9, Shanglian acupoint; LU5, Chize acupoint; LU7, Lieque acupoint; SJ6, Zhigou acupoint; SP6, Sanyinjiao acupoint; GB34, Yanglingquan acupoint; PC6, and Neiguan acupoint. Ear points: TF4 Shenmen, CO4 Wei, CO6 Xiaochang, CO7 Dachang, and CO17 Sanjiao.

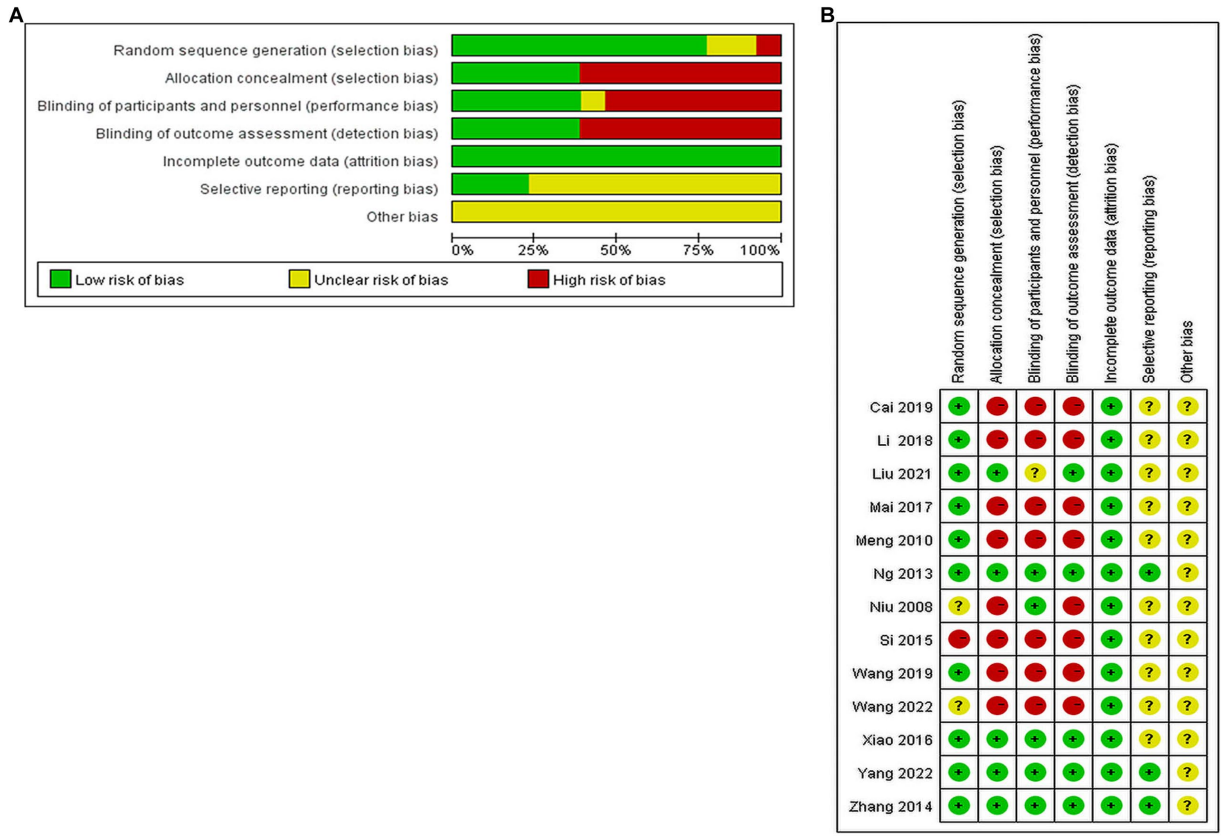

FIGURE 2
Percentage plot of the risk of bias of the included studies. **(A)** Risk of bias graph. **(B)** Risk of bias summary.

to the first flauts was significantly lower in the IA combined with ERAS group than in the ERAS group (MD, −6.41 h, 95% CI −9.34 to −3.49 h, $p < 0.0001$), as shown in Figure 3E.

Four studies reported the effect of IA combined with ERAS group on the time to the first defecation: 283 patients were involved, 141 in the IA combined with ERAS group and 142 in the ERAS group. Heterogeneity was detected ($p = 0.18$, $I^2 = 39\%$), with no significant statistical heterogeneity, low sensitivity and good stability, using the fixed-effects model combined with effect size analysis, which showed that the time to the first defecation was significantly lower in the IA combined with ERAS group than in the ERAS group (MD, −6.02 h, 95% CI −9.28 to −2.77 h, $p = 0.0003$), as shown in Figure 3F.

3.6. Publication bias

Using Revman 5.3 software, a funnel plot was drawn for "comparing the effect of IA and B/S on the time to first flauts after CRC surgery" (Figure 4), which showed good symmetry on both sides of the central axis without significant publication bias and good reliability of the Meta-analysis results.

4. Discussion

Acupuncture and related therapies are guided by Traditional Chinese Medicine (TCM) and are used to prevent and treat diseases by stimulating meridians and acupuncture points, and are used in treatment guidelines for cancer pain, post-operative pain, etc. (24, 25). Currently, some studies have proposed that acupuncture has an ameliorative effect on POI after abdominal surgery such as CRC (7, 26). However, acupuncture, in its broadest sense, involves acupuncture, moxibustion, acupoint application, physical and chemical therapy, and many other means. Acupuncture interventions are mixed and vary greatly among studies due to different interventions. This study was the first meta-analysis of IA for the prevention and treatment of POI after CRC surgery. In addition, ERAS can significantly reduce the incidence of post-colorectal complications and thus has been widely used in the post-surgical period (27, 28). We also compared for the first time the effect of ERAS combined with IA with that of ERAS alone for the prevention and treatment of POI. We concluded that IA can improve POI after CRC surgery, and IA combined with ERAS can significantly reduce the time to the first flauts and defecation compared with ERAS alone, which also suggests the potential of invasive needling in combination with ERAS.

A total of 24 acupoints were involved in the 13 included studies, and the four most frequently used acupoints were as follows: ST36 (92.3%, 12/13), ST37 (50%, 6/12), ST25 (50%, 6/12), and PC6 (50%, 6/12). ST36 and ST37 are located in the lower extremities, and ST25 is located in the abdomen. All the three acupoints belong to the stomach meridian. PC6 is located in the upper extremity and belongs to the pericardium meridian. In TCM, the points mentioned above can regulate the activities of abdominal organs,

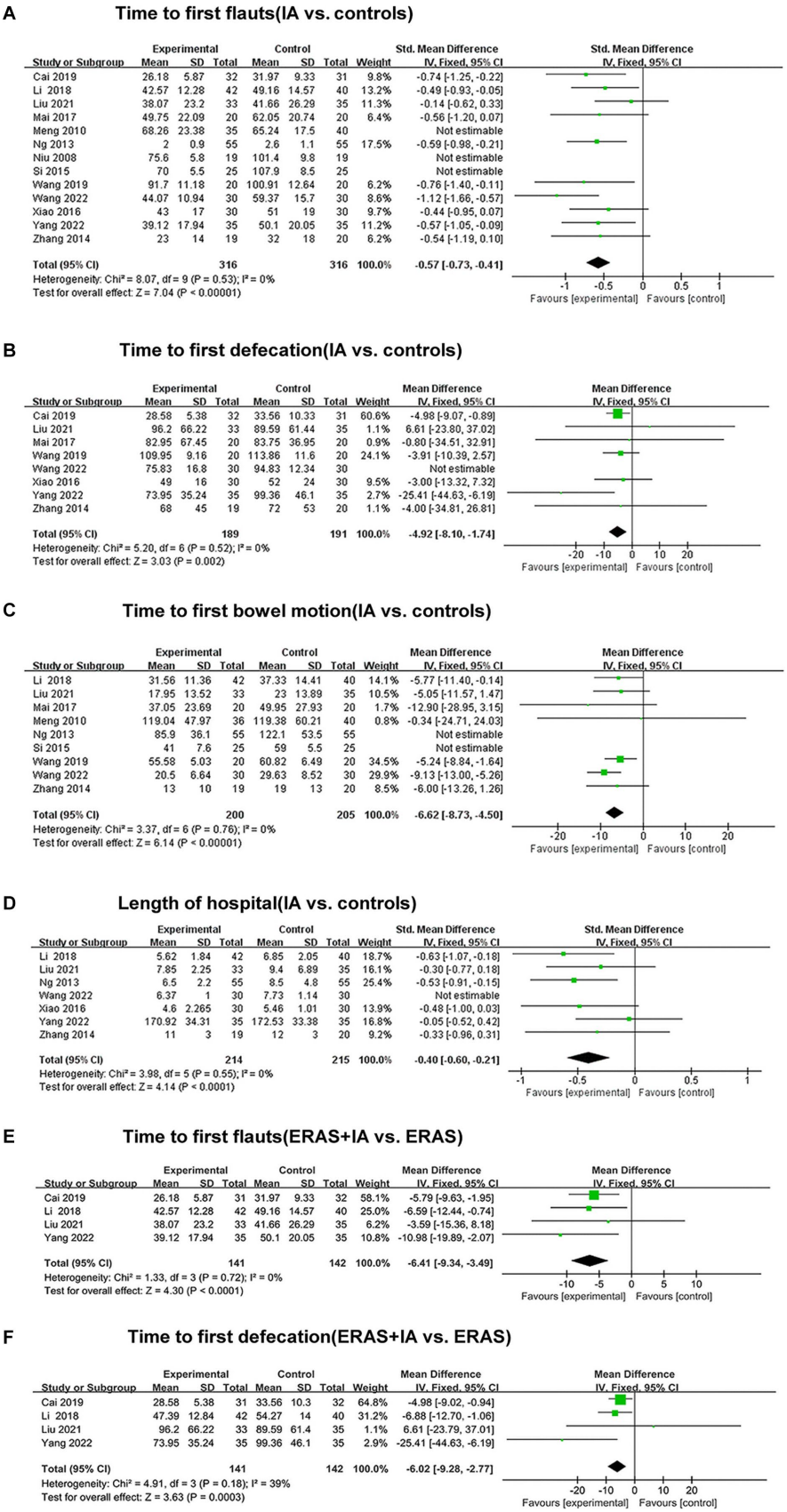

FIGURE 3
The forest plots. **(A)** Time to first flauts (IA vs. controls). **(B)** Time to first defecation (IA vs. controls). **(C)** Time to first bowel motion (IA vs. controls). **(D)** Length of hospital (IA vs. controls). **(E)** Time to first flauts (ERAS + IA vs. ERAS). **(F)** Time to first defecation (ERAS + IA vs. ERAS).

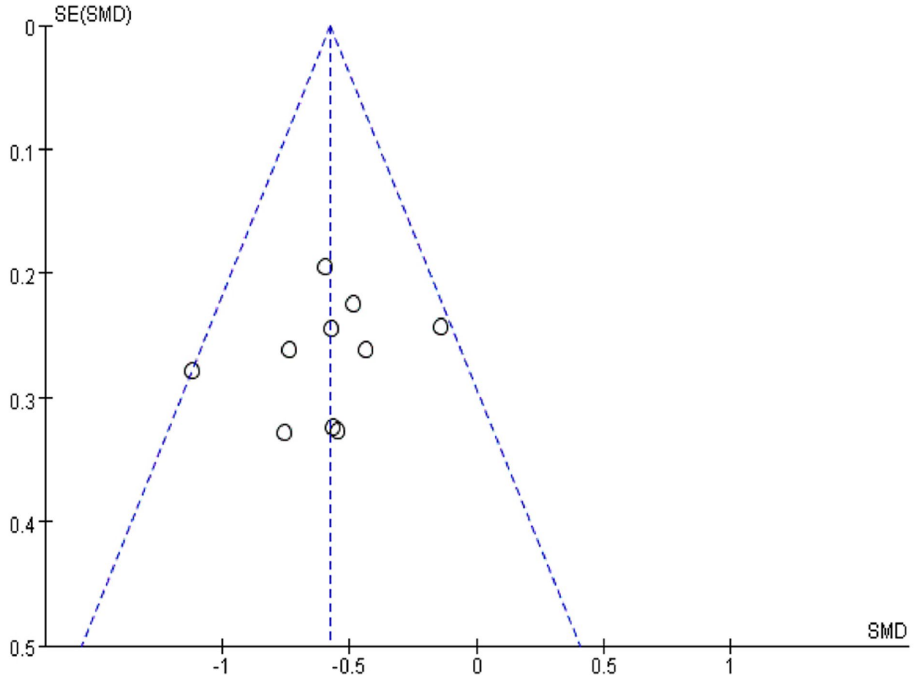

FIGURE 4
The funnel plot of comparison of the time to first flauts between IA and the B/S group.

and some experiments suggested that these points can promote gastric or intestinal motility and help with inflammation: Lu et al. used a vagus used a rat model in which the vagus or sympathetic nerve was removed and found that EA stimulation of PC6 could promote vagal electrical activity to increase gastric motility (29). Murakami et al. used EA stimulation on ST36 and PC6 in a rat model where the animals came down with POI after undergoing Intestinal manipulation (IM) surgery and came to the conclusion that EA stimulation improved the regularity of small intestinal slow waves, accelerated intestinal transit and gastric emptying, and inhibited TNF-α levels (30). However, EA stimulation of acupoints in the abdomen and lower extremities at the same frequency may produce different therapeutic effects. Yang set a mouse model where the animals came down with POI after undergoing sham Intestinal manipulation. In this experiment, 10 hz electrical acupuncture was given to stimulate acupuncture points ST25, ST36, and ST37, and the results suggested that both ST36 and ST37 could promote intestinal motility and reduce plasma inflammatory factors TNF-α and IL6, while ST25 had no significant effect (31). The difference in therapeutic effects may be related to the different anti-inflammatory physiological mechanisms involved in the different location of points. By identifying Prokr2 sensory neurons in the abdominal fascia and deep fascia of the hind limbs in mice, Liu et al. determined that stimulation on ST36 can be more effective than that on ST25 to activate the vagal-adrenal network, which is thought to stimulate the production of substances such as catecholamines and produce anti-inflammatory effects (32). Furthermore, in a lipopolysaccharide induced systemic inflammation mouse model, Liu et al. (33) found that EA stimulation of ST25 activated sympathetic nerves connecting the spinal cord to the spleen, producing norepinephrine. In conclusion, more distinct therapeutic effects found in different acupoints, optimal treatment frequency, and active clinical trials with relevant evidence may be of significance in improving the efficacy of acupuncture against POI.

Wang, Si's study had significant heterogeneity in two meta-analyses and Meng, Niu's study had significant heterogeneity in one meta-analysis, respectively. Among all studies, Meng's study was the only one that reported no significant difference in POI improvement in the IA vs. blank group, which may be the source of heterogeneity. In addition, studies with negative results may have had publication omissions that tilted the final studies included in the analysis toward positive studies, leading to publication bias. The studies by Niu, Si, and Wang either only mentioned randomization or did not mention randomization when describing the randomization method, and their selectivity bias was evaluated as unclear and high risk. The remaining studies were specific in describing their randomization methods and all were at low risk of selective bias when evaluated. The selective bias resulting from the irregular randomization method may explain the heterogeneity of the three studies. In addition, the number of acupuncture points selected, the type of acupuncture points, the frequency and intensity of electroacupuncture, and the standardization of the ERAS protocols varied among the studies included in the analysis, which could be a source of heterogeneity in outcome indicators.

Though a subgroup analysis was performed to adjust the bias, the following limitations and shortcomings will reduce the reliability of the results. The SMD was used for time to first flatus and length of hospital stay, which leaves the final combined results without a unit of measurement, so the results for these two should be viewed with caution. In addition, all the studies are from China and there was a lack of high-quality studies reported from different countries, which may

lead to selection bias. A web of science-based bibliometric study on electroacupuncture suggested that 65.1% of the electroacupuncture literature was published in China in the last decade, compared to 16.4% in the second place (34). This indicates that more countries need to be involved in acupuncture-based research. Second, there was a lack of multicenter clinical studies reported in the included studies. Third, most studies ignore allocation concealment and do not mention blinding of subjects, investigators, and assessors, which may result in selection bias, implementation bias, and measurement bias in the studies included in the analysis. Last, some of the literature does not report the basis of sample size estimation, and there is a possibility of inaccurate sample size. In conclusion, future studies need to follow the STRICTA and CONSORT statements to design and conduct trials that provide more multicenter, large-sample clinical studies with standardized outcome indicators. Further validation of the effectiveness of POI for invasive treatment of CRC surgery is still needed to provide a lower bias and higher quality evidence-based medical rationale.

5. Conclusion

This study suggested that IA can improve POI of CRC. The implementations of acupuncture usually start from 1 postoperative day 1 until the ileus ending, 1–2 times a day, about 30 min minutes, and 2–10 acupoints are selected (ST36 is the most important acupoint). In addition, ERAS combined with the above IA treatment was more effective than ERAS alone in preventing POI. This meta-analysis was based on five high-quality RCTs and eight low quality RCTs with blinding defects, and further validation is still needed by including more high quality studies in the future.

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

XZ and SS helped to conceive, design, analyze the data, conduct the study, and write the manuscript. JL helped to design the study and review the manuscript. XL and DZ designed, conducted, and reviewed the manuscript. YM and AH helped to design, conduct, and decide the final manuscript. All authors contributed to the article and approved the submitted version.

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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.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1201769/full#supplementary-material

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Effects of a sucralfate-containing ointment on quality of life and symptoms associated with hemorrhoidal disease: patient-reported results of a Slovakian, pharmacist-led observational survey

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Purpose: This pharmacist-led study evaluated the effect of a rectal ointment containing sucralfate on quality of life, symptom frequency and time to relief of symptoms in Slovakian individuals with hemorrhoidal disease (HD).

Methods: The multicenter prospective survey was conducted at 45 community pharmacies in Slovakia. Pharmacists invited adults (≥18 years) using sucralfate-containing ointment for their HD-related symptoms to participate.

Results: 241 patients completed the HEMO-FISS-QoL questionnaire and a survey of symptom frequency at the beginning and end of the 14-day survey period. The primary endpoint was the change in HEMO-FISS-QoL scores in patients with hemorrhoidal symptoms during the 7 days before the initial pharmacy visit. Of the 241 patients enrolled in the survey, 144 had experienced hemorrhoidal symptoms within the preceding 7 days (mean age 51 years; 59.0% female). For these 144 patients, the total HEMO-FISS-QoL score decreased (i.e., quality of life was improved) from baseline by a mean of −8.7 (95% confidence interval −12.6, −6.2; P<0.001) at day 14. The frequency of hemorrhoidal symptoms was significantly reduced (P<0.001 vs baseline). Symptom relief was rapid; at 1-hour post-treatment 54.6% of patients had relief from pain and 56.3% from itching, and by 24 hours post-treatment most patients had relief from these symptoms (77.2% and 73.0%, respectively). No incidents nor adverse events related to sucralfate-containing ointment were reported to pharmacists.

Conclusion: The results of this pharmacist-led observational survey suggest that the sucralfate-containing ointment could improve quality of life in patients with HD, providing rapid relief with a good safety profile. To confirm these results in a

larger, well-defined patient population, randomized controlled trials in patients with clinically diagnosed HD are warranted.

KEYWORDS

clinical pharmacist, community pharmacy, hemorrhoidal disease, minor disease, quality of life, sucralfate ointment

1 Introduction

Hemorrhoidal disease (HD) is a condition affecting the anal cushions, potentially causing pain, anal bleeding, discomfort, itching, swelling, rectal prolapse, soiling, and fecal incontinence (1, 2). Although it is common, most patients have low-grade disease and mild symptoms, and do not seek medical advice, so the exact prevalence is not well known (2). A recent international web-based survey conducted in a representative sample of the general adult population from eight countries in Europe and South America demonstrated that 11% of respondents had symptoms of HD (1). Only 40% of patients with HD seek treatment from their doctor as a first step; most will try to find an effective treatment through their own research, talking to friends, or seeing a pharmacist (1).

Low-grade HD can usually be managed conservatively using lifestyle changes (e.g., hydration, dietary changes, and fiber supplementation) to reduce constipation and improve bowel habits, as well as topical ointments or phlebotonic agents to relieve symptoms (3, 4). These treatments are commonly available from pharmacies, and according to an international survey of patients, approximately 70% of patients with HD used topical ointments as their first treatment step (1).

Despite the widespread use of topical treatments, there are limited data on the effectiveness of many of these agents (5–7). A rectal ointment containing 3% sucralfate (Emotralex®, manufactured by Egis Pharmaceuticals PLC; hereafter referred to as 'sucralfate-containing ointment'), a class IIa medical device, became available in Slovakia in 2020 for the treatment of symptoms associated with HD and its complications (e.g., eczema and anal fissures). When the ointment is applied to inflamed, itchy skin, it covers and protects the epidermis and provides care to the affected skin promoting skin regeneration. It decreases the drying out of the skin, improves wound healing, and reduces the risk of fissure and injury caused by defecation.

Previous observational research in Italy (the EMOCARE survey) indicated that this sucralfate-containing ointment improved quality of life (QoL) in patients with HD (8). The aim of the present LEONIDAS survey was to provide additional data on the effect of the ointment on QoL, symptom frequency, and time to onset of symptom relief in Slovakian individuals seeking treatment for HD at community pharmacies.

2 Patients and methods

This pharmacist-led, multicenter, observational, prospective patient survey was conducted at 45 community pharmacies in Slovakia between December 3, 2020 and March 31, 2021, in association with Allio ltd., a contract research company. Pharmacists underwent training with Allio Ltd., to aid in their identification of eligible patients. These were individuals aged ≥18 years who were seeking a local treatment for hemorrhoidal symptoms and who had chosen to use the sucralfate-containing ointment for these symptoms, with or without other hemorrhoidal treatments, after a discussion of treatment options with the participating pharmacist.

The assessment of the effect of the sucralfate-containing ointment on QoL, symptoms, and ease of use was undertaken in those patients who had been experiencing symptoms within the 7 days prior to visiting the pharmacy (QoL cohort). Because the study was conducted during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, this 7-day period allowed for inclusion of any patients with recent, but not necessarily current, symptoms who may have been prevented from attending the pharmacy promptly because of local pandemic control regulations.

On the day that treatment was sought at the pharmacy (which was also the screening and enrolment day, i.e., Day 0), the pharmacist explained the study to patients and, for those willing to participate, obtained their verbal and written informed consent to take part in the research. The pharmacist then collected information from each patient on their age, sex, hemorrhoidal anamnesis (i.e., anal complaints and constipation), and concomitant treatments for HD, and advised them how to use the sucralfate-containing ointment in accordance with the approved instructions for use (9). The ointment was sold or provided to patients as per usual practice for over-the-counter prescriptions by the pharmacists. Patients were advised to apply the ointment around the anus or insert small quantities into the rectum using the applicator once or twice daily (depending on the severity of symptoms) for approximately 14 days, or until symptoms resolved. Use of the sucralfate-containing ointment was discouraged if patients had bleeding hemorrhoids, although they could have spotting. Patients were advised to consult a doctor if symptoms did not improve within 1–2 weeks, as per the instructions for use (9).

Abbreviations: CI, confidence interval; CHORUS, Chronic venous and HemORrhoidal diseases evaluation and Scientific research; eCRF, electronic case report form; HD, hemorrhoidal disease; HEMO-FISS-QoL, Hemorrhoidal Disease and Anal Fissure Quality of Life questionnaire; QoL, quality of life; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

To assess QoL, patients in the QoL cohort completed the Slovakian version of the validated Hemorrhoidal Disease and Anal Fissure Quality of Life (HEMO-FISS-QoL) questionnaire (10) on Day 0 and Day 14 (end of study). This paper questionnaire, which was filled out by the patients, contains 23 items in four QoL domains (i.e., physical disorders, psychology, defecation, and sexuality); for each question, patients ranked their response on a 5-point Likert scale, from 1 (never) to 5 (always), where a higher score represents worse QoL (range of scores: 0–100). For each question, there was also a sixth option: not applicable.

Pseudonymized patient information, survey responses, and HEMO-FISS-QoL questionnaire responses were recorded by the pharmacist in an electronic case report form (eCRF) and held by Allio Ltd. in a secure web-based application in accordance with local privacy regulations. Any paper-based information recorded by the pharmacist was destroyed after completion of the eCRF. Only anonymized data were available to the authors and sponsor. In Slovakia, ethics committee approval is not mandatory under national legislation for surveys, and as such, no approval was requested. This study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments, and all patients provided written informed consent for personal data processing. No patient data were kept by the pharmacists upon completion of the survey.

The pharmacist conducted a telephone follow-up on Day 2. All patients were asked to report any incidents or risk of incidents, including adverse events or special situations they may have experienced. Patients in the QoL cohort were also questioned about their experience in applying the sucralfate-containing ointment and about the time to onset of symptom relief (30 minutes or 1, 12, 24, or 48 hours after the first application of the ointment).

On Day 14, patients were followed up by telephone or during a visit to the pharmacy. The pharmacist recorded whether the patient was still using the sucralfate-containing ointment, the frequency of their hemorrhoidal symptoms, their experience with applying the sucralfate-containing ointment, any incidents or risk of incidents, including adverse events or special situations occurring in relation with the sucralfate-containing ointment during the survey, and the self-reported patient responses to the HEMO-FISS-QoL questionnaire.

The primary study endpoint was the change in overall HEMO-FISS-QoL, and secondary endpoints were symptom frequency and time to symptom relief. Both primary and efficacy endpoints, as well as ease of use of the sucralfate-containing ointment, were assessed in the QoL cohort.

2.1 Statistical analysis

Sample size was not determined *a priori*. The variables were analyzed using descriptive statistics, reported as frequency for categorical variables and mean or median, standard deviation (SD) or 95% confidence intervals (CIs), and range for continuous variables. When data were missing for individual or total HEMO-FISS-QoL domain scores because the 'not applicable' option had been chosen, the score for that item was imputed using the average value of the population participating in the survey. Given the non-normal distribution of HEMO-FISS-QoL score, the change from baseline was analyzed using Wilcoxon's rank sign test. The distribution of patients according to their category of frequency of hemorrhoidal symptoms (i.e., never, rarely, sometimes, very often, or always) was compared at Day 0 and Day 14 using the Pearson's chi-squared test. A P value of <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS statistical processing software version 20.1 (IBM Corp.; Armonk, NY).

3 Results

3.1 Patient demographics and baseline characteristics

Overall, 241 patients were enrolled at 45 pharmacies, of whom 237 (98.3%) participated in the Day 14 follow-up visit. Patients were aged between 19 and 92 (mean [SD] 51.3 [15.4]) years, and 55.6% (n = 134) were female (Table 1). Concurrent constipation was reported by 61/241 patients (25.3%). Just over one-third (n = 86, 35.7%) of the patients had consulted a doctor for HD and 7.5% (n = 18) were using laxatives. Of the 86/241 patients (35.7%) who were using systemic treatment for HD, 63 (73.3%) were taking micronized purified flavonoid fraction.

The QoL cohort comprised 144 patients (i.e., patients who at the time of enrolment had hemorrhoidal symptoms or who had experienced these in the 7 days prior to the study). Compared with the overall cohort, the QoL cohort included higher proportions of women (n = 85; 59.0%), patients who had consulted a doctor about HD (n = 70; 48.6%), and patients using laxatives (n = 14; 9.7%; Table 2). Within this cohort, 52 patients (36.1%) were using systemic treatment for HD, including micronized purified flavonoid fraction (n = 35; 67.3%). Almost the entire QoL cohort (n = 142;

TABLE 1 Baseline demographic and clinical characteristics of all patients.

Characteristic	All patients (N = 241)
Female, n (%)	134 (55.6)
Age, years	
Mean ± SD	51.3 ± 15.4
Median (range)	50.0 (19–92)
Concurrent constipation, n (%)	
Never	157 (65.1)
<18 months	34 (14.1)
19 months to 5 years	11 (4.6)
>5 years	16 (6.6)
Don't know	23 (9.5)
Consulted a doctor for HD, n (%)	86 (35.7)
Laxative use, n (%)	18 (7.5)
Systemic hemorrhoid treatment, n (%)	86 (35.7)

HD, hemorrhoidal disease; SD, standard deviation.

98.4%) participated in the Day 14 visit (i.e., the last follow-up), which was by telephone in most patients (n = 121; 85.2%); only 21 patients (14.8%) completed the Day 14 follow-up by an in-person pharmacy visit.

3.2 Quality of life

QoL data were available from all 144 patients in the QoL cohort at baseline (Day 0) and from 142 of these patients at the Day 14 follow-up. The overall mean score and individual domain scores at Day 0 and Day 14 are shown in Figure 1A. The overall mean HEMO-FISS-QoL score and the mean score for each individual domain of the scale improved significantly from baseline to the end of treatment (Table 3, Figure 1B). The overall mean score decreased from 19.4 at Day 0 to 10.7 at Day 14, corresponding to an improvement of 45% (change from baseline in overall score of −8.7; 95% CI −12.6, −6.2). Defecation was the domain with the highest QoL score at Day 0, as well as the domain with the largest improvement at Day 14, with a mean change from Day 0 in score of −13.5 (95% CI −19.4, −12.1; Table 3).

3.3 Impact on symptoms

In the QoL cohort (n = 144), hemorrhoidal symptoms reported at Day 0 were pain (n = 127; 88.2%), itching (n = 126; 87.5%), bleeding (n = 112; 77.8%), swelling (n = 104; 72.2%) and prolapse (n = 104; 72.2%). In addition, 50.0% of patients (n = 72) experienced soiling and 18.1% (n = 26) experienced fecal incontinence. The proportions of patients who experienced these symptoms 'always' or 'very often' at Day 0 and at Day 14 are shown in Figure 2. At Day 14, the proportion of patients experiencing each of these symptoms had decreased significantly (Table 4).

The symptoms that were relieved most quickly after application of the sucralfate-containing ointment included the two most common symptoms, pain and itching, as well as bleeding and swelling (Table 5). Approximately one in two patients gained relief from pain and itching within 1 hour of ointment application (54.3% [n = 69/127] for pain and 56.3% [n = 71/126] for itching; Figure 3). At 24 hours after starting the sucralfate-containing ointment, 77.2% (n = 98/127) and 73% (n = 92/126) of patients reported relief from pain and itching, respectively. The corresponding proportions reporting relief of these symptoms were 90.6% (n = 115/127) and 84.1% (n = 106/126), respectively, at 48 hours after starting sucralfate-containing ointment (Figure 3).

TABLE 2 Baseline demographic and clinical characteristics of patients in the quality of life (QoL) cohort.

Characteristic	Patients in QoL cohort (n = 144)
Female, n (%)	85 (59.0)
Age, years	
Mean ± SD	50.9 ± 15.8
Median (range)	50 (19–92)
Concurrent constipation, n (%)	
Never	98 (68.0)
<18 months	16 (11.1)
19 months to 5 years	6 (4.2)
>5 years	9 (6.3)
Don't know	15 (10.4)
Consulted a doctor for HD, n (%)	70 (48.6)
Laxative use, n (%)	14 (9.7)
Systemic hemorrhoid treatment, n (%)	52 (36.1)

HD, hemorrhoidal disease; SD, standard deviation.

3.4 Ease of use

More than 95% (n = 136/142) of patients found the application of the sucralfate-containing ointment to be 'very easy', 'easy' or 'neither easy nor hard' to use at Day 2 and Day 14 (Table 6).

3.5 Treatment exposure

The mean ± SD treatment duration was 11.9 ± 0.6 (range 1–14) days, and the mean ± SD number of applications was 1.66 ± 0.5 times a day in the QoL cohort.

3.6 Safety

None of the patients in the overall cohort (n = 144) reported experiencing any incidents or risk of incidents, including adverse events or special situations in relation with the sucralfate-containing ointment or other products during the survey.

4 Discussion

To our knowledge, this is the first pharmacist-led study investigating the effects of a sucralfate-containing ointment in a routine clinical practice setting in Slovakia. This prospective study conducted across 45 Slovakian clinical pharmacies confirmed that the sucralfate-containing ointment significantly improved QoL and reduced both overall symptoms, and symptoms experienced within the last 7 days, in patients with HD.

In this survey, 'defecation' was the most severely affected QoL domain among patients with HD, consistent with data from the Italian EMOCARE survey (8). That study also used the HEMO-FISS-QoL questionnaire to assess QoL, and found a significant reduction in total scores (i.e., an improvement), as well as in each individual QoL domain, after using sucralfate-containing ointment for 14 days (8), which is consistent with our finding for use of the treatment over approximately 12 days. In both the Italian

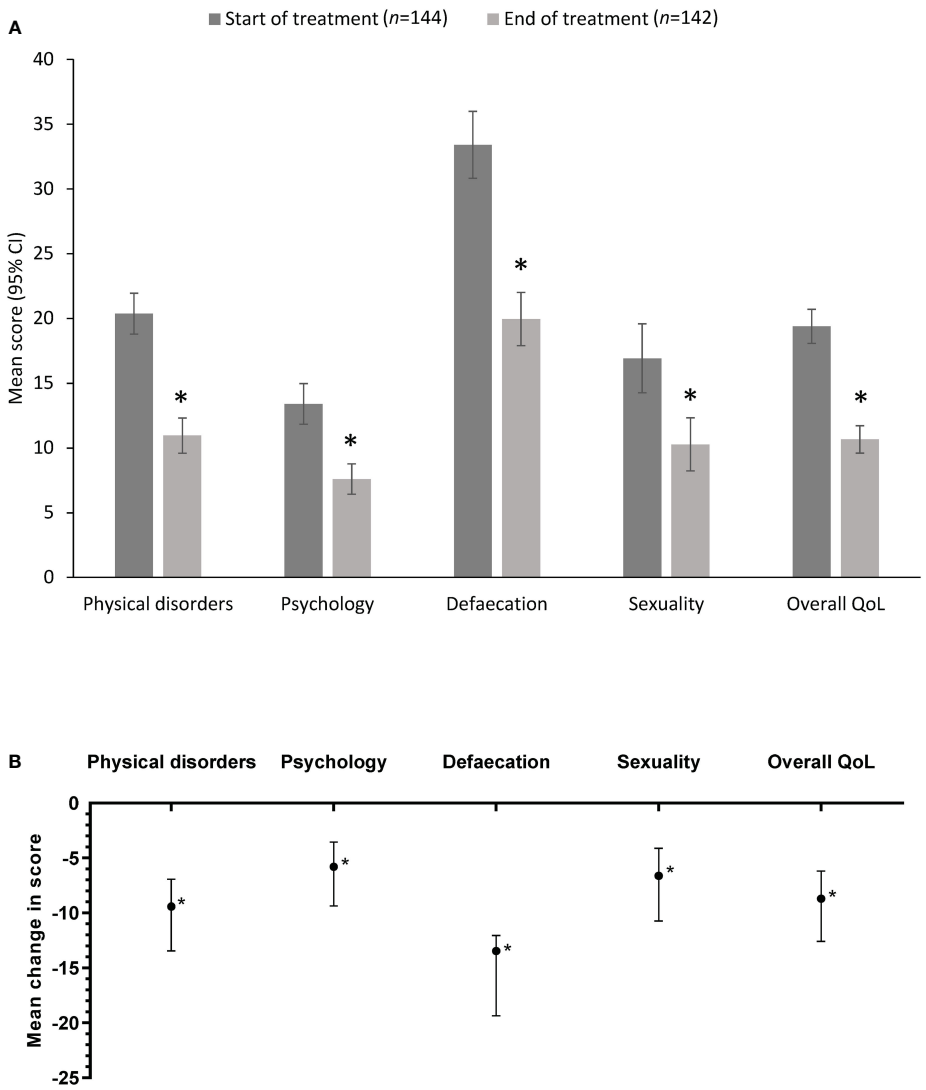

FIGURE 1
HEMO-FISS-QoL scores in the quality of life cohort **(A)** at Day 0 and Day 14 (mean values) and **(B)** as the mean difference between Day 0 and Day 14. Error bars represent 95% CI. A reduction in score indicates an improvement. *P<0.001 vs start of treatment. CI, confidence interval; HEMO-FISS-QoL, Hemorrhoidal Disease and Anal Fissure Quality of Life questionnaire; QoL, quality of life.

TABLE 3 Change from baseline in the HEMO-FISS-QoL scores in the quality of life (QoL) cohort.

Domain	HEMO-FISS-QoL scores				*P*-value[1]
	Day 0 (*n* = 144)	Day 14 (*n* = 142)	Change from Day 0 at Day 14		
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Percentage	
Individual QoL domains					
Physical disorders	20.4 (18.8, 22.0)	11.0 (9.6, 12.3)	−9.4 (−13.4, −7.0)	−46%	<0.001
Psychology	13.4 (11.8, 15.0)	7.6 (6.4, 8.8)	−5.8 (−9.4, −3.6)	−43%	<0.001
Defecation	33.4 (30.8, 36.0)	20.0 (17.9, 22.0)	−13.5 (−19.4, −12.1)	−40%	<0.001
Sexuality	16.9 (14.3, 19.6)	10.3 (8.2, 12.3)	−6.6 (−10.8, −4.1)	−39%	<0.001
Overall QoL	19.4 (18.1, 20.7)	10.7 (9.6, 11.7)	−8.7 (−12.6, −6.2)	−45%	<0.001

CI, confidence interval; HEMO-FISS-QoL, Hemorrhoidal Disease and Anal Fissure Quality of Life questionnaire.
[1]Wilcoxon's rank sign test of the mean change from baseline in QoL score.

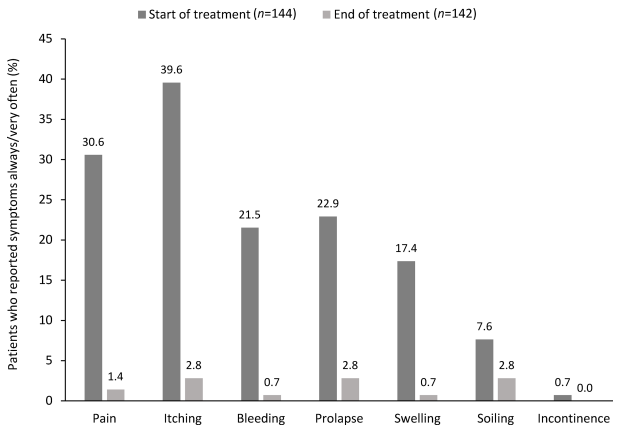

FIGURE 2
Change in the percentage of patients reporting symptom frequency as 'very often' or 'always' at Day 0 and Day 14 in the quality of life cohort.

EMOCARE survey and our study, the greatest improvement (reduction in score from baseline) was seen in the most affected domain (i.e., 'defecation').

The characteristics of the Slovakian patients with HD in our study were consistent with the known epidemiology of the disease. The peak age for HD occurrence is between 45 and 65 years (1, 11–13), and the median age of patients in our study was 50 years. The number of women with HD slightly exceeded that of men in our study, which has also been reported by some researchers (1, 13), but not others (11, 12). However, this may simply reflect a greater willingness by women to seek healthcare compared with men (14). Additionally, it could be explained by the history of pregnancies among women, pregnancies being a risk factor for HD.

The Italian EMOCARE survey reported that almost half of its patients with HD had constipation (1) and 21.4% used laxatives, whereas only about 25% of patients in the current study reported constipation and 7.5% used laxatives. Similarly, a higher proportion of EMOCARE patients (52.4%) had consulted a physician for HD compared with Slovakian patients in the current study (35.7%). These discrepancies suggest differences between the two countries in healthcare-seeking behavior by patients with HD, potentially due to different healthcare systems or patient attitudes. They may also be explained by the SARS-CoV-2 pandemic that limited patient access to physicians, or by the fact that patient responses were recorded by a third-party (pharmacist). Pharmacists recording patient responses and knowing intimate details of the disease may have biased how the patients responded to the questionnaire, in turn diminishing the reported severity of the symptoms. Irrespective of the differences, our data and the EMOCARE results are both consistent with previous research, showing that patients with HD often do not seek, or delay seeking, treatment from doctors (1, 15, 16). Individuals with HD commonly cite embarrassment or shame as key reasons for not seeking medical care (16).

Despite some differences in the incidences of symptoms, our data are generally consistent with previous research, in that pain and itching are among the most common self-reported symptoms of HD (1, 2). Pain was the most common symptom reported by patients in the current study (affecting 88.2% of patients) and in the Italian EMOCARE survey (82.8% of patients) (8). The second most common symptom in the current study was itching (affecting 87.5%), whereas swelling was the second most common symptom in the EMOCARE survey (affecting 82.4%); itching was reported by 68.6% of Italian patients (8). In contrast, itching was reported by only 35% of the 1725 patients in an international web-based survey (1). The difference in the prevalence of itching between the web-based survey (35.1%) (1) and the two pharmacy-based surveys (68.6% (8) and 87.5%) suggests that itching may be a symptom that prompts patients to seek treatment, a conclusion that is supported by qualitative research on patients' experience of HD (16).

TABLE 4 Hemorrhoidal symptoms at Day 0 and Day 14 in the quality of life cohort.

Symptom[1]	Never, *n* (%)		Rarely, *n* (%)		Sometimes, *n* (%)		Very often, *n* (%)		Always, *n* (%)		*P*-value[2]
	Day 0 (*n* = 144)	Day 14 (*n* = 142)	Day 0 (*n* = 144)	Day 14 (*n* = 142)	Day 0 (*n* = 144)	Day 14 (*n* = 142)	Day 0 (*n* = 144)	Day 14 (*n* = 142)	Day 0 (*n* = 144)	Day 14 (*n* = 142)	
Pain	17 (11.8)	99 (69.7)	33 (22.9)	33 (23.2)	50 (34.7)	8 (5.6)	34 (23.6)	2 (1.4)	10 (6.9)	0	<0.001
Itching	18 (12.5)	101 (71.1)	33 (22.9)	24 (16.9)	36 (25.0)	13 (9.2)	45 (31.3)	4 (2.8)	12 (8.3)	0	<0.001
Bleeding	32 (22.2)	113 (79.6)	40 (27.8)	22 (15.5)	41 (28.5)	6 (4.2)	21 (14.6)	1 (0.7)	10 (6.9)	0	<0.001
Prolapse	40 (27.8)	105 (73.9)	31 (21.5)	16 (11.3)	40 (27.8)	17 (12.0)	21 (14.6)	3 (2.1)	12 (8.3)	1 (0.7)	<0.001
Swelling	40 (27.8)	109 (76.8)	44 (30.6)	28 (19.7)	35 (24.3)	4 (2.8)	16 (11.1)	1 (0.7)	9 (6.3)	0	<0.001
Soiling	72 (50.0)	127 (89.4)	44 (30.6)	10 (7.0)	17 (11.8)	4 (2.8)	10 (6.9)	1 (0.7)	1 (0.7)	0	<0.0001
Incontinence	118 (81.9)	139 (97.9)	21 (14.6)	3 (2.1)	4 (2.8)	0	0	0	1 (0.7)	0	<0.0001

[1]At the Day 0 visit, patients were asked to indicate which of these hemorrhoidal symptom(s) they had experienced over the prior 7 days, and to indicate the frequency of each over that time period; 'never' meant 'not at all the prior 7 days', although this was not explicitly explained to the patients. At the Day 14 follow-up visit, it was first established whether patients were still experiencing hemorrhoidal symptoms (yes/no question), and if so, to indicate which symptom(s) and at what frequency. While not actually specified, 'never' at this follow up meant the symptom was absent on Day 14.
[2]P-values compared Day 14 versus Day 0 for all symptoms and frequency.

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TABLE 5 Time to symptom relief in the quality of life cohort.

Timing of relief, *n* (%)	Pain (*n* = 127)	Itching (*n* = 126)	Bleeding (*n* = 112)	Prolapse (*n* = 104)	Swelling (*n* = 104)	Soiling (*n* = 72)	Incontinence (*n* = 26)
30 minutes	40 (31.5)	54 (42.9)	23 (20.5)	2 (1.9)	15 (14.4)	9 (12.5)	5 (19.2)
1 hour	29 (22.8)	17 (13.5)	13 (11.6)	9 (8.7)	14 (13.5)	1 (1.4)	0
12 hours	13 (10.2)	11 (8.7)	12 (10.7)	17 (16.3)	21 (20.2)	5 (6.9)	0
24 hours	16 (12.6)	10 (7.9)	12 (10.7)	18 (17.3)	21 (20.2)	13 (18.1)	1 (3.8)
2 days	17 (13.4)	14 (11.1)	16 (14.3)	19 (18.3)	18 (17.3)	7 (9.7)	5 (19.2)
No relief in 2 days	12 (9.4)	20 (15.9)	36 (32.1)	39 (37.5)	15 (14.4)	37 (51.4)	15 (57.7)

Importantly, our data show rapid relief of both pain and itching during treatment with the sucralfate-containing ointment, with more than 50% of patients reporting relief from these symptoms within 1 hour of applying the ointment. Moreover, 77% of patients reported relief of pain at 24 hours post-treatment initiation. The pain-relieving properties of a sucralfate-containing ointment (10% sucralfate in a petrolatum base) have been previously demonstrated in a randomized comparison with lidocaine ointment used postoperatively after hemorrhoidectomy (17). In that study, pain relief was significantly better with the sucralfate-containing ointment than lidocaine ointment on postoperative Days 1, 3, and 7 (17).

Prolapse was reported more frequently in the current study (72.2%) than in the Italian EMOCARE survey (43.8%) (8), the international web-based survey (15%) (1), and the international Chronic venous and HemORrhoidal diseases evaluation and Scientific research (CHORUS) study (36.2%) (2). The prevalence of prolapse in our study was unexpectedly high, but could not be confirmed because symptoms were self-reported, and patients did not undergo physical examination. It is possible that patients did not fully understand what the term meant or were mistaking swelling for prolapse. The true prevalence of prolapse among Slovakian patients with HD warrants further investigation.

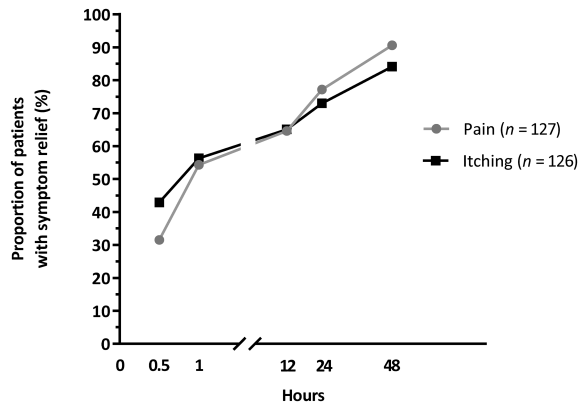

FIGURE 3
The percentage of patients reporting relief from pain and itching at each time point after starting treatment in the quality of life cohort.

The data from this study and previous research provide reassurance that sucralfate-containing ointments can improve QoL and rapidly relieve symptoms in patients with HD. In addition, patients found the treatment easy to use. While prolonged use of topical treatments can cause local reactions or skin irritation (7), none of the patients in the current study reported adverse effects to the pharmacists, indicating that 12 days of therapy with the sucralfate-containing ointment was well tolerated. Confirmation of the tolerability and safety of sucralfate-containing ointments over prolonged periods requires further investigation.

The current study was conducted during the SARS-CoV-2 pandemic, highlighting the vital role pharmacists and telepharmacy play in providing rapid and sufficient healthcare, particularly when patient access to general practitioners is limited. The early and effective management of HD relies heavily on community pharmacists assessing symptoms promptly, providing the patient with sufficient information on all treatment options, offering pharmacological advice and early intervention for rapid symptom alleviation, and providing lifestyle advice and follow-up counselling to prevent disease recurrence.

The current study has some limitations. As the survey was conducted among patients who had chosen to use this particular sucralfate-containing ointment, the study population was subject to selection bias, and patient self-reported responses were subject to response bias. No control group was included, making it difficult to draw firm conclusions about the effectiveness of the sucralfate-containing ointment. Data imputation was conducted for missing values. Additionally, as patients could take concomitant treatments, a synergistic effect could not be excluded. Furthermore, the proportion of patients using concomitant therapies with the sucralfate-containing ointment was only recorded at the start of treatment, so the impact of the concomitant medications throughout the study cannot be determined. Another limitation is that the diagnosis of HD was based on self-reported anal symptoms and could not be confirmed by physical medical examination; some patients may have misdiagnosed themselves. Of note, this study was conducted during the SARS-CoV-2 pandemic when access to doctors was limited. Since patients sought advice from community pharmacists who do not utilize clinical assessment tools such as the Goligher classification as a means to assess HD severity (given their unfamiliarity with the scale and the

TABLE 6 Ease of use of the sucralfate-containing ointment in the quality of life cohort.

Category	Ease of use, *n* (%)	
	Day 2 (*n* = 144)	Day 14 (*n* = 142)
Very easy	50 (34.7)	47 (33.1)
Easy	37 (25.7)	39 (27.5)
Neither easy nor difficult	52 (36.1)	50 (35.2)
Difficult	1 (0.7)	2 (1.4)
Very difficult	4 (2.8)	4 (2.8)

impossibility of performing anal examinations at community pharmacies), prolapse could not be verified. This may have constituted a significant bias in the target population to be treated with this product, and consequently, interpretation of the study results. A clearly defined population assessed and followed by physicians will be needed to confirm the product's potential benefits.

5 Conclusion

The results of this pharmacist-led, Slovakian, multicenter, observational, prospective study suggest that treatment with a sucralfate-containing ointment could improve QoL and provide rapid symptom relief, is easy to use, and is safe and well tolerated in patients with symptoms of HD. Randomized controlled trials in patients with clinically-diagnosed HD would be useful to confirm these results in a larger, well-defined patient population. The role pharmacists play in the rapid and effective resolution of HD is also highlighted, particularly when patient access to general practitioners is limited.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: MS and OS. Formal analysis: JM. Writing-review and editing: all authors. All authors approved the final version for submission, understand and adhere to the ICMJE criteria for authorship and had complete access to the study data. All listed collaborators are members of SLeK (Slovak Chamber of Pharmacists). All authors contributed to the article and approved the submitted version.

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Conflict of interest

Author JM is employed by Allio Ltd., Šamorín, Slovakia.

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.

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