frontiers | Research Topics

Surgical management of colorectal pathologies

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Published in
Frontiers in Surgery

ISSN 1664-8714
ISBN 978-2-8325-6333-5
DOI 10.3389/978-2-8325-6333-5

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Surgical management of colorectal pathologies

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Citation

Ambe, P. C., Sokmen, S., Karanikas, M., eds. (2025). *Surgical management of colorectal pathologies*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-8325-6333-5

Table of contents

frontiers | Frontiers in Surgery

TYPE Editorial
PUBLISHED 28 April 2025
DOI 10.3389/fsurg.2025.1607005

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 06 April 2025
ACCEPTED 08 April 2025
PUBLISHED 28 April 2025

CITATION
Ambe PC, Karanikas M and Sokmen S (2025) Editorial: Surgical management of colorectal pathologies.
Front. Surg. 12:1607005.
doi: 10.3389/fsurg.2025.1607005

Editorial: Surgical management of colorectal pathologies

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KEYWORDS

colorectal cancer, laparoscopic oncologic surgery, appendicitis, diverticular disease, oncologic resection

Editorial on the Research Topic
Surgical management of colorectal pathologies

The surgical management of colorectal pathologies constitutes a huge aspect of the surgical workload in daily practice. Understanding the evolution in the trends of colorectal surgery is paramount in stay on top of our rapidly evolving specialty. This is only possible by constantly updating our knowledge on both benign and malignant conditions of the colon and rectum.

The recently completed research topic on the "*Surgical Management of Colorectal Pathologies*" highlighted recent developments in the management of both benign and malignant conditions of the anorectum. Twenty-one manuscripts looking at different aspects on colorectal pathologies were submitted and nine were accepted for publication following peer review. This acceptance quotient reflects the high standards set by the editors and esteemed reviewers while working on this topic. This editorial briefly summarizes the articles published in the research topic:

Laparoscopic appendectomy is probably one of the most commonly performed procedures in general surgery. Despite being a common procedure, the best means of approaching the appendix during laparoscopic appendectomy remains a matter of debate. The retrograde technique is performed be creating a small peritoneal window within the mesoappendix at the basis of the appendix prior to division of the appendix. This technique was compared with the anterograde technique by Ko et al., indicating that retrograde dissection was significantly longer than antegrade dissection (34.85 min vs. 40. 92 min, $p = 0.002$). However, there was no statistically significant difference amongst both techniques with regards to perioperative complications. While the meaning of a delta of about six minutes between both techniques remains questionable, this study demonstrates the safety of the retrograde technique of laparoscopic appendectomy (Ko et al).

The surgical management of complicated diverticular disease can be very challenging. Amongst the complications of diverticular disease, colovesical fistula warrants special attention due to the involvement of both the bowel and the urinary system. Rizzuto et al. reported their experience shifting from an open to a laparoscopic approach, indication the advantages of minimally invasive access in this challenging surgical population (Rizzuto et al.).

In a study with the title "*Microsatellite Instability is highly prevalent in older patients with Colorectal Cancer*", Jakob et al. questioned the practice of performing screening for microsatellite instability (MSI) in an age – based manner. The authors found MSI-H

tumor in 18.2% of cases >50 years, and in 20.6% of patients >60 years in their collective. The authors argued that both the role of MSI-H as an indicator of a hereditary cancer predisposition (Lynch Syndrome) as well as its relevance in the decision-making with regard to the need and choice of additive chemotherapy should warrant a systematic screening, independent of age and clinical criteria (Jakob et al.).

Malignant colonic obstruction remains a serious complication of colorectal cancer and it´s management can not only be challenging but may also be associated with poor overall outcome. Evidence-guided management is literally not available, and the current clinical practice is mostly guided by small retrospective series with well known flaws. Compiling existing data to help guide clinical decision-making in the critical subset of patients. This clinical meaningful task was undertaken by Mikalonis et al. in the article titled "*Danish guidelines for treating acute obstruction caused by colorectal cancer – a review*" (Mikalonis et al.).

Besides bowel obstruction, distance metastasis is not uncommon in patients with CRC. About 20% of patients with CRC present with hepatic lesions at the time of diagnosis and about 50% is expected to develop liver metastasis in the course of time. Of clinical importance is also the observation of recurrence following partial hepatectomy. This important cancer dynamic was investigated in a mouse model by Luenstedt et al., indicating that regenerative pathways secondary to partial hepatectomy may lead to accelerated colorectal metastasis by priming a premetastatic niche in the liver (Luenstedt et al.).

Focusing on the right colon, Qin et al. used the SEER database to design and test a prognostic nomogram for survival in patients with right-sided colon cancer after colectomy. The authors identified age, chemotherapy, CEA and disease stage per TNM classification as prognostic factors to develop a nomogram with high performance in prediction 1-year, 3-year and 5-year overall survival in patients following right-sided colectomy for colon cancer. The results reported in this study may be helpful in counselling patients e.g., with regards to the need of adjuvant chemotherapy and for follow – up after right colectomy for cancer (Qin et al.).

Total mesorectal excision (TME) represents the standard technique for radical resection of rectal cancer and the laparoscopic approach has been established a standard procedure. Laparoscopic TME requires a high level of expertise and thus may pose some degree of challenge. Thus, predicting the difficulty of surgery may ease decision-making with regard to patient selection. In the paper titled "*Interpretable machine learning model to predict surgical difficulty in laparoscopic resection for rectal cancer*" Yu et al. demonstrated an XGBoost model for predicting the difficulty of laparoscopic TME, thus providing a useful tool to help surgeons select appropriate candidates for laparoscopic TME (Yu et al.).

Postoperative pain management represents an important aspect of enhanced recovery after surgery (ERAS). However, striking a balance between pain management and medication -induced adverse events, including bowel paralysis following colorectal surgery, may be challenging. In the RCT by Cao et al., the efficacy of postoperative pain control using a combination of ropivacaine and parecoxib was compared with patient controlled intravenous analgesia (PCIA) consisting of 100 ug sufentanil and 16 mg ondansetron after laparoscopic surgery for CRC. The study endpoint included pain measured via the VAS as well as biochemistry markers including Interleukin 6 (IL-6) and C-reactive protein (CRP). The results of this RCT confirmed a statistically significant reduction in postoperative pain control using PCIA. This trend correlated with a significantly lower expression of IL-6 in the PCIA group. As expected, there was no statistically significant difference amongst both groups with regard to postoperative CRP. This RCT addresses two important issues: First, PCIA is associated with effective postoperative pain control and should be part of standard ERAS programs following colorectal resection and second, IL-6 may represent an objective tool for measuring postoperative pain (Cao et al.).

In the manuscript with the title "*Effect of prehabilitation exercises on postoperative frailty in patients undergoing laparoscopic colorectal cancer surgery*" Yang et al. explored a new intensive prehabilitation program that combines prehabilitation exercises with stand enhanced recovery after surgery on frailty in a randomized controlled trial (Yang et al.). The study indicated that prehabilitation exercises can improve postoperative frailty and accelerate recovery in elderly patients undergoing laparoscopic oncologic colorectal resections. This is a meaningful finding in light of the changing global demographics with an increasingly aging population.

While only 43% of all submissions was accepted for publication, the editors and reviewers applauded all submitting groups for their contribution to the success of this special issue. More importantly, all manuscript that didńt qualify for publication received fair-minded comments to help the authors improve their work.

Author contributions

PA: Writing – original draft, Writing – review & editing. MK: Writing – review & editing. SS: Writing – review & editing.

Acknowledgments

Our specialty would not evolve without the dedicated input of international colleagues who provided peer review on the submitted works. The editors are very thankful to these colleagues. We also thank all the authors and study groups for their contribution to the success of this research topic. Many thanks to the colleagues at the editorial offices for their input and guidance to the success of this project. We look forwards to working with you guys in future.

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 author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

frontiers | Frontiers in Surgery

TYPE Original Research
PUBLISHED 11 September 2023
DOI 10.3389/fsurg.2023.1256256

OPEN ACCESS

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RECEIVED 10 July 2023
ACCEPTED 28 August 2023
PUBLISHED 11 September 2023

CITATION
Ko A, Lindsay P and Choi J (2023) The safety and efficacy of laparoscopic retrograde appendicectomy, base-to-tip approach. Front. Surg. 10:1256256. doi: 10.3389/fsurg.2023.1256256

The safety and efficacy of laparoscopic retrograde appendicectomy, base-to-tip approach

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Background: Laparoscopic appendicectomy is one of the most frequently performed surgical procedures worldwide. There is limited evidence evaluating the role and safety of laparoscopic retrograde appendicectomy (LRA), base to tip approach, compared to standard laparoscopic antegrade appendicectomy (LAA), tip to base approach. This study aims to assess the safety of LRA compared to LAA in terms of intra-abdominal collection (IAC) rate and using Sunshine Appendicitis Grading System (SAGS).

Methods: Records of two-hundred and seventy-three patients undergoing laparoscopic appendicectomy by LAA and LRA approaches were analysed. The severity of appendicitis was rated using a standardised Sunshine Appendicitis Grading System (SAGS) score intra-operatively. The primary outcome measure was the occurrence of an intra-abdominal collection, and secondary measures were procedure time, post-operative length of stay and other complications.

Results: Of the two-hundred and seventy-three patients, there were two patients who developed an intra-abdominal collection. Both patients were in the LAA group with SAGS IV scores. Between SAGS IV patients, Chi-squared p value of 0.6691. Therefore, there was no statically significant difference in the intra-abdominal collection (IAC) rate between LAA and LRA groups from this study.

Conclusions: The current study has shown that laparoscopic retrograde appendicectomy (LRA) does not increase risk of intra-abdominal collection compared to laparoscopic antegrade appendicectomy (LAA) within the limit of this study.

KEYWORDS

appendicitis, retrograde appendicectomy, appendicectomy methods, surgical management of appendicitis, base to tip approach

Introduction

Appendicitis is one of the most common causes of abdominal pain, with an estimated lifetime risk of 7%–8% globally (1, 2). Surgical approaches to appendicectomy have developed significantly since McBurney first described an open approach in 1894, with laparoscopic appendicectomy first described by Semm in 1983 (3, 4). The laparoscopic method is now the standard treatment for acute appendicitis with reduced rate of wound site infection and shortened hospital length of stay (1, 5).

In Laparoscopic Antegrade Appendicectomy (LAA), the tip of appendix is first identified and its mesentery is serially divided using diathermy and clips toward the base of appendix, which is divided after securing with applying an endo-loop (4). This can be challenging when the tip of the appendix is not easily accessible (6).

Another approach is the laparoscopic retrograde appendicectomy (LRA), first described by Motson and Kelly in 2002 (7), in which the base of the appendix is first identified and divided prior to mobilisation of the appendix to its tip. Given the base of the appendix is divided prior to controlling the stump, there is perceived risk of faecal contamination and subsequent development of intra-abdominal collection (IAC). However, there is lack of evidence in efficacy and safety of LRA compared to LAA especially in terms of risk of IAC. Thus, this study aims to review the surgical technique and utility of LRA and examine the results of the LRA compared with LAA including; the risk of IAC, length of inpatient stay post procedure, intra-operative time for procedure and other complications.

The Sunshine Appendicitis Grading System (SAGS) score is an intraoperative grading system for acute appendicitis, first described in 2015 by F. Reid et al. (8), which correlates severity of disease with the risk of post-operative intra-abdominal collection.

Method

Data collection

This retrospective observational study was designed to evaluate the rate of post-operative complications following the LRA in comparison to the LAA according to their SAGS classifications. Medical records of two hundred seventy-two patients who underwent laparoscopic appendicectomy performed by a single surgeon at one institution between January 2014 and July 2021 were reviewed including; type of surgical approach including antegrade vs. retrograde appendicectomy, Sunshine Appendicitis Grading System (SAGS) score (**Table 1**), operative time, post-operative length of stay, post-operative complications and readmissions. Primary outcome was the rate of intra-abdominal collection (IAC), diagnosed on computed tomography (CT) or by ultrasound scanning in those with clinical suspicion of IAC. Secondary outcome measures include procedural time, readmission rate and other post-operative complications. Patients who underwent appendicectomy in conjunction with another procedure were included in this study. Ethics approval is achieved.

TABLE 1 The SAGS score (9).

SAGS Score	Intra-operative findings
0	No appendicitis
1	Simple appendicitis (any of the following): i. Injected appendix ii. Thickened appendix iii. Serous free fluid
2	Purulent appendicitis (any of the following): i. Pus localised to right iliac fossa ii. Right paracolic gutter iii. Pelvis
3	Purulent appendicitis with 4 quadrant contaminations
4	Perforated appendix (any of the following): i. Free faecolith, faeces ii. Faecal staining iii. Visible hole in appendix

Operative technique of LRA

In this study, LRA is performed in patients with retro-colic, retro-iliac and pelvic appendicitis. After an open Hassan port entry, pneumoperitoneum with CO_2 insufflation up to 12–15 mmHg is established. Following insertion of two 5 mm ports into the right and the left iliac fossa under direct vision the base of the appendix is identified. A small peritoneal window is created in the mesoappendix adjacent to the base and is gently compressed using a non-tooth grasper to displace any faecolith away from the base. The appendiceal stump is cut 1–2 cm from the base with laparoscopic scissors and a PDS Endoloop (Ethicon Endo-Surgery, Johnson and Johnson, Cincinnati, OH, USA) is placed on both cut ends of the appendix. The remaining appendix is mobilised by dividing the mesoappendix with diathermy and clips or with a 5 mm LigaSure Maryland (Metronic, Dublin, Ireland). When the base of appendix is friable or necrotic, the caecum is mobilised and *en bloc* caecectomy is performed using a laparoscopic stapling device. The specimen is retrieved with an EndoCatch bag (Metronic, Dublin, Ireland) after ensuring haemostasis.

Statistical analysis

Collected data was analysed using excel spreadsheets and statistical programs R [R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.] and STATA (StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC.), with Chi-square test, Fisher's exact test and t test as required.

Results

Patient demographics

A total of 273 patients were included. There were 134 male and 139 female patients, aged between 9 and 84 years with a mean age of 35. 47% of patients had SAGS grade I appendicitis. The rate of follow up was 87% which was conducted via surgeon's private rooms within 30 days post discharge. Patient demographics are shown in the **Table 2**.

Severity of disease/prognosis

With increasing SAGS score and appendicitis severity the proportion of LRA utilised increased, as shown in the **Figure 1**. This was statistically analysed using a chi-squared test

TABLE 2 Patient demographics.

		Number	%	Mean	Median	Range
Gender	Male	134	49			
	Female	139	51			
Age				35	32	9–84
SAGS	0	55	20.1			
	I	128	46.9			
	II	70	25.6			
	III	2	0.7			
	IV	18	6.6			

demonstrating a p value of 0.003, therefore this difference was shown to be statistically significant.

Intra-abdominal collection occurrence analysis

209 patients underwent the LAA and 64 the LRA. Out of 273 patients, there were only two patients who developed IAC, who both underwent LAA approach with perforated appendicitis (SAGS IV). There was no IAC for SAGS score 3 and below. Overall, there was no statistically significant difference in occurrence of IAC between patients having LAA and LRA appendicectomy. Chi-squared test p value of the analysis was 0.43 with power of 0.195. The overall rate of IAC for SAGS IV was 11% (2/18); LAA was 18% (2/11) and none in LRA (0/7), with Fisher's exact test p value of 0.50. Therefore, there was no statistically significant difference in post-operative IAC rate between LAA and LRA overall and amongst SAGS IV groups from this study. Both patients with IAC were managed non-operatively, one requiring percutaneous radiologically guided drainage.

Secondary outcome measures

The mean procedural times for LAA and LRA were 34.85 min and 40.92 min respectively [$p = 0.002$, CI (−9.29, −2.86)], indicating a statistically significant longer procedural time for LRA. The mean length of stay for LAA and LRA patients were 1.6 days and 1.77 days respectively [$p = 0.208$, CI (−0.57, 0.12)], which was not statistically significant. Three patients were re-admitted within 30 days for post-operative pain, one with pulmonary embolism and two with post-operative ileus. The two patients who suffered ileus both underwent LAA appendicectomies with SAGS score of 4.

Discussion

In difficult appendicectomies, LRA (base to tip approach) has been described as a valuable alternative to LAA (tip to base approach) (6, 7, 9). However, there has been limited literature on the safety and efficacy of LRA given there has not been a standardised way of classifying the intraoperative severity of appendicitis. This is the first study to compare the risk of post-operative complications for LRA with the LAA, using a classification for severity of acute appendicitis such as SAGS (8, 10).

As demonstrated in Figure 1, LRA was used in preference to LAA as severity of appendicitis increases in SAGS scores. Although there was a statistically significant increase in operation time for LRA, this six minute difference is unlikely to be clinically relevant. In fact, LRA was used in technically more challenging cases, where the tip of the appendix is not easily identifiable. Thus, LRA may have decreased overall procedural time, rate of open conversion and need for right hemicolectomy. Despite LRA being utilised for more severe appendicitis there were no intra-abdominal collections found following LRA. However, this study is limited with low power due to

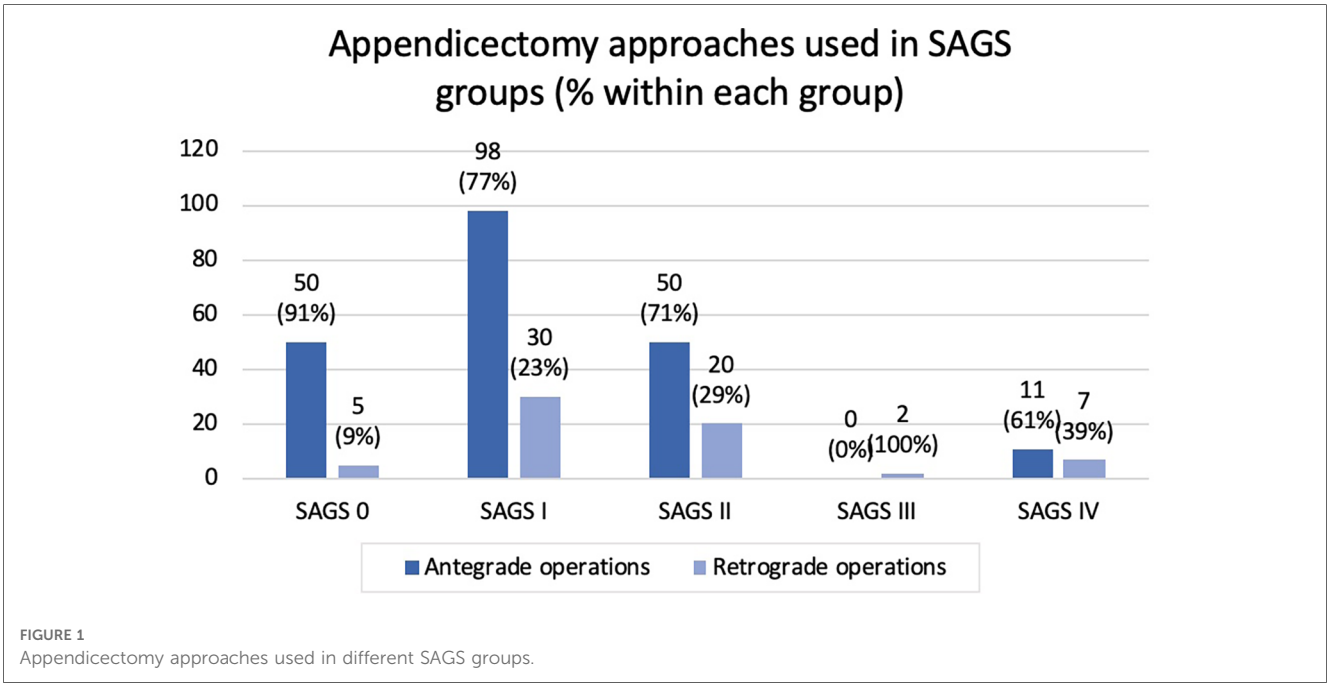

FIGURE 1
Appendicectomy approaches used in different SAGS groups.

the low rate of IAC and small number of patients with SAGS score III and IV. Although LAA or LRA did not affect post-operative IAC rate, rate of IAC increased with SAGS scores as previously shown by Reid et al. (8) This study is also limited due to the nature of the retrospective study design, small sample size and in that data was solely collected from cases performed by a single operator from one institution.

There was no significant difference in post-operative admission length or secondary outcome measures such as readmission and post-operative ileus. This suggests that there was no increase in immediate post-operative complications or increased cost associated with LRA.

Given the base of the appendix is divided prior to controlling the stump, there is perceived risk of faecal contamination and subsequent development of IAC. More recently, Mathews in 2020 further developed LRA method where a window is dissected in the mesoappendix and the base is initially divided with diathermy instead of cut using a pair of scissors (7, 9). As described by Matthews, there are various methods of LRA which may alter the rate of post-operative complications (9). For example, the base of the appendix can be stapled if concerned about the integrity of the appendiceal stump (6).

There are a number of advantages of LRA over LAA: LRA is relatively easy to perform as long as the appendiceal stump can be identified; it is effective and efficient in difficult appendicectomies such as retro-caecal, retro-ileal and pelvic appendicitis; and it is not associated with higher rates of complications including IAC.

Conclusion

In conclusion, LRA (Laparoscopic retrograde appendicectomy, base to tip) is a safe alternative to LAA (Laparoscopic antegrade appendicectomy, tip to base) in surgically challenging appendicitis without increased risk of complication within the limit of this study.

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 humans were approved by Ingrid Winship AO. Group Director Research and Chief Research Officer. Epworth HealthCare. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because retrospective research on medical records only.

Author contributions

AK: Formal Analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. PL: Data curation, Writing – review & editing. JC: Conceptualization, Methodology, Resources, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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frontiers | Frontiers in Oncology

TYPE Review
PUBLISHED 06 February 2024
DOI 10.3389/fonc.2024.1337219

OPEN ACCESS

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RECEIVED 22 November 2023
ACCEPTED 15 January 2024
PUBLISHED 06 February 2024

CITATION
Yu M, Yuan Z, Li R, Shi B, Wan D and Dong X (2024) Interpretable machine learning model to predict surgical difficulty in laparoscopic resection for rectal cancer.
Front. Oncol. 14:1337219.
doi: 10.3389/fonc.2024.1337219

Interpretable machine learning model to predict surgical difficulty in laparoscopic resection for rectal cancer

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Background: Laparoscopic total mesorectal excision (LaTME) is standard surgical methods for rectal cancer, and LaTME operation is a challenging procedure. This study is intended to use machine learning to develop and validate prediction models for surgical difficulty of LaTME in patients with rectal cancer and compare these models' performance.

Methods: We retrospectively collected the preoperative clinical and MRI pelvimetry parameter of rectal cancer patients who underwent laparoscopic total mesorectal resection from 2017 to 2022. The difficulty of LaTME was defined according to the scoring criteria reported by Escal. Patients were randomly divided into training group (80%) and test group (20%). We selected independent influencing features using the least absolute shrinkage and selection operator (LASSO) and multivariate logistic regression method. Adopt synthetic minority oversampling technique (SMOTE) to alleviate the class imbalance problem. Six machine learning model were developed: light gradient boosting machine (LGBM); categorical boosting (CatBoost); extreme gradient boost (XGBoost), logistic regression (LR); random forests (RF); multilayer perceptron (MLP). The area under receiver operating characteristic curve (AUROC), accuracy, sensitivity, specificity and F1 score were used to evaluate the performance of the model. The Shapley Additive Explanations (SHAP) analysis provided interpretation for the best machine learning model. Further decision curve analysis (DCA) was used to evaluate the clinical manifestations of the model.

Results: A total of 626 patients were included. LASSO regression analysis shows that tumor height, prognostic nutrition index (PNI), pelvic inlet, pelvic outlet, sacrococcygeal distance, mesorectal fat area and angle 5 (the angle between the apex of the sacral angle and the lower edge of the pubic bone) are the predictor variables of the machine learning model. In addition, the correlation heatmap shows that there is no significant correlation between these seven variables. When predicting the difficulty of LaTME surgery, the XGBoost model performed best among the six machine learning models (AUROC=0.855). Based on the decision curve analysis (DCA) results, the XGBoost model is also superior, and feature importance analysis shows that tumor height is the most important variable among the seven factors.

Conclusions: This study developed an XGBoost model to predict the difficulty of LaTME surgery. This model can help clinicians quickly and accurately predict the difficulty of surgery and adopt individualized surgical methods.

KEYWORDS

rectal cancer, pelvimetry, surgical difficulty, prediction model, machine learning, Shapley additive explanations

1 Introduction

According to the latest statistics, the incidence of colorectal cancer in the world has ranked the third among malignant tumors, and the mortality rate has ranked second, among which the incidence of rectal cancer ranks eighth (1). To a large extent, it has become a public health problem threatening human health. Rectal cancer has a rate approaching that of colon cancer and is a heavy health burden in the world. Since the introduction of total mesorectal excision (TME) in the 1980s by Heald (2)et al., the quality of TME directly affects the recurrence of local tumor and the prognosis of patients. So TME has become the gold standard for surgical treatment of rectal cancer. In the past two decades, with the development of minimally invasive surgery, laparoscopic surgery can be combined with classical surgery to achieve minimally invasive. Compared with open surgery, laparoscopic total mesorectal excision (LaTME) has the advantages of less invasive nature, faster recovery and better visualization of surgical field (3, 4), so it has become one of the main surgical methods for rectal cancer. Due to the fixed bony structure of pelvis and the limited space for pelvic surgery, it is hardto keep a clear surgical field of vision, identify accurate anatomical structures and perform accurate rectal resection (5). So, In rectal cancer, especially in deep and narrow pelvises, LaTME can be technically challenging. However, open surgery can better expose the surgical field of vision and accurately touch the extent of the tumor. Also, emerging techniques such as transanal total mesorectal excision (TaTME) and robotic surgery may help overcome the difficulties encountered during LaTME (6–8). Therefore, early identification of difficult LaTME surgery is necessary. Magnetic resonance imaging (MRI) has been widely used in routine (9–11) preoperative evaluation in the diagnosis and treatment of rectal cancer. It can not only clearly show the pelvic anatomy and soft tissue structure around the rectum, but also evaluate the depth of tumor invasion and suspected lymphatic metastasis around the mesorectum. A recent meta-analysis (12) shows that pelvic measurements based on MRI pelvic measurements can predict the difficulty of TME surgery. Therefore, MRI is a very useful tool in rectal cancer.

In recent years, artificial intelligence has developed rapidly, especially machine learning has been widely used in many medical fields because of its excellent performance (13, 14). Currently, there are few reports on machine learning models predicting the difficulty of LaTME surgery. In clinical practice, only some traditional statistical tools like nomograms that predict surgical difficulty (15, 16).Therefore, the purpose of this study is to explore the risk factors affecting the difficulty of LaTME surgery, to develop a preoperative, non-invasive and quantitative accurate strategy, and to establish an interpretable machine learning model to help clinicians choose appropriate surgical approach.

2 Materials and methods

2.1 Study design and subjects

This retrospective study collected the data of rectal cancer patients undergoing LaTME at The First Affiliated Hospital of Soochow University from 2017 to 2022. Patient inclusion criteria were as follows (1): colonoscopy showed that the distance from the lower margin of the tumor to the anal margin was less than 15cm, and it was confirmed as rectal adenocarcinoma by biopsy (2), preoperative rectal MRI scan was performed in our hospital within 15 days before surgical resection (3), execute LaTME strictly according to the principle of TME.

The exclusion criteria were as follows (1): without rectal MRI in our hospital (2), multiple primary cancer, secondary tumor, recurrence, distant metastasis (3), underwent abdominoperineal resection (APR) or other surgeries (e.g., Hartmann's procedure, emergency surgery, palliative surgery, multivisceral resection, or lateral pelvic lymph node dissection) (4), history of previous pelvic surgery (5), patients receiving neoadjuvant therapy. Moreover, all rectal cancer operations are performed by an experienced laparoscopic surgery team (the chief surgeon has more than ten years of experience in laparoscopic surgery) to follow the TME procedure. Some patients underwent ileostomy at the same time of resection. In order to reduce the impact of this operation, the operation time of these patients was recorded as the initial time minus 15 minutes (17). When the entire operation cannot be completed by laparoscopy, it should be changed to acombined approach (transabdominal and transanal surgery).

Figure 1 shows a flowchart outlining patient enrollment and study design. Finally, 626 rectal cancer patients who received LaTME were randomly divided into training group (80%) and test group (20%). The training group uses machine learning

algorithm to train and optimize the models, and the test group is used to test the prediction performance of these models.

2.2 Definition of surgical difficulty

We evaluate the difficulty of LaTME by intraoperative and postoperative parameters. Because there are many differences between eastern and western patients, we modify the standard of surgical difficulty proposed by Escal (18) et al. Surgical difficulty score: duration of surgery > 240 min (3 points),blood loss >200 ml (1 point), conversion to laparotomy (3 points), postoperative complications (grade II and III) (1 point), use of transanal dissection (2 points), and postoperative hospital stay >12 days (2 points). And the patients were divided into two groups: low surgical difficulty group (<6 points) and high surgical difficulty group (≥ 6 points). The postoperative complications was graded according to the Clavien–Dindo classification (19). Grade II: Medical treatment is required, including blood transfusion or total parenteral nutrition. Grade III: surgical, endoscopic, or radiological intervention is required.

2.3 MRI pelvimetry and other variables

All rectal cancer patients underwent abdominal pelvic 3.0T MRI examination within 15 days before surgery. The publicly available software (3DSlicer, version 5.2.2) funded by the National Institutes of Health was used for pelvic measurement and analysis (20). T2-weighted imaging (T2WI) was used to measure pelvic measurements, and all pelvic MR images were reviewed retrospectively by an observer blinded to the patients' clinicopathological information. Specific measurement parameters are shown in Figure 2. The measurements obtained are as follows (21, 22):

1. Pelvic inlet: the distance from the median surface of the superior symphysis pubis to the promontory;
2. Middle pelvis: the distance between the midpoint of the lower margin of the symphysis pubis and the midpoint of the anterior edge of the sacrococcygeal junction;
3. Pelvic outlet: the distance from the lower margin of the symphysis pubis to the coccyx;
4. Interischial distance: the distance between the sciatic spines on both sides.

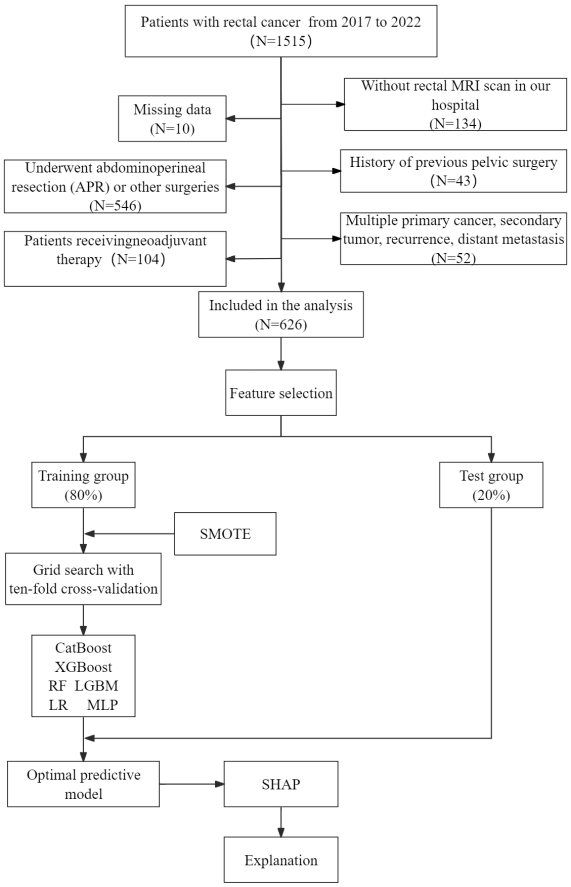

FIGURE 1
Flowchart of patient selection and machine learning model development process. LR, logistic regression; LGBM, light gradient boosting machine; CatBoost, categorical boosting; MLP, multilayer perceptron; RF, random forests; XGBoost, extreme gradient boost; SMOTE, synthetic minority oversampling technique; SHAP, shape additive explanation.

5. Intertuberous distance: the distance between the innermost points of the ischial tuberosities;
6. Pubic symphysis height: the distance between the upper and lower margins of the symphysis pubis;
7. Sacrococcygeal distance: the distance from the promontory to the tip of the tailbone;
8. Internal diameter of sacrum and pubis: the distance from the promontory to the inferior margin of pubis;
9. Mesorectal fat area: the mesentery and fatty area surrounding the rectum at the tip of the fifth sacral vertebra;
10. Sacrococcygeal–pubic angle: the angle between an extension of the line forming the anteroposterior diameter of the pelvic inlet and that of the anteroposterior diameter of the pelvic outlet the angle between the extension of the anteroposterior diameter line of the pelvic inlet and the extension of the anteroposterior diameter line of the pelvic outlet;
11. Angle 1: the angle between the pubic symphysis, the upper boundary of the promontory and the middle of the S3 vertebral body;
12. Angle 2:the angle between the cape, the middle of the S3 vertebrae, and the tailbone;
13. Angle 3: the angle between the middle of the S3 vertebral body, the coccyx and the lower edge of the pubic symphysis;
14. Angle 4: the angle between the coccyx, the upper and lower borders of the pubic symphysis;
15. Angle 5: the angle between the superior and inferior border lines of the pubic symphysis and the midpoint of the superior border of the pubic symphysis and the line between the sacral promontory;
16. Angle T1: the angle between the apex of the sacral angle and the lower edge of the third sacrum;
17. Angle T2: the angle between the lower margin of the tubercle of the third sacrum and the apex of the coccyx;
18. Angle T3: the angle between the apex of the tailbone and the lower margin of the pubis;
19. Angle T4: the angle between the upper and lower borders of the pubic symphysis with the lower border of the tumor as the vertex;
20. Angle T5: the angle between the superior margin of the pubis and the apex of the promontory.

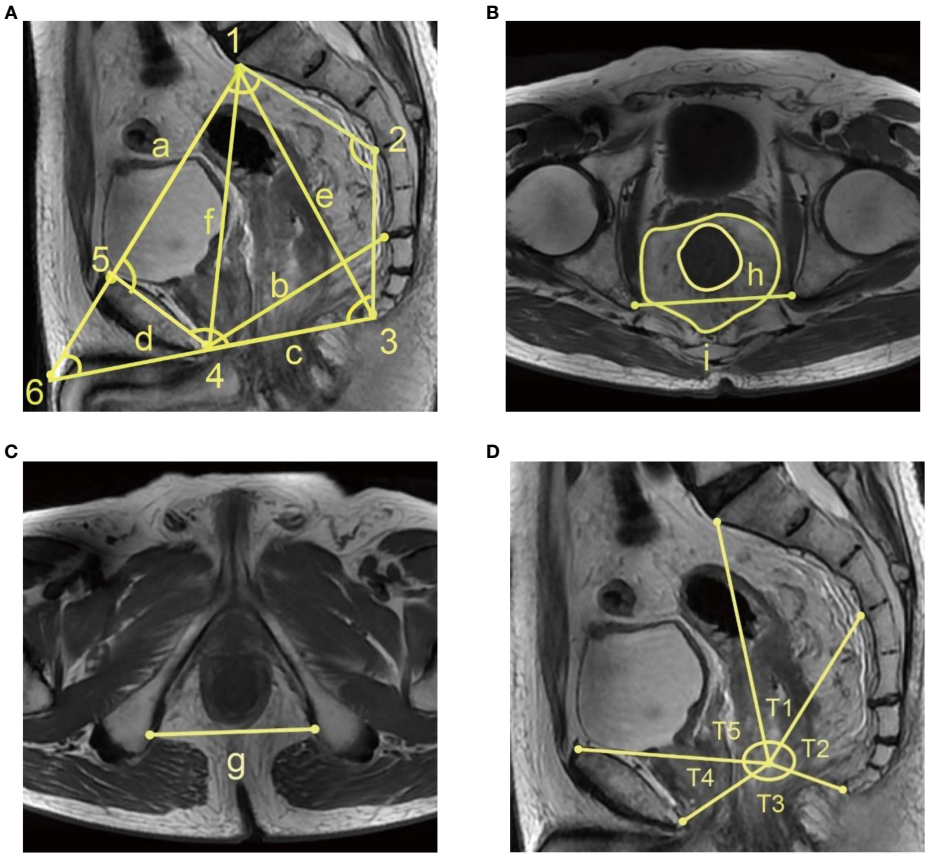

FIGURE 2
MRI T2 weighted image pelvimetry **(A)** Median sagittal position: (a) pelvic inlet, (b) middle pelvis, (c) pelvic outlet (d) Pubic symphysis height, (e) sacrococcygeal distance, (f) Internal diameter of sacrum and pubis (1), Angle 1 (2), Angle 2 (3), Angle 3 (4), Angle 4 (5), Angle 5 (6), Sacrococcygeal–pubic angle **(B)** Ischiatic tuberosity horizontal transverse position:(g) Intertuberous distance **(C)** Fifth sacral vertebral tip horizontal transverse position: (h) mesorectal fat area, (i) Interischial distance **(D)** Median sagittal position: (T1) Angle T1, (T2) Angle T2, (T3) Angle T3, (T3) Angle T3, (T4) Angle T4, (T5) Angle T5.

In addition, we obtained the baseline characteristics of the patients from the medical record: age, gender, BMI, albumin, globulin, lymphocyte count and tumor height. Among them, hematology nutritional indicators are added (23), and the calculation is as follows: albumin to globulin ratio (AGR)=albumin/globulin, prognostic nutrition index (PNI)=serum albumin (g/L) +5*lymphocyte count (10^9/L). Blood samples were collected within one week before surgery. We also collected the pathological stages of the patients' surgical specimens, and the tumors were staged according to the 8th tumor-node-metastasis (TNM) classification of the National Comprehensive Cancer Network (NCCN) and American Joint Committee on Cancer (AJCC) (24).

2.4 Development and validation of prediction models

In order to ensure the simplicity of our model, T-test, Mann-Whitney U test and Chi-square test were carried out to screen the variables with statistical differences between the high and low surgical difficulty groups. Then we use the LASSO regression of 10-fold cross-validation to reduce the dimension. Finally, the variables with non-zero coefficients are analyzed by multivariable logistics regression to screen independent risk factors to build a machine learning model. In our study, there was a serious imbalance between the low surgical difficulty group and high surgical difficulty group. Unbalanced data sets are frequently encountered in medical research due to the disproportionate number of non-patients compared to patients, leading to diminished predictive performance (25). The Synthetic Minority Oversampling Technique (SMOTE) is an efficient algorithm for addressing class imbalances (26), employing k-neighbor synthesis to focus on a limited number of classes and achieve a balanced dataset (27), which has demonstrated commendable efficacy in disease detection. So, we use the SMOTE to solve the problem of data imbalance and reduce the over-fitting of the model. SMOTE was only applied to our training group, and we did not oversample the test set, thus maintaining the natural frequency of results.

We use the data set after SMOTE to build six machine learning prediction models, including light gradient boosting machine (LGBM); categorical boosting (CatBoost); extreme gradient boost (XGBoost), logistic regression (LR); random forests (RF); multilayer perceptron (MLP). The subjects were randomly divided into training group (80%) and test group (20%). The training group was used for model development and hyperparameter tuning, the test group was used for model evaluation verification, and we use grid search with ten-fold cross-validation to find and determine optimal parameters for machine learning algorithms. The grid search algorithm systematically arranges and combines all possible parameter values, subsequently substituting the results of each combination into the model training process. The objective is to identify the optimal parameter combination from the exhaustive set of possibilities. Use discrimination and calibration to validate the model's predictive ability. The area under the receiver operating characteristic curve (AUROC) represents a measure of discrimination, and the performance of a model is evaluated through accuracy, sensitivity, specificity and F1 score. The Brier score and calibration curve were employed for model calibration. The Brier score represents the average squared deviation between the predicted outcome probability and the true label. A lower Brier score indicates superior model performance. The clinical effective rate and net benefit were evaluated by decision curve analysis (DCA). The Shapley Additive Interpretation (SHAP) is employed to directly elucidate the impacts of significant variables on the model. SHAP, a model interpretation technique grounded in cooperative game theory (28), has recently demonstrated its efficacy in explicating diverse machine learning models (29–31). Specifically, SHAP assigns each feature with a Shapley value by classifying the model's output value. Intuitively, estimating the Shapley value for each feature enables us to explicate its contribution to the outcome. The Shapley value accurately reflects the influence of a feature in each sample and facilitates a deeper understanding of whether it acts as a protective or risk factor for the model. The SHAP summary chart is generated from the Shapley value, the importance of the features is ranked, and the SHAP force plot is constructed to analyze and interpret the prediction results of a single sample.

2.5 Statistical analysis

All statistical analysis was carried out with IBM SPSS (version 26.0), R (version 4.2.3) and Python(version 3.10.0). The Shapiro-Wilk test was utilized to assess the normality of the data. Continuous data conforming to a normal distribution were presented as mean and standard deviation (SD), while continuous data deviating from a normal distribution were expressed as median and interquartile range (IQR). Student's t-test was employed for comparing continuous data following a normal distribution, whereas Mann-Whitney U test was used for comparing non-normal distribution data. Disaggregated data were reported as frequency (percentage), and comparisons between the two groups were conducted using the χ^2 test or Fisher's exact test (if the theoretical frequency $T < 5$). A p-value less than 0.05 in bilateral testing was considered statistically significant.

3 Results

3.1 Patient characteristics and surgical outcomes

Table 1 shows the clinical features and MRI pelvimetry of all participants. A total of 626 patients were included in this study, of which the median age was 64 (56–71) years old. The majority of the patients were male, accounting for 59.7% of the total. The median height of tumor was 9 (7 ~ 12) cm. Among the indicators related to the surgical difficulty, the probability that the median time of operation, blood loss and postoperative hospital stay were 198.5 (160.0, 240.5) min, 100 (50, 200) ml and 10 (8, 12) days. Use of transanal dissection, conversion to open procedure and morbidity (grade II and III) were 21.6%, 27.3% and 29.7%, respectively. Other indicators are shown in Table 1. Compared with the patients with low

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TABLE 1 Clinical features and MRI pelvimetry of all participants in different groups.

Variables	Overall (N=626)	Low surgical Difficulty group (N=516)	High surgical Difficulty group (N=110)	*P*
Baseline characteristics				
Gender (%)				0.221
Male	374 (59.7%)	314 (60.85%)	60 (54.55%)	
Female	252 (40.3%)	202 (39.15%)	50 (45.45%)	
Age (median [IQR], year)	64 (56, 71)	64 (56,71)	64 (58,71)	0.647
BMI (median [IQR], kg/m^2)	23.63 (21.54,25.52)	23.66 (21.61,24.02)	23.44 (21.06,25.27)	0.316
Tumor height (median [IQR], cm)	9 (7,12)	10 (7,12)	7 (5,10)	**<0.001**
Hematology nutritional indicators				
AGR (median [IQR])	1.52 (1.37,1.69)	1.51 (1.37,1.69)	1.59 (1.38,1.73)	0.248
PNI (mean [SD])	49.5 (5.22)	49.81 (4.86)	48.00 (6.47)	**0.006**
Pathological stage				
Pathological T stage (%)				0.115
T1	7 (1.12%)	5 (0.97%)	2 (1.82%)	
T2	100 (15.97%)	75 (14.53%)	25 (22.73%)	
T3	469 (74.92%)	396 (76.75%)	73 (66.36%)	
T4	50 (7.99)	40 (7.75%)	10 (9.09%)	
Pathological N stage (%)				0.115
N0	320 (51.12%)	255 (49.42%)	65 (59.09%)	
N1	168 (26.84%)	145 (28.10%)	23 (20.91%)	
N2	138 (22.04)	116 (22.48%)	22 (20%)	
Pathological TNM stage (%)				0.838
I	79 (12.62%)	61 (11.82%)	18 (16.36%)	
II	247 (39.46%)	209 (40.50%)	38 (34.55%)	
III	300 (47.92%)	246 (47.67%)	54 (49.09%)	
MRI pelvimetry				
Pelvic inlet (mean [SD], cm)	11.74 (1.07)	11.82 (1.05)	11.36 (1.08)	**<0.001**
Middle pelvis (mean [SD], cm)	12.55 (0.99)	12.57 (0.97)	12.49 (1.03)	0.444
Pelvic outlet (mean [SD], cm)	8.78 (0.89)	8.83 (0.91)	8.53 (0.77)	**0.001**
Interischial distance (median [IQR], cm)	9.74 (8.92,10.66)	9.74 (8.98,10.60)	9.74 (8.70,10.80)	0.738
Intertuberous distance (median [IQR], cm)	9.97 (8.79,11.20)	9.98 (8.81,11.09)	9.94 (8.68,11.39)	0.904
Pubic symphysis height (median [IQR], cm)	4.74 (4.27,5.15)	4.71 (4.26, 5.14)	4.80 (4.28,5.18)	0.388
Sacrococcygeal distance (median [IQR], cm)	12.60 (11.66,13.37)	12.50 (11.58,13.26)	12.98 (11.99,13.66)	**<0.001**
Internal diameter of sacrum and pubis (mean [SD], cm)	12.84 (1.14)	12.81 (1.13)	12.96 (1.15)	0.222
Mesorectal fat area (median [IQR], cm^2)	16.65 (11.57,21.88)	16.3 (10.97,21.40)	18.08 (13.36,23.60)	**0.001**
Angle 1 (median [IQR], °)	116.1 (107.0,124.2)	116.1 (107.6,124.4)	116.8 (104.4,124.0)	0.463

(Continued)

TABLE 1 Continued

Variables	Overall (N=626)	Low surgical Difficulty group (N=516)	High surgical Difficulty group (N=110)	*P*
Angle 2 (mean [SD], °)	108.3 (10.9)	108.4 (10.9)	107.6 (11.2)	0.439
Angle 3 (median [IQR], °)	127.2 (122.2,132.8)	127.3 (122.7,133.2)	126.8 (120.5,131.9)	0.086
Angle 4 (median [IQR], °)	89.1 (82.6,96.4)	89.0 (82.2,96.0)	90 (83.2,97.7)	0.486
Angle 5 (median [IQR], °)	98.5 (93.7,103.8)	97.7 (93.5,103)	101 (95.8,109.5)	**<0.001**
Sacrococcygeal–pubic angle(median [IQR], °)	46.9 (41.0,52.5)	46.4 (40.8,51.6)	49.0 (41.9,56.0)	**0.008**
Angle T1 (median [IQR], °)	53.9 (46.8,68.5)	54.2 (47.0,68.6)	53.0 (44.8,68.0)	0.342
Angle T2 (median [IQR], °)	79.9 (59.0,101.6)	81.0 (60.9,101.9)	72.8 (51.1,100.6)	0.089
Angle T3 (median [IQR], °)	112.1 (80.1,143.2)	110.4 (80.8,141.0)	114.8 (78.0,150.5)	0.380
Angle T4 (median [IQR], °)	27.0 (23.0,31.0)	27.0 (23.1,31.2)	26.0 (22.2,30.0)	0.134
Angle T5 (median [IQR], °)	72.6 (66.7,80.0)	72.6 (67.0,79.9)	72.6 (64.5,80.9)	0.690
Surgical difficulty				
Duration of surgery (median [IQR], min)	198.5 (160.0,240.5)	187 (153,221.5)	260 (222.3,291.5)	**<0.001**
Blood loss (median [IQR], ml)	100 (50,200)	100 (50,200)	150 (100,200)	**<0.001**
Postoperative hospital stays (median [IQR], day)	10 (8,12)	9 (8,11)	13 (9,16.3)	**<0.001**
Morbidity (grade II and III) (yes/no, %)	186/440 (29.7/70.3)	131/385 (25.4/74.6)	55/55 (50/50)	**<0.001**
Use of transanal dissection (yes/no, %)	135/491 (21.6/78.4)	74/442 (14.3/85.7)	61/49 (55.5/44.5)	**<0.001**
Conversion to open procedure (yes/no, %)	171/455 (27.3/72.7)	102/414 (19.8/80.2)	69/41 (62.7/37.3)	**<0.001**

IQR, interquartile range; SD, standard deviation; BMI, body mass index; AGR, albumin to globulin ratio; PNI, prognostic nutrition index; The bold values P <0.05.

surgical difficulty, the patients in the high surgical difficulty group had lower tumor height, lower PNI, shorter pelvic inlet, pelvic outlet, longer sacrococcygeal distance, more mesorectal fat area and larger angle 5 and sacrococcygeal-pubic angle. However, preliminary analysis showed that there was no significant difference in gender, age, BMI, AGR, pathological T stage, pathological N stage, pathological TNM stage, middle pelvis, interischial distance, Intertuberous distance, pubic symphysis height, internal diameter of sacrum and pubis, angle 1, angle 2, angle 3, angle4 and tumor related angle between the two groups.

3.2 The relationship between clinicopathological factors and the definition of surgical difficulty

The comparison of clinicopathological parameters of rectal cancer patients with six definitions of surgical difficulty is shown in Supplementary Table 1. Intertuberous distance had an association with duration of surgery, an association mesorectal fat area between and more estimated blood loss was found BMI PNI pathological T stage internal diameter of sacrum and pubis had an association with conversion to open procedure, angle T1 angle T2 angle T3 had associations with morbidity and use of transanal dissection, and there was an association of angle T4 with postoperative hospital stay. Also pubic symphysis height angle 3 angle 5 can influence the morbidity, and tumor height pathological TNM stageIII can affect use of transanal dissection. All the above associations were statistically significant (all $p < 0.05$).

3.3 Feature selection

LASSO can compress variable coefficients to prevent over-merging to solve serious collinearity problems (32). We use LASSO regression analysis and ten-fold cross-validation to filter variables. Use 1 standard error's lambda to select seven variables (Figure 3), including tumor height, PNI, pelvic inlet, pelvic outlet, sacrococcygeal distance, mesorectal fat area and angle 5. In order to further control the influence of confounding factors, the above seven independent variables were analyzed by multivariate logistic regression analysis (Table 2). We found that the above seven variables are independent influencing factors for the difficulty of

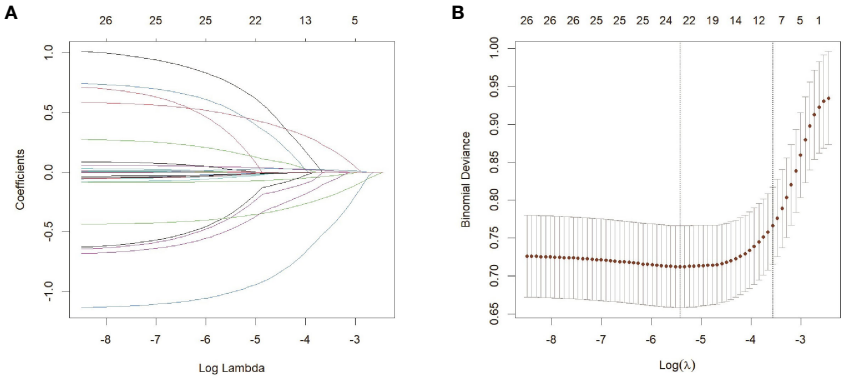

FIGURE 3
Feature selection based on LASSO regression analysis**(A)** LASSO coefficient profiles of the 26 variables. **(B)** Selection of the optimal penalization coefficient lambda in the LASSO model used ten-fold cross validation based on minimum criteria. The partial likelihood deviance is plotted against log (lambda), where lambda is the tuning parameter. Red dots indicate average deviance values for each model with a given lambda, and partial likelihood deviance values are shown, with error bars representing SE. Dotted vertical lines were drawn at the optimal values by using the minimum criteria and the 1 SE of the minimum criteria (the 1-SE criteria).

LaTME surgery. The correlation heatmap (Figure 4) results show that the correlations between variables are all less than 0.4, there is no significant correlation between variables, and there is no multicollinearity. Finally, tumor height, PNI, pelvic inlet, pelvic outlet, sacrococcygeal distance, mesorectal fat area and angle 5 were selected to be included in the machine learning model.

3.4 Performance of the machine learning model and model interpretability

The data were randomly divided into a training group (80%, N = 500) and a test group (20%, N = 126) as shown in Supplementary Table 2. There was no statistical difference in most predictive variables between the training group and test group. In the training group, there were 84 high-difficulty operations and 416 low-difficulty operations. In the test group, 26 patients underwent high-difficulty surgery and 100 patients underwent low-difficulty surgery. There is a serious imbalance. After resampling the training set, SMOTE 416 cases of high difficulty and 416 cases of low difficulty. The seven variables after feature selection are used as predictor variables to build different prediction models. The optimization model was ten-fold cross-validation on the training data set, and the mesh search algorithm was used to find the optimal parameters of the machine learning algorithm. The best parameters of each model are shown in Supplementary Table 3. The ability to validate previously established predictive models with test queues. The results of AUROC, accuracy, sensitivity, specificity, F1 score and Brier score in the test set are shown in Table 3. From the overall performance of each model, in terms of discrimination, as shown in Figure 5, the AUROC of LGBM model is 0.848, the AUROC of CatBoost model is 0.836, the AUROC of XGBoost model is 0.855, the AUROC of RF model is 0.801, the AUROC of LR model is 0.828,

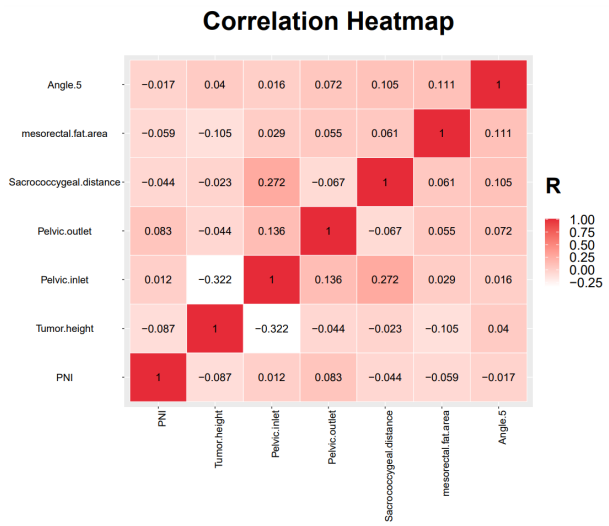

FIGURE 4
Results of the correlation heatmap between all variables.

TABLE 2 Based on the coefficients and Lambda.1se values of the LASSO regression, multivariable logistics regression to validate the validity of each variable.

Variables	LASSO regression		Multivariable logistics regression	
	Coefficients	Lambda.1se	OR (95%CI)	*P*
Tumor height	-0.20860369	0.02837605	0.656 (0.588-0.733)	<0.001
PNI	-0.03522676		0.916 (0.874-0.960)	<0.001
Pelvic inlet	-0.48595986		0.351 (0.264-0.467)	<0.001
Pelvic outlet	-0.09046064		0.730 (0.547-0.975)	0.033
Sacrococcygeal distance	0.2097511		1.686 (1.346-2.112)	<0.001
Mesorectal fat area	0.01126133		1.041 (1.003-1.081)	0.035
Angle 5	0.02102902		1.043 (1.021-1.064)	<0.001

Coefficients, coefficients of each variable in LASSO regression; Lambda.1se, among all lambda values, the lambda value of the simplest model within a variance of the mean value of the minimum target parameter is obtained; OR, odds ratio; CI; confidence interval; PNI, prognostic nutrition index.

and AUROC of MLP model is 0.835. The corresponding Brier score is 0.151, 0.117, 0.122, 0.121, 0.158 and 0.172 as shown in Figure 6. Decision curve analysis (DCA) showed that XGBoost model showed better clinical than other models before the threshold probabilities of 0.6(Figure 7). The XGBoost algorithm is selected to construct the prediction model after a comprehensive comparison.

By calculating the contribution of each variable to the prediction, the results of the XGBoost model are interpreted using SHAP. The SHAP summary chart and importance matrix diagram of the XGBoost model is shown in Figure 7. The SHAP summary plot (Figure 8A) is based on estimates, with each patient having a data point for each feature. Red indicates higher values while blue represents lower values of the same. The horizontal axis shows the SHAP value, and larger shapes indicate features that have a higher predictive value for surgical difficulty in a given sample. The importance bar chart (Figure 8B) displays the significance of each variable in predicting surgery difficulty. To sum up, the features in descending order of importance are: tumor height, pelvic inlet, sacrococcygeal distance, angle 5, PNI, mesorectal fat area and pelvic outlet.

Applying predictive model SHAP force plot can effectively clarify and explain model predictions for individual patients. The SHAP force plot for the XGBoost model is shown in Figures 8C, D. SHAP values represent the relevant predictive features of individual patients and the contribution of each feature to the prediction of the difficulty of LaTME surgery. Red indicates high surgical difficulty characteristics; blue indicates low surgical difficulty characteristics. The length of the arrow helps to achieve the size of the predicted effect. The longer the arrow, the greater the effect. Figure 8C shows a rectal cancer patient whose tumor height is 5.0cm, PNI is 39.1, angle 5 is 101.0°, pelvic inlet is 13.39cm, pelvic outlet is 7.62cm, mesorectal fat area is 14.44cm^2 and sacrococcygeal distance is 13.40cm, with a Shapley value of 5.00(>base value). Figure 8D shows a rectal cancer patient whose tumor height is 5.0cm, PNI is 54.05, angle 5 is 97.3°, pelvic inlet is 12.18cm, pelvic outlet is 8.73cm and sacrococcygeal distance is 13.28cm, with a Shapley value of -2.94 (<base value). The advantage of this force plot is that it gives a clear combination of parameters that contribute greatly to the model.

4 Discussion

In our study, an accurate model was developed to predict the difficulty of rectal cancer surgery, and six machine learning prediction models were developed and evaluated. The prediction performance of XGBoost model is generally the best, AUC (0.855), F1 score (0.583), accuracy (0.841), sensitivity (0.538), specificity (0.92). However, LGBM has the highest specificity (0.93), LR has the highest sensitivity (0.731), and MLP has the highest F1 score (0.590). Seven core predictors of the difficulty of rectal surgery were determined by LASSO method, ten-fold cross-validation and multivariable logistic regression. The smaller the value of tumor height, PNI, pelvic inlet and pelvic outlet is, the higher the difficulty of operation is, while the higher the value of sacrococcygeal distance, mesorectal fat area and angle 5 is, the more difficult the operation is. Therefore, this study may be helpful to identify patients at risk of difficulty in operation. SHAP found that tumor height, pelvic inlet, sacrococcygeal distance, angle 5, PNI, mesorectal fat area and pelvic outlet, were ranked in order of importance related to surgical difficulty of LaTME.

It is well known that laparoscopic surgery for rectal cancer is considered technically difficult. Recent studies have shown that a variety of factors related to the difficulty of LaTME surgery, including doctors' surgical skills, previous abdominal surgery history, preoperative radiotherapy, tumor height, body mass index (BMI), pelvic size, preoperative nutritional status and other factors can affect the difficulty of laparoscopic surgery (18, 23, 33–36). Actually, the definition of the difficulty of rectal surgery is actually vague. The definition of surgical difficulty should be a representative parameter, which can represent the factors related to the surgical results. In our study, we adopted the surgical difficulty classification criteria proposed by Escal (18) et al.: duration of surgery, estimated blood loss, conversion to open procedure, morbidity (grade II and III), use of transanal dissection and postoperative hospital stay, and slightly modified them. It makes sense to include both surgical and postoperative parameters in the criteria, as impaired surgical quality and variable postoperative course may increase local recurrence and impaired survival (37).

TABLE 3 Performance of predictive models generated by five machine learning models.

Model	AUROC	Accuracy	Sensitivity	Specificity	F1 score
LGBM	0.848	0.841	0.500	0.93	0.565
XGBoost	0.855	0.841	0.538	0.92	0.583
CatBoost	0.84	0.817	0.423	0.92	0.489
LR	0.828	0.770	0.731	0.78	0.567
RF	0.820	0.817	0.423	0.92	0.489
MLP	0.835	0.802	0.692	0.83	0.590

In our study, tumor height was the most important factor for surgical difficulty in LaTME, and this result is consistent with previous studies (38). Tumor height is one of the main factors in selecting surgical methods. The lower the tumor location, the more difficult transabdominal surgery is, and the more likely the surgeon is to choose laparoscopically assisted transsphincter plane ultra-low anterior rectal resection (35). In our study, univariable logistic regression showed that tumor height was associated with use of transanal dissection (P=0.009). The closer the tumor is to the anal verge, the greater the extent of dissection and exposure, and the more difficult the operation.

Our research shows that pelvic anatomy is the independent influencing factor affecting the difficulty of laparoscopic rectal cancer surgery. Pelvic measurement was originally used to evaluate the possibility of successful vaginal delivery (39). With the continuous development of laparoscopic technology, many colorectal experts are more and more interested in pelvic measurement in recent years. Pelvic measurement has been used to evaluate the difficulty of rectal cancer surgery, but the relationship between quantitative pelvic measurement and surgical difficulty has not been determined (18, 40–42), and even some studies have found that there is no relationship between pelvimetry and surgical difficulty (5, 43, 44). However, there are also some differences between our research and theirs. For example, Ogiso (5) et al. studied patients undergoing laparoscopic resection of rectal cancer, and the results showed that there was no correlation between pelvic parameter and operation time, but their study was based on only 50 cases. 626 patients who underwent laparoscopic rectal surgery were included in our study, and we used 20 pelvic measurement parameters based on MRI, including 8 longitudes, 11 angles, and 1 region. Multivariate logistic regression showed that pelvic inlet, pelvic outlet and sacrococcygeal distance were independent influencing factors for the difficulty of LaTME. This is partially consistent with previous findings. Multivariate analysis by Zhou (45) et al. showed that BMI, tumor height, lymph node metastasis, pelvic inlet, pelvic outlet, superior and inferior diameter of pubis, depth of sacrococcyx curvature, sacrococcyx-pubic angle and distance from pubic bone to coccyx were the main factors affecting operation time. By studying patients with rectal cancer receiving TaTME, Ferko (46) et al. found that the sharper the Angle 5, the more difficult the operation, and the worse the quality of TME. This is contrary to our results and may be due to different definitions of surgical difficulty and surgical methods. Laparoscopic surgery differs from other surgical techniques in its ability to access the pelvis, providing a multi-angle surgical field of view that is not achievable with open surgery. However, laparoscopic rectal cancer surgery presents greater challenges due to the deep anatomical position of the rectum within a narrow funnel-shaped pelvis, intricate surrounding tissue, and limited surgical space. Moreover, this procedure necessitates the use of rigid long-handled endoscopic instruments for complex operations such as cutting, separation, hemostasis, and anastomosis. These instruments differ significantly from traditional manual techniques and lack tactile feedback. Consequently, our study found that the narrow pelvic entrance and outlet, increased pelvic depth, and larger angle5 pose difficulties in terms of visual field visibility, accessibility to the operating area for LaTME in rectal cancer cases (47, 48), thereby increasing surgical complexity.

PNI is a protective factor to predict the difficulty of LaTME. The nutritional status of patients before operation is usually considered to be closely related to postoperative complications, such as postoperative anastomotic fistula, intestinal obstruction, ascites and so on (48, 49). In our study, PNI is related to conversion to open procedure, and low preoperative PNI is independently related to high difficulty of rectal surgery. However, Sun (23) et al. included 294 patients with locally advanced rectal cancer who underwent LaTME after preoperative radiotherapy and chemotherapy. It was

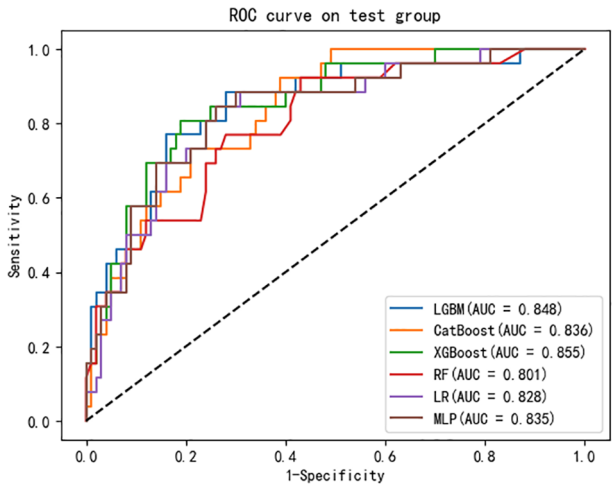

FIGURE 5
Evaluation of the six machine learning models based on the AUC of the ROC curve in validation set. AUC, area under the curve; ROC, receiver operating characteristic.

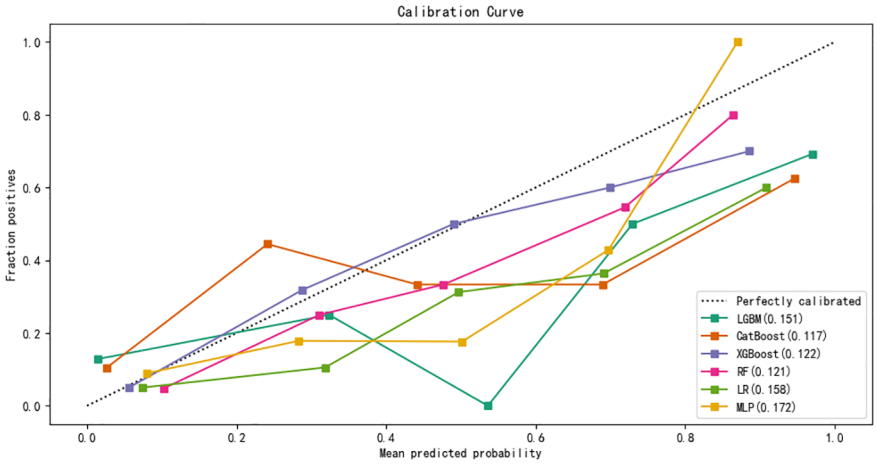

FIGURE 6
Calibration curves of five machine learning models in the validation set.

found that preoperative AGR can predict the difficulty of rectal surgery after preoperative radiotherapy and chemotherapy. The difference is that the patients with preoperative radiotherapy and chemotherapy were excluded from our study. The PNI=49.5 ± 5.22 and AGR=1.52 (1.37~1.69) in our study were higher than those in their study PNI=46.0 ± 6.4 and AGR=1.3 ± 0.2. Therefore, preoperative radiotherapy and chemotherapy will damage the nutritional status of patients with rectal cancer. Often malnutrition and preoperative radiotherapy and chemotherapy are easy to cause tissue edema, fibrosis, extensive fog and exudate (47), which hinder tissue anatomy and increase the difficulty of operation. Unfortunately, it is not clear whether nutritional status will lead to different tissue responses to radiotherapy and chemotherapy. In addition, the mechanism of nutritional status predicting the difficulty of operation remains to be further discussed.

The current findings indicate that mesorectal fat area is considered an independent risk factor for surgical difficulty. In general, obesity can make rectal surgery more difficult (50, 51). The main reasons for these difficulties are dissection difficulties caused by the reduced relative space in the abdomen due to obesity, exposure problems (bowel layering, mesorectal volume) and the thickness of adipose tissue. In addition, the bulky mesentery is prone to tearing and bleeding. Lacerations resulting from mesenteric traction may result in unacceptable bleeding and thus clutter the surgical field. Unclear anatomy, intraoperative bleeding,

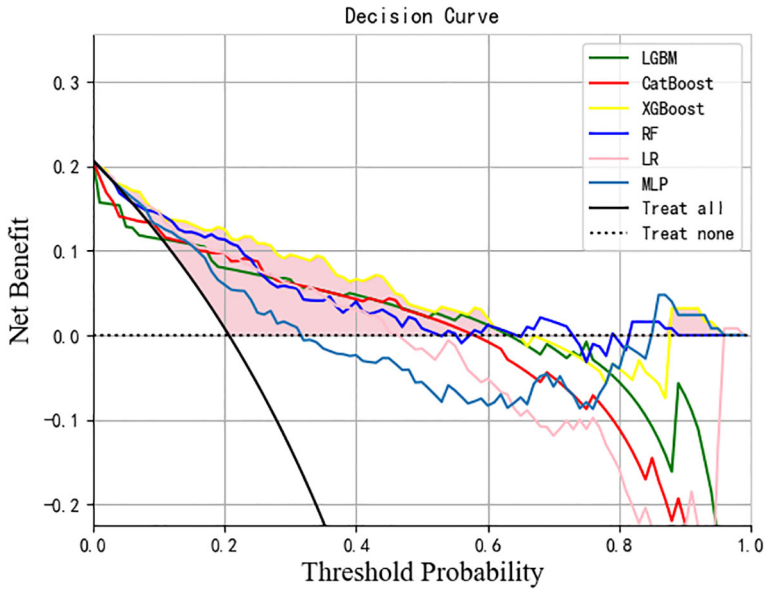

FIGURE 7
DCA analysis was performed to evaluate the clinical usefulness. The y-axis indicated the net benefit; the x-axis indicated the threshold probability. The solid yellow line shows the net benefit rate of the XGBoost forecast model. Within a certain threshold range, the XGBoost model has a higher net benefit. DCA, Decision curve analysis.

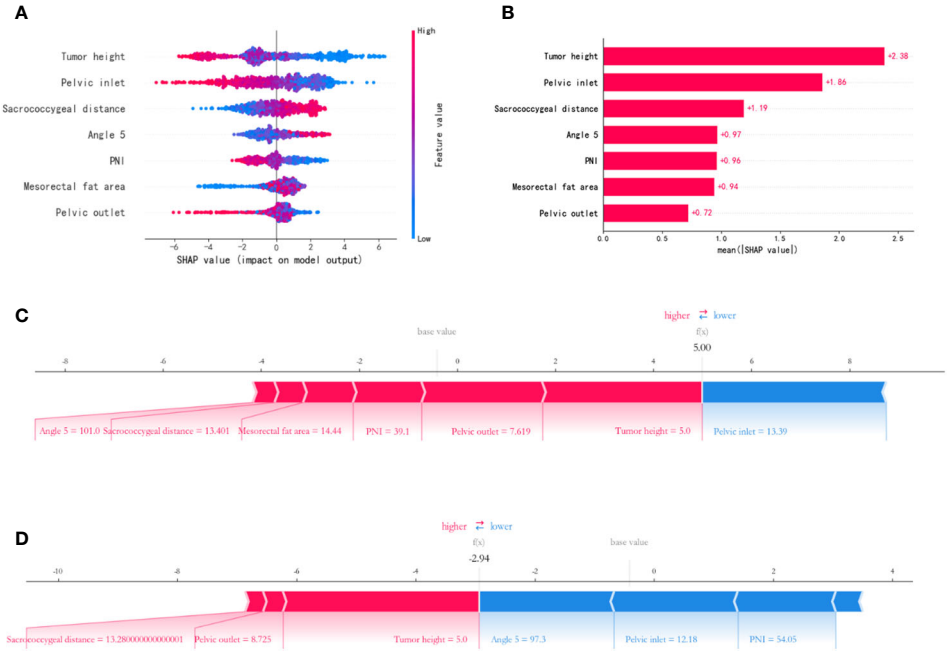

FIGURE 8
Feature importance SHAP summary chart and bar chart. **(A)** The left dot plot represents the direction of contribution of each value of each variable, with red representing larger values and blue representing lower values of each variable. **(B)** The bars on the right represent the importance of the variables and their overall contribution to the model predictions. **(C, D)** SHAP scores explain the predicted risk of osteoporosis in two subjects.

intra-abdominal adhesions and intestinal perforation are common reasons for conversion to open surgery in obese patients (52). In addition, a recent meta-analysis (53) suggested that the incidence of anastomotic leakage, pulmonary events, and postoperative intestinal obstruction was significantly higher in the obese group, but this did not directly affect pathological safety. BMI represents the most common index describing overall obesity, and multiple studies have confirmed the negative impact of BMI on rectal surgery (5, 45, 54, 55). However, in our study, BMI was closely related to conversion to open procedure (p=0.037) and had no significant impact on surgical difficulty. This is because BMI may not accurately reflect changes in visceral fat distribution or overall obesity in the body. According to research, BMI is less sensitive, and for any given BMI value, there are large age, race, and gender differences in body fat percentage. For example, at the same BMI, Asians have higher body fat percentages than Caucasians (56). Therefore, BMI does not reflect the impact of obesity on laparoscopic rectal surgery, and mesorectal fat area may be a better indicator of the difficulty of laparoscopic rectal surgery.

Our research shows that the method of machine learning is feasible and has high accuracy. At present, because most prediction tools are developed in a linear and cumulative manner based on the interaction of variables (57), their clinical applicability is limited and their predictive ability is poor. However, the surgical complexity of LaTME is multifactorial, and the relationship between surgical difficulty and influencing factors is not entirely linear. In recent years, machine learning algorithms have been extensively utilized in the field of medicine and have emerged as a powerful tool for addressing numerous clinical predictions. Machine learning algorithms can effectively overcome the limitations of traditional methods and serve as a more accurate and non-linear approach to predicting patient prognosis (58, 59). In fact, previous studies have developed models that use machine learning techniques to predict the difficulty of rectal cancer surgery. For example, Lv (60)et al. established a blood loss and resection duration (BLADE) scoring system, and used RF algorithm to establish a preoperative prediction model of BLADE score. Our research focuses on early identification of predictors that affect the difficulty of LaTME surgery. In addition, many machine learning models are black-box models, lack of variable relationship analysis in clinical application, and this problem also exists in our model. Therefore, we introduce SHAP to explain the output prediction model, which provides a convincing explanation for the relationship between nonlinear variables (61). As an interpretable omnipotent method of the model, SHAP can be used for global and local interpretation. SHAP analysis can guide clinicians to pay attention to target variables in patients with high surgical difficulty, which is more beneficial to the evaluation of patients before operation.

The results of the current study have several clinical implications. First, for patients with poor preoperative nutritional status, the patient's albumin level should be improved first before LaTME is performed. Second, for patients with rectal cancer in a difficult pelvis, it can help improve patient-physician communication by informing patients of possible perioperative risks and complications and selecting an appropriate surgical approach (e.g., open, laparoscopic, robotic, or transanal Operation). Finally, early career surgeons can select appropriate cases during the learning process, and patients with difficult pelvises can be referred to more specialized doctors and experienced

surgeons to improve surgical quality and minimize the risk of complications and adverse consequences due to lack of experience. Other surgeons can collect clinicopathological and MRI pelvimetry from their patients and input them into our XGBoost machine learning models to get accurate clinical predictions. The SHAP force plot can be output to show the influence of each variable on the difficulty of LaTME surgery.

This study has some limitations. On the one hand, this is a single-center retrospective study, there is inevitable selection bias, difficult surgical risk factors and predictive models can be widely used in patients with rectal cancer, need to be further studied and verified. On the other hand, this study did not explore the survival and prognosis of the two groups of patients, and the data are limited. Therefore, it is necessary to conduct prospective randomized studies with larger samples and longer follow-up periods to simulate the interaction between variables. In addition, we only use 2D MRI pelvic measurements, excluding 3D features. 3D pelvic measurements should be further evaluated to better explore the relationship between pelvic features and surgical difficulty.

5 Conclusion

In our study, we developed a model based on the XGBoost machine learning algorithm to predict the surgical difficulty of LaTME. The model has good prediction accuracy and clinical practicability, which is helpful for surgeons to identify patients with high surgical difficulty as early as possible. The model identifies tumor height, PNI, pelvic inlet, pelvic outlet, sacrococcygeal distance, mesorectal fat area and angle 5 as independent influencing factors.

Author contributions

MY: Writing – original draft, Data curation, Software, Validation, Methodology. ZY: Conceptualization, Investigation, Writing – original draft, Data curation, Validation. RL: Data curation, Investigation, Writing – original draft. BS: Data curation, Methodology, Writing – original draft. DW: Conceptualization, Supervision, Validation, Writing – review & editing, Visualization. XD: Conceptualization, Resources, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We are grateful to the authors of the primary study.

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.2024.1337219/full#supplementary-material

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frontiers | Frontiers in Surgery

TYPE Original Research
PUBLISHED 01 March 2024
DOI 10.3389/fsurg.2024.1370370

OPEN ACCESS

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RECEIVED 14 January 2024
ACCEPTED 22 February 2024
PUBLISHED 01 March 2024

CITATION
Rizzuto A, Andreuccetti J, Bracale U, Silvestri V, Pontecorvi E, Reggio S, Sagnelli C, Peltrini R, Amaddeo A, Bozzarello C, Pignata G, Cuccurullo D and Corcione F (2024) Shifting paradigms: a pivotal study on laparoscopic resection for colovesical fistulas in diverticular disease.
Front. Surg. 11:1370370.
doi: 10.3389/fsurg.2024.1370370

Shifting paradigms: a pivotal study on laparoscopic resection for colovesical fistulas in diverticular disease

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Background: Colovesical fistulas (CVFs) pose a challenge in diverticulitis, affecting 4% to 20% of sigmoid colon cases. Complicated diverticular disease contributes significantly, accounting for 60%–70% of all CVFs. Existing studies on laparoscopic CVF management lack clarity on its effectiveness in diverticular cases compared to open surgery. This study redefines paradigms by assessing the potentiality, adequacy, and utility of laparoscopy in treating CVFs due to complicated diverticular disease, marking a paradigm shift in surgical approaches.
Methods: Conducting a retrospective analysis at Ospedale Monaldi A.O.R.N dei Colli and University Federico II, Naples, Italy, patients undergoing surgery for CVF secondary to diverticular disease between 2010 and 2020 were examined. Comprehensive data, including demographics, clinical parameters, preoperative diagnoses, operative and postoperative details, and histopathological examination, were meticulously recorded. Patients were classified into open surgery (Group A) and laparoscopy (Group B). Statistical analysis used IBM SPSS Statistic 19.0.
Results: From January 2010 to December 2020, 76 patients underwent surgery for colovesical fistula secondary to diverticular disease. Laparoscopic surgery (Group B, $n = 40$) and open surgery (Group A, $n = 36$) showed no statistically significant differences in operative time, bladder suture, or associated procedures. Laparoscopy demonstrated advantages, including lower intraoperative blood loss, reduced postoperative primary ileus, and a significantly shorter length of stay. Postoperative morbidity differed significantly between groups. Mortality occurred in Group A but was unrelated to surgical complications. No reoperations were observed. Two-year follow-up revealed no fistula recurrence.
Conclusion: This pivotal study marks a paradigm shift by emphasizing laparoscopic resection and primary anastomosis as a safe and feasible option for managing CVF secondary to diverticular disease. Comparable conversion, morbidity, and mortality rates to the open approach underscore the transformative potential of these findings. The study's emphasis on patient selection and surgeon experience challenges existing paradigms, offering a progressive shift toward minimally invasive solutions.

KEYWORDS

diverticular disease, colovesical fistula, enterovesical fistula, laparoscopic sigmoidectomy, minimally invasive surgery, colorectal surgery

Introduction

Diverticular disease, particularly affecting the sigmoid colon, poses a challenge for 10%–25% of individuals with this condition (1, 2). Complications arise in about 15% of diverticular disease cases (3–5). Among the management options for these complications, laparoscopic colectomy has become the leading choice globally for addressing symptomatic sigmoid diverticulitis (6–9).

One significant complication associated with diverticular disease is the occurrence of colovesical fistulas (CVFs) (Figure 1) happening in 4%–20% of cases and representing a substantial majority, around 60%–70%, of all CVF instances (10, 11). The causes of these fistulas are complex, involving the direct extension of a perforated diverticulum or erosion through the bladder wall (12, 13). This complexity is further influenced by the anatomical intricacies of the pelvis, physiological functions, and the distinct pressure gradient between the bowel and the bladder (14).

Clinical symptoms often manifest as lower urinary tract issues, with patients reporting problems such as pneumaturia, fecaluria, and recurrent urinary tract infections. These symptoms highlight the intricate pathological mechanism involved in CVF development (15). Traditionally, CVFs were considered a historical contraindication to minimally invasive approaches due to concerns about safety and feasibility (10). However, recent reports, such as those by Badic et al. (11), challenge this belief, emphasizing the safety and feasibility of laparoscopic management, even though there are higher conversion rates and associated morbidity.

Despite the growing literature on laparoscopic management of CVFs, there is still a significant gap in our understanding of the actual effectiveness and utility of the minimally invasive approach compared to open surgery (16). Adding to this challenge, recent studies may lack definitive conclusions as they often include a diverse group of patients with CVFs of varying causes, failing to distinguish between those secondary to diverticular disease and those arising from different factors (16).

This report aims to address these knowledge gaps by focusing on evaluating the adequacy and utility of laparoscopy in treating CVFs complicating diverticular disease, directly comparing it to open surgery. By examining this specific group of patients, our goal is to provide nuanced insights that can guide clinicians and surgeons in optimizing their approach to these intricate cases.

Material and methods

Patient recruitment

A retrospective analysis included 410 patients who underwent surgery for diverticular disease from 2010 to 2020 at Ospedale Monaldi A.O.R.N dei Colli and University Federico II, Naples, Italy. Demographic and clinical data were collected from CPT

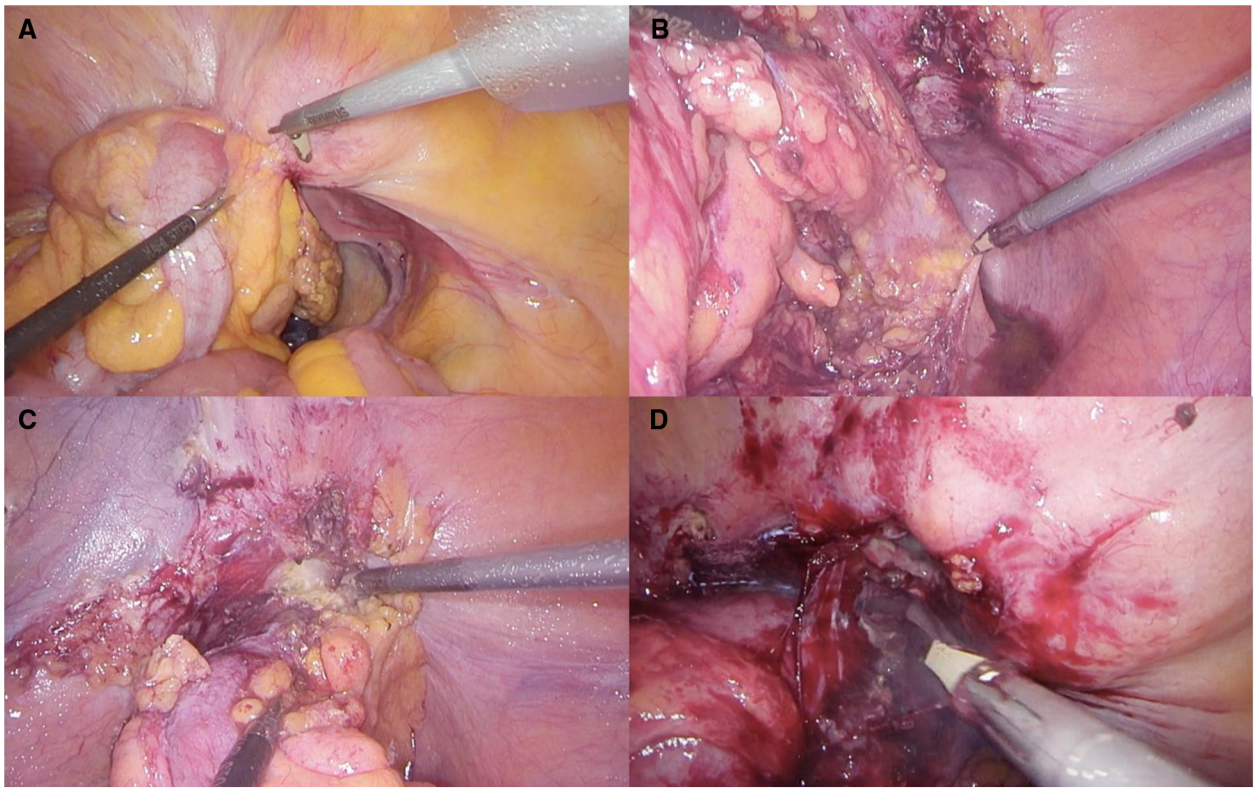

FIGURE 1
(A) Colovesical fistula visualization; (B) preparation of the posterior section of the colon (C) preparation of the anterior section of the colon (D) dissection of fistulous communication.

codes. Eligible participants were 18 years or older without contraindications for major elective surgery. Patients with colovesical fistula (CVF) were divided into two groups: those undergoing open surgery (Group A) and laparoscopy (Group B).

Data collection

Prospective recording covered demographic details, clinical parameters, preoperative diagnoses, operative data (operative time, procedure specifics, anastomosis type, conversion rates, intraoperative complications), postoperative outcomes (complications graded by Clavien-Dindo classification, postoperative ileus, hospital stay, reintervention, mortality), and histopathological examination. Routine preoperative examinations included blood tests, cardiological examination, chest x-rays, CT scans, colonoscopy, cystoscopy, and abdominal ultrasounds. Specific informed consent was obtained from each patient.

Preoperative and postoperative management

No mechanical bowel preparation was administered, and no preoperative diet restrictions were applied. Deep venous thrombosis (DVT) prophylaxis included early mobilization and Low Molecular Weight Heparin (LMWH). Antimicrobials were given within 1 h before incision. Postoperatively, patients were allowed to drink on the first day if tolerated, and oral nutritional support was initiated from the second day onwards. Antiemetics were administered regularly for 72 h postoperatively. Discharge criteria included the return of bowel function, absence of nausea or vomiting, tolerance of oral intake, no abdominal distention, absence of complications, adequate mobility, and patient acceptance.

Laparoscopic surgical technique

General anesthesia was administered, and patients were placed supine with abducted legs in a mild reverse Trendelenburg position. The procedure was conducted with a totally laparoscopic approach. Pneumoperitoneum was established using the open Veress-assisted technique with a 30-degree scope. Dissection utilized atraumatic graspers and an ultrasonic energy device. The surgical steps of laparoscopic sigmoid colectomy, including splenic flexure takedown and colonic mobilization, were performed. The Inferior Mesenteric Artery (IMA) was divided after exposing the common arterial trunk and its branches. The mesenteric defect was closed using fibrin glue. No drain was placed as per the standard approach in colorectal surgery. The specimen was extracted through an enlargement of the suprapubic port site. When technically feasible, Sigmoid Colectomy with IMA Preservation for Diverticular Disease was performed. Bladder wall repair was conducted for patients with a positive leak test.

Statistical analysis

The Mann–Whitney *U*-test and Fisher exact tests were employed for statistical analysis, considering a P-value < 0.05 as significant. IBM SPSS Statistics 19.0 software facilitated data analysis.

Results

Between 2010 and 2020, 76 patients (29 males, 46 females) underwent surgery for colovesical fistula secondary to complicated diverticulitis. Of these, 40 underwent laparoscopic surgery (Group B), and 36 had open surgery (Group A). Most patients presented with pathognomonic signs of CVF.

Refer to Table 1 for an overview of demographic data. Comprehensive details on patient demographics are provided in Table 2.

Preoperative findings

Groups A and B demonstrated similar preoperative demographics, including median age (69 vs. 65 years), sex distribution (M:F 14/22 vs. 15/25), and BMI (25.33 vs.

TABLE 1 Presenting complaints of patients undergoing surgery for colovesical fistulas secondary to diverticular disease.

Presenting complaint	Patients (%)	
Recurrent urinary tract infections.	54	71.0
Pneumaturia	34	44.7
Abdominal pain	16	21
Fecaluria	25	32.8
Diarrhea	8	10.5
Septicemia	8	10.5

TABLE 2 Demographic data and outcome of patients undergoing surgery for colovesical fistula secondary to diverticular disease.

	Open surgery ($n = 36$)	Laparoscopic surgery ($n = 40$)	P
Age (year)	Mean 69.21 (52–88)	Mean 65.45 (46–88)	0.1687 n.s.
Sex (M/F)	14/22	15/25	0.63 ns
ASA	30/36	16/43	0.45 ns
Previous abdominal Surgery %	18/36 50%	26/40 65%	0.94 ns.
Body mass index	25.32 ± 0.75	25.50 ± 0.65	0.858 ns.
Operative TIME (m)	164.8 ± 11.22 (75/300)	173.5 ± 9.8 (95/350)	0.56 ns
Bladder suture %	31/33 93.9%	32/40 80%	0.168 ns.
Urinary catether (d)	13.35 ± 1.12	11.77 ± 1.12	0.33 ns
Dindo clavien (1–5)	2.68 ± 0.21	1.56 ± 0.14	<0.0001
Blood loss (ml)	115.9 ± 20.35	73.21 ± 5.08	0.04
Prolonged ileus (d)	2.67 ± 0.13	2.23 ± 0.12	0.003
Associated surgical Procedures (pt)	11 (30.5.9%)	23 (57.5%)	0.09
Total hospital Stay (d)	10.79 ± 0.88	7.24 ± 0.36	<0.0001

25.50) (Figure 2). Concomitant colovaginal fistula occurred in 9.2%, and 3.9% had a concomitant ileovesical fistula. More than half of the patients in both group A and B ($P = 0.94$) had a history of prior abdominal surgeries, and over 63% of female patients had previously undergone hystero-annessiectomy.

Intraoperative findings

Mean operative time did not significantly differ between groups (164.8 vs. 173.7 min) (Figure 3). No statistical significance was observed between groups in terms of bladder suture and associated surgical procedures (Figure 4) Intraoperative blood loss was significantly higher in Group A (115.9 vs. 73.21 ml) (Figure 5). Sigmoid colectomy with IMA preservation was performed in 16 patients of Group B. Conversion to open surgery was required for 5% of Group B due to chronic tissue inflammation and severe fibrosis.

Postoperative outcomes

Postoperative primary ileus was significantly lower in the laparoscopic group (2.67 vs. 2.3 days; $P = 0.003$) (Figure 6). Overall postoperative morbidity (Clavien-Dindo classification grade 3 or higher) was 16.3%, with significantly higher morbidity in Group A ($P < 0.0001$) (Figure 7). No reoperation for postoperative complications was performed. Median time of Foley catheter removal was not statistically different between the two cohorts (13.35 vs. 11.77 days) (Figure 8). However, the median length of hospitalization was significantly shorter in patients who underwent laparoscopic procedures (7.2 vs. 10.7 days; $P < 0.0001$) (Figure 6). Mortality was observed in Group A (two patients), with an overall mortality of 2.6%. Notably, the two observed deaths were unrelated to surgical complications. After a two-year follow-up, no recurrence was observed.

Discussion

In the realm of laparoscopic interventions for colovesical fistulas (CVF) complicating diverticular disease, our in-depth investigation emerges as a cornerstone, assuming even greater significance when situated within the broader landscape of existing research. The synthesis of insights from various studies, coupled with the recent systematic review by Cirocchi et al. (17), establishes a comprehensive foundation. Moreover, we incorporate crucial findings from three pivotal papers—by Badic et al. (11), N. L. Bertelson et al. (12) that not only enrich our understanding but also contribute essential perspectives to the ongoing discourse on this challenging condition.

Within our 76-patient cohort, evenly distributed between genders and categorized into Group A (undergoing open surgery) and Group B (undergoing laparoscopy), we robustly affirm the safety and efficacy of laparoscopy. Our emphasis on routine applicability in a homogeneous patient cohort underscores the potential versatility of the minimally invasive approach. Importantly, despite no significant differences in operative time, blood loss, and associated surgical procedures between the two groups, the laparoscopic approach showcases distinct advantages. These include reduced intraoperative blood loss ($P = 0.04$), diminished postoperative primary ileus ($P = 0.003$), lower postoperative morbidity ($P < 0.0001$), and a shorter median length of stay ($P < 0.0001$).

Crucially, our findings challenge historical perceptions regarding laparoscopy's time-intensive nature, with no significantly higher median operation times for laparoscopic resection compared to open surgery. The low conversion rate of 5%, notably lower than earlier studies, underscores the evolving landscape of laparoscopic techniques and the pivotal role of surgeon experience in mitigating conversion risks.

Cirocchi (17) and colleagues, through their systematic review, provide a panoramic view that likely encompasses diverse patient cohorts and procedural nuances across various studies. This collective evidence enriches our findings by offering nuanced

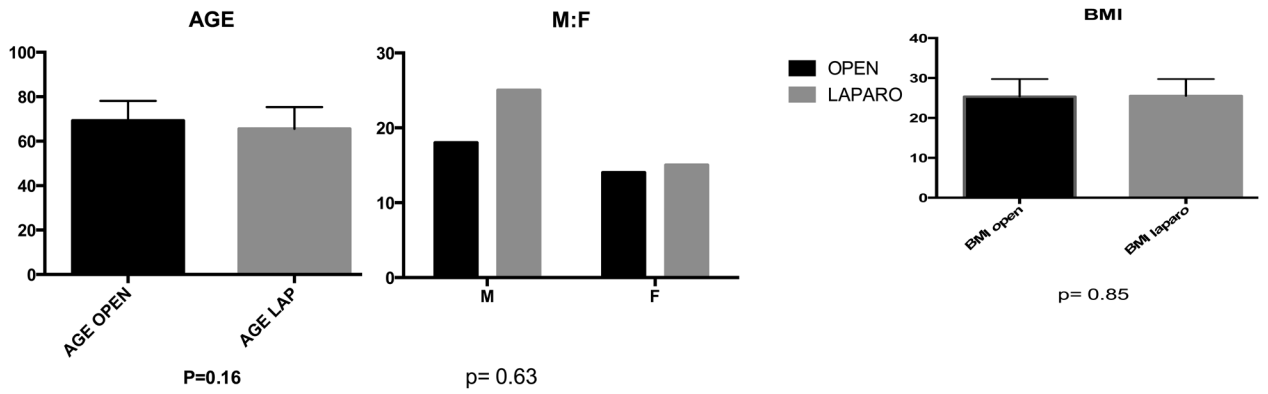

FIGURE 2
In the comparative analysis of two groups, comprising age, sex, and BMI, no statistically significant differences were observed, with p-values exceeding 0.05 for (**A**)age, (**B**) sex distribution, and (**C**) body mass index (BMI). A ($p = 0.16$) B ($p = 0.63$) C ($p = 0.85$).

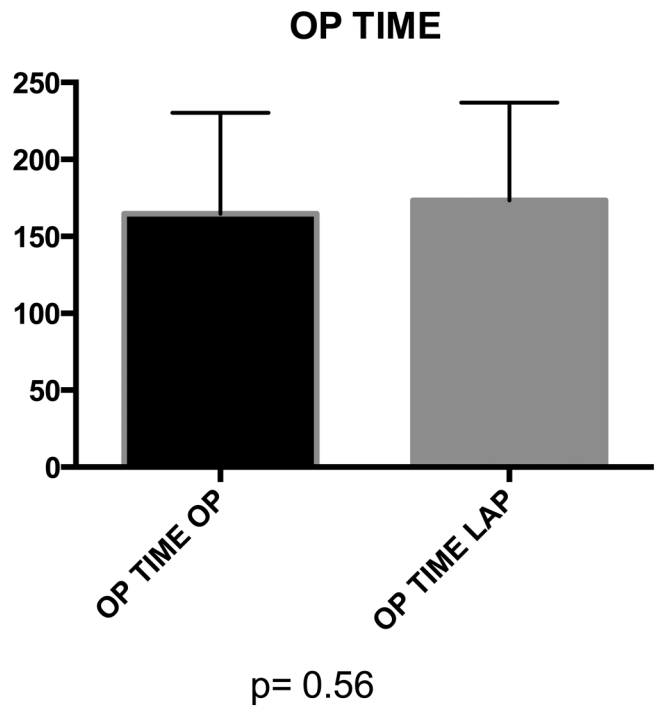

FIGURE 3
Group A (mean ± SD): [164.8 ± 11.22] group B (mean ± SD): [173.5 ± 9.8] *p*-value: [$p = 0.56$]. No statistically significant difference was found in the operation time distribution between Group A and Group B ($p > 0.05$).

insights into the evolving realm of laparoscopic interventions for CVF. Building upon this foundation, the insights presented by Badic et al. (11) in their paper, "Colovesical Fistula Complicating Diverticular Disease: A 14-Year Experience," contribute a valuable 14-year experience in managing CVF. Their extensive retrospective analysis sheds light on long-term trends, challenges, and outcomes associated with laparoscopic interventions, thereby significantly broadening the temporal understanding of laparoscopic management for CVF.

Additionally, N. L. Bertelson et al.'s work in "Diverticular Colovesical Fistula: What Should We Really Be Doing?" (12) introduces a nuanced perspective on the current state of managing diverticular colovesical fistulas. By delving into the question of optimal practices, this paper addresses key considerations that not only inform but also complement our study. This valuable insight into the ongoing discourse on best practices enhances our understanding of how our findings align or diverge from current approaches. This multifaceted

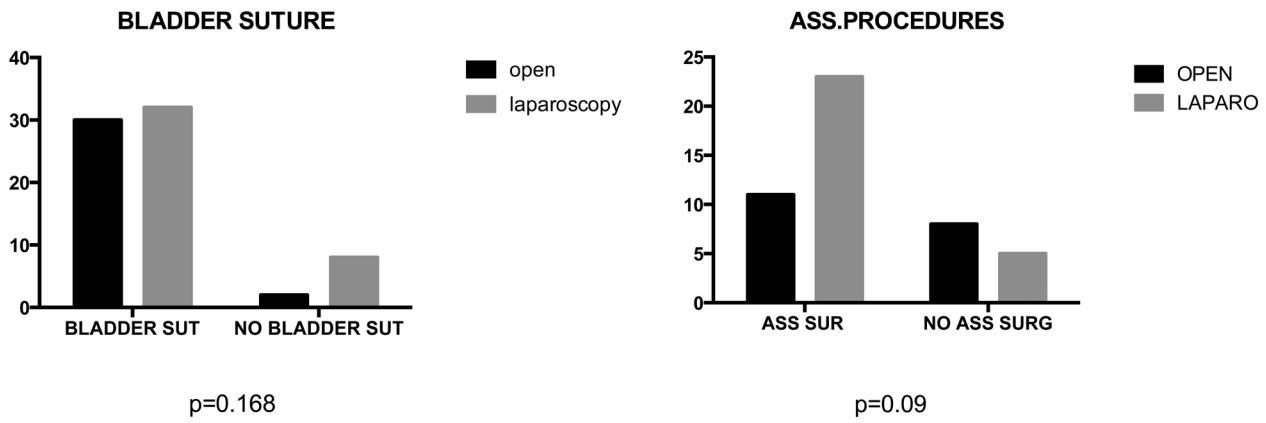

FIGURE 4
In the comparative analysis of two groups, comprising percentage of bladder suture or associated surgical procedures, no statistically significant differences were observed, with *p*-values exceeding 0.05.

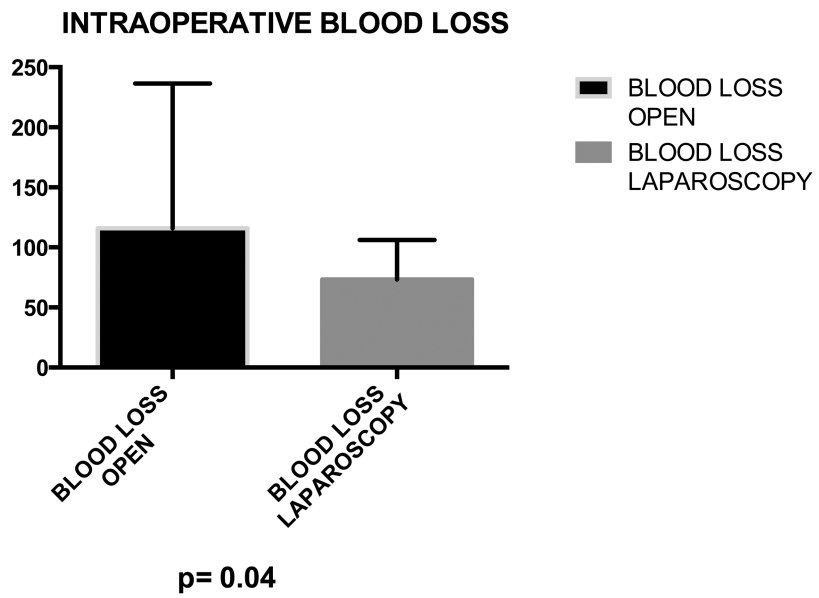

FIGURE 5
Group A (mean ± SD): [115.9 ± 20.35] group B (mean ± SD): [73.21 ± 5.08] *p*-value: [$p = 0.04$]. Group A exhibited a mean blood loss of 115.9 ± 20.35, while Group B showed 73.21 ± 5.08. The *p*-value of 0.04 suggests a statistically significant difference between the groups.

approach, incorporating insights from Cirocchi et al. (16), Bogdan Badic et al. (11), N. L. Bertelson et al. (12), contributes to a more comprehensive and nuanced understanding of laparoscopic interventions for CVF.

Delving into the systematic review by Cirocchi et al. (16), reveals a more nuanced exploration of parameters such as operative time, blood loss, conversion rates, and postoperative outcomes. By comparing our specific findings with this broader evidence base (18), a more comprehensive and nuanced understanding of laparoscopic benefits may emerge, thereby enhancing the applicability of these techniques in diverse clinical contexts.

The historical trajectory of laparoscopic resection for diverticular fistulizing disease, initiated in 1994 by Puente et al. (25). And subsequently reported by Hewett et al. (26) in 1995, underscores the initial challenges faced. Despite early promising experiences, the use of a mini-invasive technique for CVF caused by diverticular disease encountered obstacles due to the

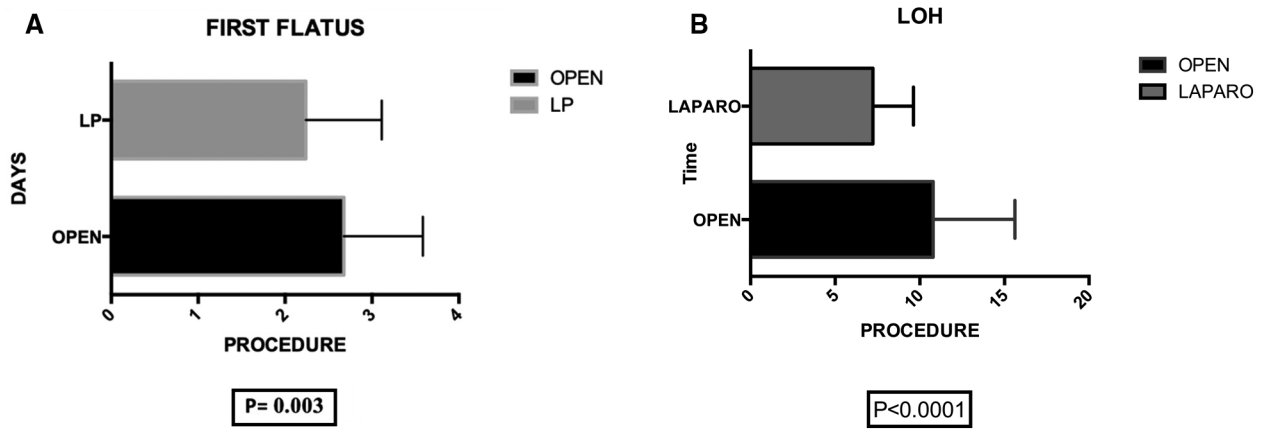

FIGURE 6
(**A**) Group A (mean ± SD): [2.67 ± 0.13] group B (mean ± SD): [2.23 ± 0.12] *p*-value: [0.003] the statistical analysis indicates a significant difference between group A (2.67 ± 0.13) and group B (2.23 ± 0.12) with a *p*-value of 0.003, suggesting a noteworthy variation in the measured parameter." (**B**) group A (mean ± SD): [10.79 ± 0.88] group B (mean ± SD): [7.24 ± 0.36] *p*-value: [<0.0001]. The analysis reveals a significant difference in length of hospitalization (LOH) between group A (10.79 ± 0.88) and group B (7.24 ± 0.36) with a *p*-value of <0.0001, indicating a substantial disparity in the duration of hospital stay.

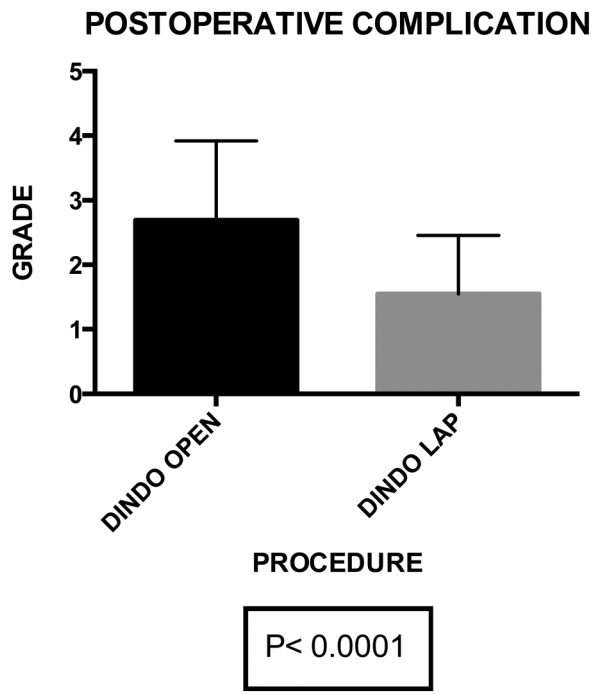

FIGURE 7
Group A (mean ± SD): [2.68 ± 0.21] group B (mean ± SD): [1.56 ± 0.14]. *p*-value: [$p < 0.0001$]. The post-operative complications exhibit a statistically significant difference between group A (2.68 ± 0.21) and group B (1.56 ± 0.14) with a *p*-value of <0.0001, highlighting a substantial variance in complication rates between the two groups.

longer operative times of laparoscopy compared to open surgery and the high conversion rate (up to 60% in certain series) attributable to fibrosis and/or severe inflammation (16–32).

Our present study represents the largest series of laparoscopically treated CVF to date, distinguishing itself by exclusively including patients affected by CVF secondary to diverticular disease. Notably, there are few reports in the literature focusing exclusively on CVF by diverticulitis (33, 34), with most published studies encompassing fistulas of mixed etiology (35) or mixed diverticular fistula (16).

Furthermore, the inclusion of patients who were not previously selected, with a significant percentage (57.8%) having undergone previous abdominal operations, adds a real-world dimension to our study. The recent review by Keady and co-worker (10) on morbidity and mortality in the surgical management of CVF reported variable rates across studies. In our series, we observed an overall morbidity of 14.9%, significantly higher in the open surgery group. Remarkably, mortality was zero in the laparoscopic group, attributed to the high volume of laparoscopic operations performed and the adherence to standardized procedures by the same surgeons.

In contrast to previous reports (10, 11–34), the median operation time for laparoscopic resection for CVF was not significantly higher than the time for open surgery. Notably, the low conversion rate of 5% in the present cohort, considerably lower than rates reported in previous studies (10–16), reflects the evolving experience of surgeons and advancements in surgical techniques. Conversion was necessary in two patients due to severe fibrosis, impeding safe dissection. One of these patients presented with a concomitant colovaginal fistula, highlighting the complexity of cases. Engledow et al. (36) reported different rates of conversion over a period of 10 years (64% vs. 29%) based on surgeon experience. Accordingly, Kockerling et al. (37) concluded that laparoscopy, for fistulizing diverticular disease, should only be carried out by experienced laparoscopic surgeons.

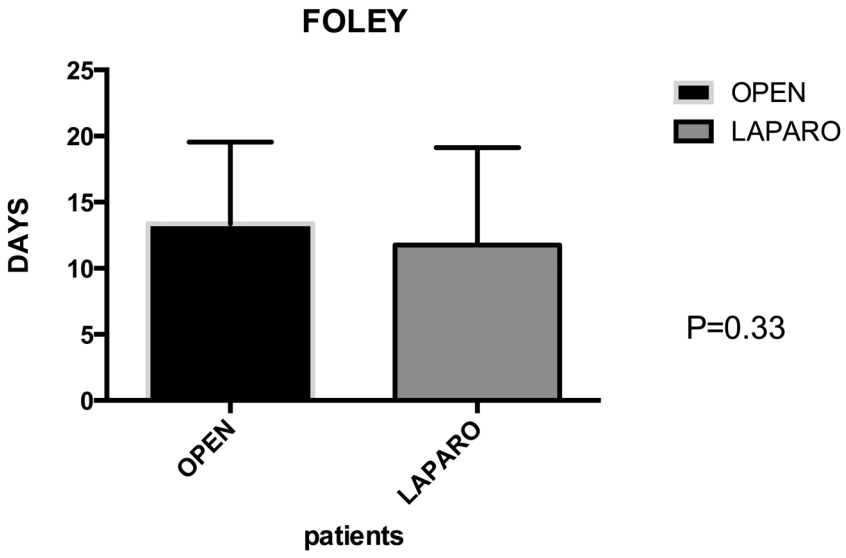

FIGURE 8
Group A (mean ± SD): [13.35 ± 1.12] group B (mean ± SD): [11.77 ± 1.12] *p*-value: [0.33 NS]. The permanence of urinary catheter demonstrates no statistically significant difference between group A (13.35 ± 1.12) and group B (11.77 ± 1.12), with a *p*-value of 0.33 (NS), indicating similarity in catheter duration between the two groups.

The advantages of the laparoscopic approach in terms of intraoperative blood loss ($P = 0.04$), postoperative primary ileus ($P = 0.003$), and median hospitalization ($P < 0.0001$) further underscore its potential to offer the benefits of minimally invasive surgery to patients with CVF due to diverticular disease. This reaffirms and extends the findings proposed in previous studies (10–17).

In summary, our study, interwoven with insights from pivotal research and guided by a robust patient cohort, contributes significantly to the evolving discourse on laparoscopic interventions for CVF complicating diverticular disease. Through a comprehensive exploration of historical challenges, contemporary advantages, and nuanced comparisons, our findings provide valuable considerations for future research and clinical practice in the management of this challenging condition.

Study limitations

While our study contributes valuable insights into the laparoscopic management of colovesical fistulas (CVFs) secondary to diverticular disease, it is essential to acknowledge certain limitations that temper the generalizability and depth of our findings. The retrospective nature of our study introduces inherent limitations. Reliance on historical data and medical records may result in incomplete or biased information, potentially impacting the accuracy of our conclusions.

Our study draws exclusively from the experience of two institutions, potentially limiting the external validity of our findings. Variations in patient demographics, surgical practices, and institutional protocols may not fully capture the diversity encountered in broader healthcare settings.

While our study cohort provides valuable insights, the relatively modest sample size may constrain the robustness of our conclusions. Larger-scale, multi-center studies would offer a more comprehensive perspective on the nuances of laparoscopic interventions for CVFs.

Over the decade covered by our study, surgical techniques and practices may have evolved. Technological advancements and changes in clinical approaches could impact the relevance of our early data. While emphasizing the importance of surgeon experience, our study does not delve deeply into the specifics of individual experience levels. Variability in surgeon experience may contribute to outcome disparities that are not fully explored in our analysis.

External factors, such as advancements in perioperative care, shifts in patient demographics, or changes in healthcare policies, are not comprehensively considered. These external dynamics, beyond the scope of our study, could influence outcomes.

Our study focuses primarily on the comparison between laparoscopic and open surgery, neglecting exploration of other emerging modalities or technologies in the field of minimally invasive interventions.

Certain patient-related variables, including comorbidities, socioeconomic factors, and patient preferences, remain largely unexplored in our analysis. These variables may play a significant role in treatment choices and outcomes.

In acknowledging these limitations, we aim to provide a transparent context for the interpretation of our study findings, encouraging future research to address these constraints for a more comprehensive understanding of laparoscopic interventions for CVFs.

Conclusions

In the crucible of limitations, our study emerges unyielding, a force challenging the status quo in laparoscopic interventions for colovesical fistulas complicating diverticular disease. Amidst the retrospective constraints, our findings act as a catalyst for change, daring the medical community to break free from tradition. We beckon towards a future where innovation trumps limitations, urging a paradigm shift in the approach to colovesical fistula treatment.

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 approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

AR: Supervision, Writing – review & editing, Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. JA: Data curation, Conceptualization, Methodology, Writing – original draft. UB: Data curation, Writing – review & editing. VS: Data curation, Writing – review & editing. EP: Data curation, Software, Writing – review & editing. SR: Data curation, Formal Analysis, Writing – review & editing. CS: Data curation, Investigation, Software, Writing – review & editing. RP: Writing – review & editing. AA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft. CB: Writing – original draft. GP: Writing – review & editing. DC: Writing – review & editing. FC: Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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 author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 14 March 2024
DOI 10.3389/fonc.2024.1330344

OPEN ACCESS

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RECEIVED 07 November 2023
ACCEPTED 29 February 2024
PUBLISHED 14 March 2024

CITATION
Qin T, Yu C, Dong Y, Zheng M, Wang X and Shen X (2024) Prognostic nomogram in patients with right-sided colon cancer after colectomy: a surveillance, epidemiology, and end results–based study.
Front. Oncol. 14:1330344.
doi: 10.3389/fonc.2024.1330344

Prognostic nomogram in patients with right-sided colon cancer after colectomy: a surveillance, epidemiology, and end results–based study

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Objective: This study aimed to develop and validate a nomogram for predicting overall survival (OS) in patients undergoing surgery for right-sided colon cancer (RCC).

Methods: We collected 25,203 patients with RCC from the Surveillance, Epidemiology, and End Results (SEER) database and randomly divided them into 7:3 training and internal validation set. Utilizing the Cox proportional hazards regression model, we constructed a nomogram based on prognostic risk factors. Furthermore, for external validation, we retrospectively followed up with 228 patients from Jiaxing First Hospital and assessed and calibrated the nomogram using the C-index and calibration curves.

Results: After identifying independent prognostic factors through univariate and multivariate analyses, a nomogram was developed. The c-index values of this nomogram differed as follows: 0.851 (95% CI: 0.845-0.857) in the training set, 0.860 (95% CI: 0.850-0.870) in the internal validation set, and 0.834 (95% CI: 0.780-0.888) in the external validation set, indicating the model's strong discriminative ability. Calibration curves for 1-year, 3-year, and 5-year overall survival (OS) probabilities exhibited a high level of consistency between predicted and actual survival rates. Furthermore, Decision Curve Analysis (DCA) demonstrated that the new model consistently outperformed the TNM staging system in terms of net benefit.

Conclusion: We developed and validated a survival prediction model for patients with RCC. This novel nomogram outperforms the traditional TNM staging system and can guide clinical practitioners in making optimal clinical decisions.

KEYWORDS

nomogram, overall survival, prognosis, right-sided colon cancer, SEER

Introduction

By 2020, an estimated 19,292,789 new cases of cancer were reported globally. Among these cases, colorectal cancer (CRC) ranked as the third most common cancer, accounting for approximately 10.0% of the total (1, 2). According to the sources, colorectal cancer led to 935,173 deaths, representing 9.4% of the total cancer-related mortality. This makes colorectal cancer the second leading cause of cancer-related deaths, following only lung cancer. Predictions suggest that by 2030, the incidence of colorectal cancer is expected to significantly increase, with an estimated 2.2 million new cases and approximately 1.1 million related death (3).

Colorectal cancer stands apart from other malignant tumor sites due to its distinct anatomical distribution. The colon and rectum can be anatomically categorized into three main segments: the right colon (including the cecum, ascending colon, hepatic flexure of the colon, and transverse colon), the left colon (encompassing the descending colon, sigmoid colon, and splenic flexure of the colon), and the rectum (encompassing the junction of the rectum and sigmoid colon). These distinct anatomical regions exhibit differential sensitivity to carcinogens due to variations in embryology and physiology. Consequently, tumors arising in these segments may demonstrate disparate pathogenic mechanisms, varying diagnostic sensitivity, distinct clinicopathological characteristics, and differing prognostic outcomes (4). As a result, some researchers advocate for the consideration of colon cancer as comprising two or more distinct disease types (5). Recent investigations have revealed a shifting incidence trend in colorectal cancer towards the right colon (6). Notably, in China, the incidence rate of right colon cancer surpasses that of rectal cancer. Data analysis spanning from 1980 to 1990 demonstrates an increase in the incidence of right colon cancer from 10.9% to 15.2% in China. Furthermore, relative to left colon cancer, right colon cancer is associated with a less favorable prognosis (7).

Presently, the preeminent framework utilized for forecasting cancer survival and guiding clinical decisions is the American Joint Committee on Cancer (AJCC) staging guidelines (8). However, it's noteworthy that the prognostic guidelines established by AJCC solely incorporate parameters such as tumor size, lymph node involvement, and metastasis status, inadvertently overlooking additional variables that possess the potential to significantly influence a patient's postoperative prognosis. It is imperative to acknowledge that these guidelines primarily extrapolate outcomes for population rather than tailoring predictions for individual patient.in previous studies on CRC, several predictive models have been established (9, 10), but models specific to RCC are scarce. In many cancers, nomograms have demonstrated superiority over the traditional TNM staging system (11, 12). Clinicians can estimate the cumulative effects of all prognostic factors for a given patient and predict the probabilities of 1-year, 3-year, and 5-year survival rates from the nomogram (13). The primary objective of this study is to develop and validate a nomogram tailored for RCC, combining multiple indicators to predict postoperative survival outcomes for RCC patients.

Methods

Patients and selection criteria

In this study, we extracted data from Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov), SEER*Stat Database: Incidence - SEER Research Plus Data, 18 Registries, Nov 2020 Sub (2000 - 2018). Between 2010 and 2015, we diagnosed 451,241 patients with RCC. Based on the inclusion and exclusion criteria, we ultimately selected 25,203 eligible patients. Patients were randomly assigned to an internal validation set (n = 7,561) or a training set (n = 17,642). The inclusion and exclusion criteria for the external validation set were the same as those used for the training set.

The inclusion and exclusion criteria were the same in the training and validation set. The inclusion criteria were (1) year of diagnosis between 2010 and 2015; (2) primary site code C18.0, C18.2, C18.3, or C18.4; (3) histologically confirmed diagnosis; (4) adenocarcinoma (histology codes 8140–8147, 8210, 8211, 8220, 8221, and 8260 - 8263), mucinous adenocarcinoma (histology codes 8480, 8481, and 8490); and (5) no history of another malignant tumor (sequence number: 1 primary only; first malignant primary indicator: yes). The exclusion criteria were (1) age < 18 years, (2) death or no follow-up within 30 days, and (3) other variables were unknown or missing from the database.

Ethical approval is not required for this article, as all data from the SEER database are obtained using publicly available methods. Participants involved in external validation have already received ethical approval from our institution (Ethics No. LS2021-KY-367).

Include variables and processing

This study included a total of 17 variables, encompassing demographic information, tumor characteristic details, and treatment information.

Demographic information comprised age at diagnosis, gender, and race. Tumor-specific details consisted of primary site, histologic type, grade, derived AJCC T stage (7th ed), derived AJCC N stage (7th ed), derived AJCC M stage (7th ed), summary stage, preoperative carcinoembryonic antigen level (CEA), regional lymph nodes removed (LN), liver metastasis, lung metastasis, brain metastasis, and bone metastasis. Treatment details included postoperative chemotherapy status. Additionally, the patients' vital status and survival time in months were incorporated.

Given that age is a continuous variable in the SEER database, this study classified ages using 10-year intervals: <31, 31-40, 41-50, 51-60, 61-70, 71-80, 81-90, and >90 years. LN were categorized as 1-3 and ≥4. Race were categorized as White, Black, Asian/Pacific Islander, and other races. Patients' tumor primary sites were categorized as cecum, ascending colon, hepatic flexure, and transverse colon. Tumor grade was categorized as stages I (well-differentiated), II (moderately differentiated), III (poorly differentiated), and IV (undifferentiated), and tumor histologic types included adenocarcinoma and mucinous adenocarcinoma.

TNM staging was based on the 7th edition of the American Joint Committee on Cancer guidelines, classifying primary tumor extent (T1, T2, T3, T4a, and T4b), lymph node involvement (N0, N1a, N1b, N1c, N2a, and N2b), and distant metastasis (M0, M1a, and M1b), while summary stage classified tumor spread as local, regional, or distant. This study's follow-up initiation point was the diagnosis date of RCC, with overall survival (OS) as the endpoint, representing the time interval from diagnosis to patient death.

Construction of the nomogram

The patients from the SEER database were randomly divided into training and validation dataset in a 7:3 ratio. A univariate Cox proportional hazards regression analysis was conducted, and factors with statistical significance ($P < 0.05$) were included in the multivariate Cox regression analysis to determine independent prognostic impact factors. For each variable, the corresponding 95% Confidence Interval (CI) and Hazard Ratio (HR) were calculated (14). All independent prognostic factors ($P < 0.05$) from the multivariate Cox regression analysis were integrated. Utilizing LASSO regression analysis and optimal subset regression analysis, factors selected were combined with the results from the multivariate Cox proportional hazards analysis to identify the prognostic factors to be included in the nomogram.Based on these independent prognostic factors, we employed statistical software (R 4.1.1, http://www.rproject.org/) to establish a nomogram for predicting the probabilities of 1-year, 3-year, and 5-year postoperative overall survival (OS) for RCC patients.

Calibration and validation of the nomogram

Concordance index (C-index) and calibration curves are commonly used to evaluate the performance and accuracy of the nomogram. The C-index values range between 0.5 and 1, positively correlating with the predictive capability of the model. When this value surpasses 0.7, it indicates a reliable discriminative ability of the model (15). For model validation, internal validation was performed using the validation set, external validation was conducted using cases collected at our institution, and calibration curves were generated using bootstrapping resampling.

The calibration curve is a line passing through the origin with a slope of 1. The higher the predictive calibration curve approaches the standard curve, the greater the predictive capacity of the nomogram. Decision curve analysis (DCA), a novel analytical technique, integrates all clinical consequences of a decision and quantifies the clinical utility of a predictive model (16).

Furthermore, DCA was employed to ascertain whether the nomogram is more accurate than the AJCC TNM staging system, aiming to further assess the benefits and advantages of the nomogram.

Results

Patient clinicopathologic characteristics

According to the inclusion and exclusion criteria, a total of 25,203 patients diagnosed with RCC were included from the SEER database. These patients were randomly divided in a 7:3 ratio, resulting in a training set (n = 17,642) and a validation set (n = 7,561). The training set was utilized for determining independent prognostic factors and constructing the nomogram, while the validation set was used for internal validation of the nomogram. The results indicated no significant differences between various indicators in the training and validation set ($P > 0.05$, as shown in Table 1), suggesting comparability between the two patient groups. The validation set's patients could be utilized to verify the performance of the nomogram model. The follow-up period for all patients ranged from 1 to 107 months, with 7,864 patients having died during the follow-up period, resulting in a mortality rate of 31.2%.

Independent risk factors in the training set

After conducting univariate analysis using the COX proportional hazards regression model, the results indicated that the following factors significantly influenced postoperative overall survival (OS) with a significance level of $P < 0.05$: age, tumor differentiation grade, histologic type, T stage, N stage, M stage, summary stage, liver metastasis, brain metastasis, lung metastasis, bone metastasis, CEA level, and chemotherapy. On the other hand, gender and race showed no significant influence on postoperative OS ($P > 0.05$). The significant variables identified from the univariate analysis were included in the multivariate COX regression analysis, with a significance level of $P < 0.05$ defining them as independent prognostic factors. Through the multivariate COX analysis, it was found that gender, race, tumor site, and histologic type were not significantly correlated with postoperative overall survival (OS) ($P > 0.05$). The results of univariate and multivariate analyses are presented in Table 2.

After performing LASSO regression and best subset regression analyses (Figure 1), the variables tumor differentiation, number of regional lymph nodes removed, lung metastasis, brain metastasis, and bone metastasis were eliminated. Instead, the variables age, chemotherapy, CEA, T stage, N stage, M stage, summary stage, and liver metastasis were retained.

Prognostic nomogram for OS

We constructed a traditional nomogram based on the results of the multiple regression and LASSO regression analyses mentioned earlier (Figure 2). The model incorporated age, chemotherapy, CEA, T stage, N stage, M stage, summary stage, and liver metastasis. The scores for each variable are shown in Table 3. The

10.3389/fonc.2024.1330344

TABLE 1 Clinicopathological characteristics of patients with right-sided colon cancer.

Variable	Training set (*n* = 17,642)	Validation set (n = 7,561)	*p*
Gender			0.779
Female	8,274 (46.8)	3,448 (45.6)	
Male	9,368 (53.2)	4,113 (54.3)	
Age (years)			< 0.001
<31	97 (0.5)	48 (0.6)	
31-40	414 (2.3)	183 (2.4)	
41-50	1,497 (8.4)	632 (8.3)	
51-60	3,296 (18.6)	1,367 (18.0)	
61-70	4,902 (27.7)	2,170 (28.6)	
71-80	4,429 (25.1)	1,913 (25.3)	
81-90	2,722 (15.4)	1,143 (15.1)	
>90	285 (1.6)	105 (1.3)	
Race			0.121
White	13,723 (77.7)	5,883 (77.8)	
Black	2,466 (13.9)	1,031 (13.6)	
Asian or Pacific Islander	1,313 (7.4)	592 (7.8)	
American Indian	140 (0.7)	55 (0.7)	
Site			< 0.001
Cecum	7,115 (40.3)	3,026 (40.2)	
Ascending colon	6,117 (35.1)	2,597 (34.3	
Hepatic flexure	1,398 (7.9)	672 (8.8)	
Transverse colon	2,952(16.7)	1,266 (16.7)	
Histologic type			< 0.001
COAD	15,449 (87.5)	6,640(87.8)	
MC	2,193 (12.5)	921 (12.2)	
Grade			< 0.001
Grade I	1,168 (6.6)	527 (6.9)	
Grade II	12,140 (68.8)	5,260 (69.5)	
Grade III	3,573 (20.2)	1,464 (19.3)	
Grade IV	761 (4.3)	310 (4.0)	
T.stage			< 0.001
T1	1,540 (8.7)	818 (7.2)	
T2	2,495 (14.1)	1856 (16.4)	
T3	10,126 (57.3)	6527 (57.8)	
T4a	2,127 (12.0)	2091 (18.5)	
T4b	1,354 (7.6)		
N.stage			< 0.001
N0	9,446 (53.5)	4,098 (54.1)	
N1a	2,065 (11.7)	861 (11.3)	
N1b	2,337 (13.2)	955 (12.6)	
N1c	252 (1.4)	126 (1.6)	
N2a	1,640 (9.2)	733(9.6)	
N2b	1,902 (10.7)	788 (10.4)	
M.stage			< 0.001
M0	14,934 (84.6)	6,429 (85.0)	
M1a	1,537 (8.7)	669 (8.8)	
M1b	1,171 (6.6)	463 (6.1)	
Summary.stage			< 0.001
Localized	6,429 (36.4)	2,850 (37.6)	
Regional	8,403 (47.6)	3,522 (46.5)	
Distant	2,810 (15.9)	1,189 (15.7)	
LN			< 0.001
<4	184 (1.0)	70 (1.0)	
≥4	17,458 (99.0)	7491 (99.0)	
Chemotherapy			< 0.001
Yes	7,105 (40.2)	3,015 (39.0)	
No	10,537 (59.8)	4,546 (61.0)	
Bone metastasis			< 0.001
Yes	68 (0.3)	19 (0.2)	
No	17,574 (99.7)	7,542 (99.8)	
Brain metastasis			< 0.001
Yes	22 (0.2)	7 (0.1)	
No	17,620 (99.8)	7,554 (99.9)	
Lung metastasis			< 0.001
Yes	378 (2.2)	474 (2.3)	
No	17,264 (97.8)	7,387 (97.7)	
Liver metastasis			< 0.001
Yes	1,866 (10.5)	803 (10.6)	
No	15,776 (89.5)	6,758 (89.4)	
CEA			< 0.001
Normal	10,443 (59.2)	4,524 (59.8)	
Positive	7,199 (40.8)	3,037 (40.2)	

(Continued)

TABLE 1 Continued

Variable	Training set (*n* = 17,642)	Validation set (n = 7,561)	*p*
Survival status			
Alive	12,140 (68.8)	5,199 (68.8)	
Dead	5,502(31.2)	2,362 (31.2)	

COAD, colon adenocarcinoma; MC, mucinous adenocarcinoma; RNE, regional nodes examined; RNP, regional nodes positive.

variables yielded total scores predicting 1-, 3-, and 5-year OS probabilities. By summing up the scores for each factor, a total score is obtained. This total score can be matched with the corresponding 1-year, 3-year, and 5-year OS coordinates at the bottom of the nomogram, providing the probability values for survival at these time points for RCC patients. Higher total scores indicate a worse prognosis.

Specifically, age, N stage, and T stage are considered key factors influencing the scoring system. It is noteworthy that for individuals aged over 90 years, with N2b and T4b stages, their corresponding scores are 100, 93, and 88, respectively. Conversely, scores associated with CEA positivity, liver metastasis, and chemotherapy tend to be relatively lower, at 25, 28, and 34, respectively. For instance, a 73-year-old patient, undergoing chemotherapy, without liver metastasis but with CEA positive, and with a T4a, N1c, M0, and regional summary stage, accrues a total score of 206 according to the nomogram. This places the patient within the intermediate-risk category, with an estimated 5-year survival rate of approximately 56.75%.

C-index and AUC values were used to evaluate the accuracy and discrimination of the nomogram. In the training set, the C-index of the nomogram for OS was 0.851 (95% CI: 0.845-0.857), and the 1-, 3-, and 5-year AUCs were 0857、0.869、0.724, respectively (Figure 3A). The C-index in the internal validation set was 0.860 (95% CI: 0.850-0.870), and the 1-, 3-, and 5-year AUCs were 0.864, 0.871, and 0.859, respectively (Figure 3B). To assess model performance internally, the time-dependent area under the receiver operating characteristic curve was calculated at different time-points. Calibration curves for the

TABLE 2 Univariate and Multivariate COX Regression Analysis.

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Gender				
Male	Reference			
Female	0.99 (0.94 - 1.05)	0.779		
Age (years)				
< 31	Reference		Reference	
31-40	0.65 (0.45-0.95)	0.026	0.71 (0.49-1.03)	0.075
41-50	0.72 (0.51-1.00)	0.053	0.84 (0.60-1.18)	0.322
51-60	0.72 (0.52-1.00)	0.049	0.92 (0.66-1.28)	0.632
61-70	0.69 (0.50-0.95)	0.025	0.99 (0.72-1.38)	0.969
71-80	0.79 (0.57-1.10)	0.160	1.30 (0.94-1.81)	0.116
81-90	1.23 (0.89-1.70)	0.217	2.02 (1.45-2.81)	< 0.001
>90	2.13 (1.49-3.05)	< 0.001	3.03 (2.11-4.35)	< 0.001
Race				
White	Reference			
Black	1.26 (1.18-1.36)	< 0.001		
Asian or Pacific Islander	0.93 (0.84-1.03)	0.185		
American Indian	0.90 (0.66-1.24)	0.532		
Site				
Cecum	Reference		Reference	
Ascending colon	0.77 (0.72-0.82)	< 0.001	0.96 (0.90-1.02)	0.169
Hepatic flexure	0.83 (0.75-0.92)	< 0.001	1.05 (0.94-1.16)	0.389
Transverse colon	0.82 (0.76-0.88)	< 0.001	1.01 (0.94-1.10)	0.731

(Continued)

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TABLE 2 Continued

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Histologic type				
COAD	Reference		Reference	
MC	1.39 (1.29-1.49)	< 0.001	1.03 (0.98-1.09)	0.194
Histological grade				
Grade I	Reference		Reference	
Grade II	1.58 (1.38-1.82)	< 0.001	1.04 (0.96-1.13)	0.319
Grade III	2.93 (2.55-3.38)	< 0.001	1.12 (1.03-1.28)	0.008
Grade IV	3.39 (2.87-4.01)	< 0.001	1.14 (1.12-1.32)	0.016
T.stage				
T1	Reference		Reference	
T2	1.89 (1.50-2.37)	< 0.001	1.46 (1.16-1.83)	< 0.001
T3	5.25 (4.30-6.41)	< 0.001	1.98 (1.60-2.44)	0.001
T4a	13.88 (11.31-17.03)	< 0.001	3.01 (2.42-3.74)	< 0.001
T4b	16.10 (13.08-19.83)	< 0.001	3.38 (2.70-4.22)	< 0.001
N.stage				
N0	Reference		Reference	
N1a	2.28 (2.07-2.51)	< 0.001	1.51 (1.35-1.68)	< 0.001
N1b	3.66 (3.38-3.97)	< 0.001	2.19 (1.98-2.41)	< 0.001
N1c	3.36 (2.75-4.12)	< 0.001	1.82 (1.48-2.24)	< 0.001
N2a	5.54 (5.10-6.02)	< 0.001	2.70 (2.44-2.99)	< 0.001
N2b	9.31 (8.64-10.03)	< 0.001	3.64 (3.30-4.01)	< 0.001
M.stage				
M0	Reference		Reference	
M1a	6.43 (6.02-6.88)	< 0.001	1.75 (1.30-2.34)	< 0.001
M1b	9.94 (9.26-10.68)	< 0.001	2.26 (1.69-3.02)	< 0.001
Summary.stage				
Localized	Reference		Reference	
Regional	3.84 (3.51-4.20)	< 0.001	1.90 (1.69-3.02)	< 0.001
Distant	19.00 (17.34-20.82)	< 0.001	2.88 (2.13-3.90)	< 0.001
LN				
1-3	Reference		Reference	
≥4	0.64 (0.52-0.80)	< 0.001	0.67 (0.54-0.84)	< 0.001
Chemotherapy				
Yes	Reference		Reference	
No	1.91 (1.81-2.01)	< 0.001	1.62 (1.51-1.73)	< 0.001
Bone metastasis				
No	Reference		Reference	

(Continued)

TABLE 2 Continued

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Bone metastasis				
Yes	8.71 (6.78-11.2)	< 0.001	1.53 (1.18-1.99)	0.012
Brain metastasis				
No	Reference		Reference	
Yes	7.00 (4.46-10.99)	< 0.001	1.38 (1.17-1.59)	0.016
Lung metastasis				
No	Reference		Reference	
Yes	5.86 (5.24-6.55)	< 0.001	1.13 (1.00-1.29)	0.046
Liver metastasis				
No	Reference		Reference	
Yes	6.69 (6.30 - 7.10)	< 0.001	1.52 (1.38-1.67)	< 0.001
CEA				
Normal	Reference		Reference	
Positive	2.91 (2.76 - 3.08)	< 0.001	1.44 (1.36-1.53)	< 0.001

HR, hazard ratio; CI, confidence interval; COAD, colon adenocarcinoma; MC, mucinous adenocarcinoma; RNE, regional nodes examined.

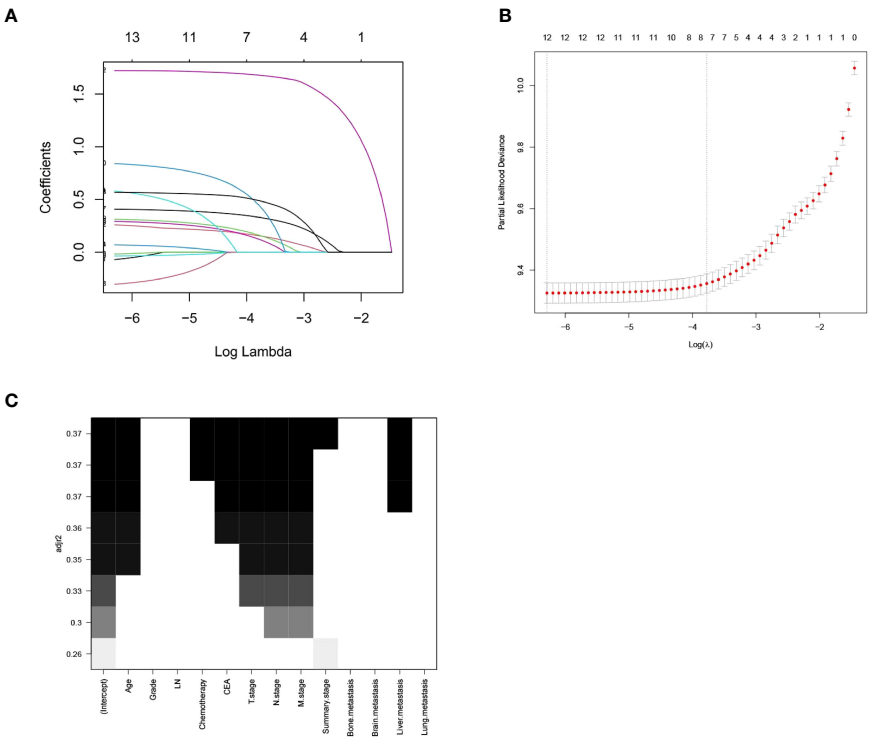

FIGURE 1
LASSO Regression Analysis and Optimal Subset Regression Analysis. **(A)** Distribution of LASSO coefficients for all variables of RCC. **(B)** 8 variables identified by LASSO analysis. **(C)** Optimal subset regression model selecting 8 variables.

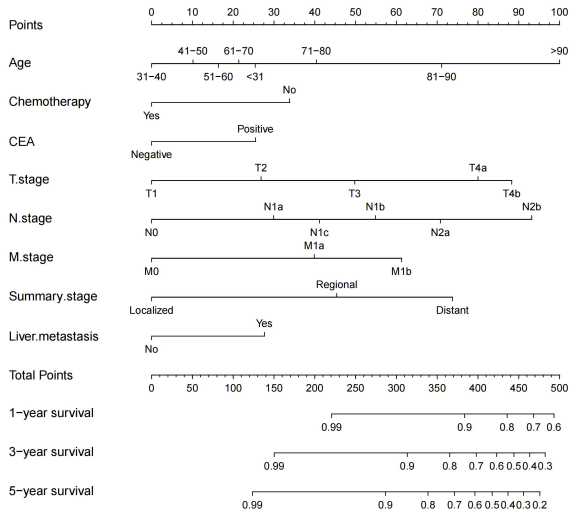

FIGURE 2
Nomogram for predicting 1-, 3-, and 5-year OS probabilities in patients with RCC after colectomy.

probability of postoperative OS at 1-year, 3-year, and 5-year (Figures 4, 5) indicated that there was good consistency between the actual observation and the prediction. In contrast to the AJCC TNM staging approach, the decision curve analysis (DCA) exhibited a substantial rise in the net advantage for the novel nomogram graph, spanning a broad and feasible spectrum of threshold probabilities (Figure 6).

External validation of the predictive accuracy of the nomogram for OS

Following the same inclusion and exclusion criteria as the SEER database, a total of 228 cases of primary RCC patients who underwent surgery in the Department of Gastrointestinal Surgery at the First Hospital of Jiaxing from January 2014 to December 2017 were ultimately collected for external validation to further assess the predictive capability of the nomogram (Table 4). In the external Verification set, the C-index was 0.834(95%CI:0.780 - 0.888), and the 1-, 3- and 5-year AUCs were 0.693, 0.766, and 0.747 respectively (Figure 3C). The calibration curves for 1-year, 3-year, and 5-year survival (Figure 7) demonstrated a high level of agreement between predicted values and actual survival probabilities. These validation results indicate that the nomogram developed in this study exhibits a high level of accuracy and precision, making it suitable for predicting 1-year, 3-year, and 5-year overall survival in patients with right-sided colon cancer after surgery.

Development and production of a web-based nomogram

To facilitate clinicians' use of our Nomograms, we've created dynamic line graphs utilizing the "DynNom" package from R software. You can directly access it via the following https://tian1234.shinyapps.io/DynNomapp/. Once you input the predictor variables, the calculated survival probabilities can be easily displayed. It's user-friendly and doesn't require any permission or login credentials from clinicians.

TABLE 3 Scores of the variables.

Variable	Score	Variable	Score	Variable	Score
Age (years)		M.stage		N.stage	
<31	25	M0	0	N0	0
31-40	0	M1a	40	N1a	30
41-50	10	M1b	61	N1b	55
51-60	16	**T.stage**		N1c	41
61-70	21	T1	0	N2a	71
71-80	40	T2	27	N2b	93
81-90	71	T3	50	**CEA**	
>90	100	T4a	80	Normal	0
Summary.stage		T4b	88	Positive	25
Localized	0	**Chemotherapy**		**Liver metastasis**	
Regional	45	Yes	0	No	0
Distant	74	No	34	Yes	28

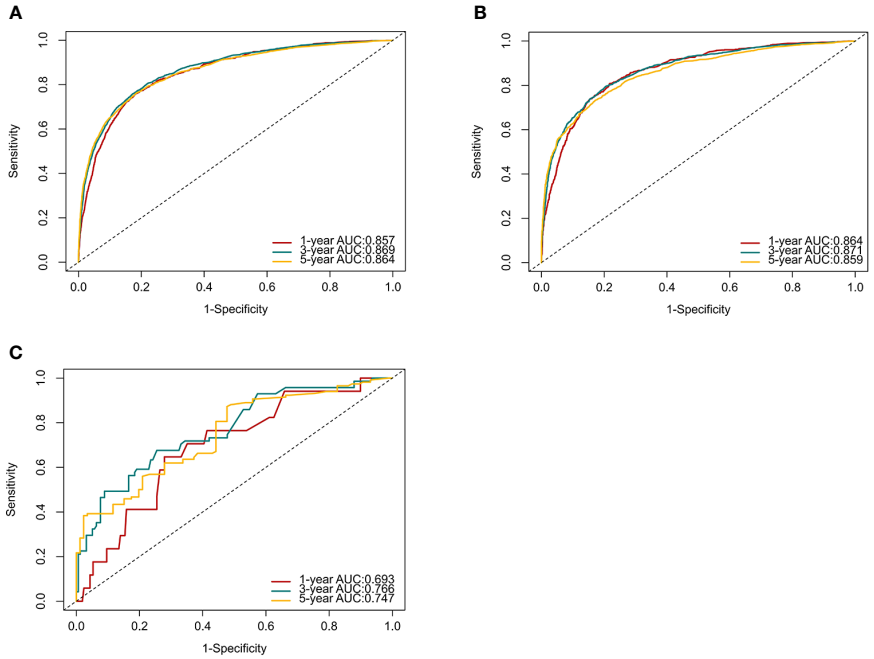

FIGURE 3
ROC curves and AUCs at 1, 3, and 5 years in the training set **(A)**, internal validation set **(B)** and the external validation set **(C)** were used to estimate the prognostic accuracy of the nomogram.

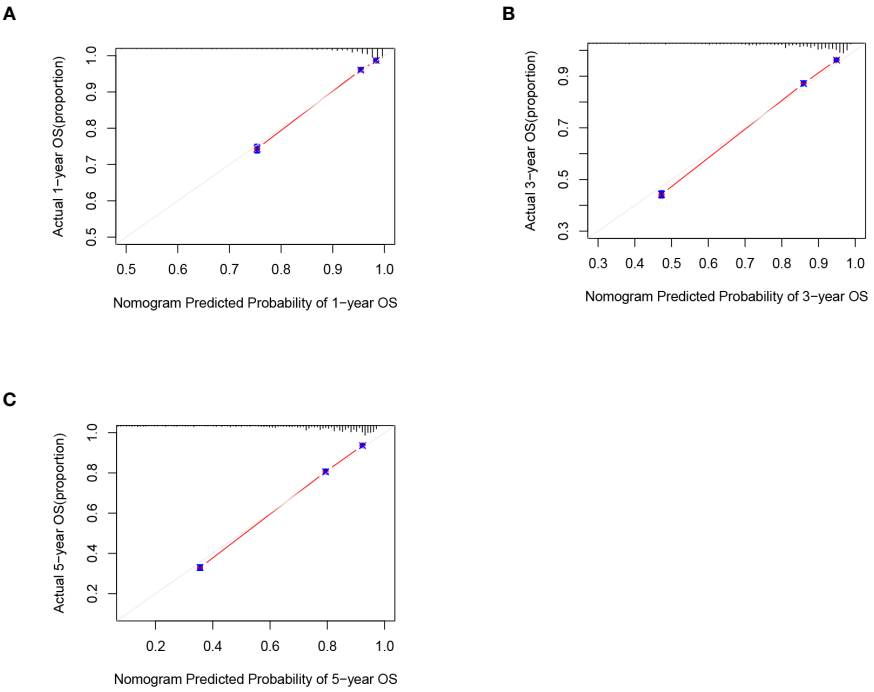

FIGURE 4
Calibration graphs forecasting the 1-, 3-, and 5-year overall survival (OS) of patients within the training set **(A)**, 1-year overall survival **(B)**, 3-year overall survival**(C)**. 5-year overall survival.

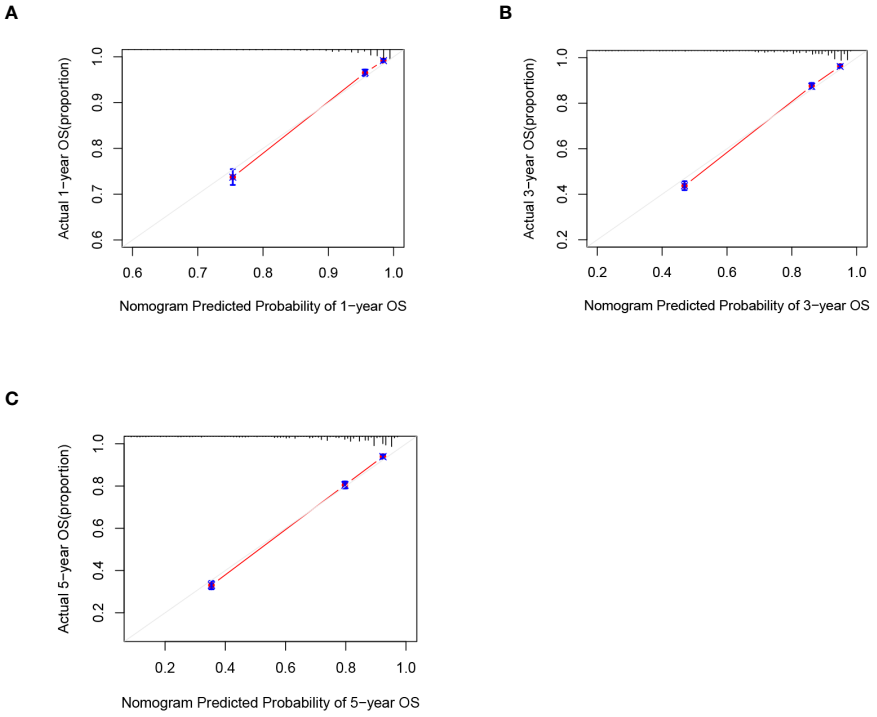

FIGURE 5
Calibration graphs forecasting the 1-, 3-, and 5-year overall survival (OS) of patients within the internal validation set **(A)**, 1-year overall survival **(B)**, 3-year overall survival **(C)**. 5-year overall survival.

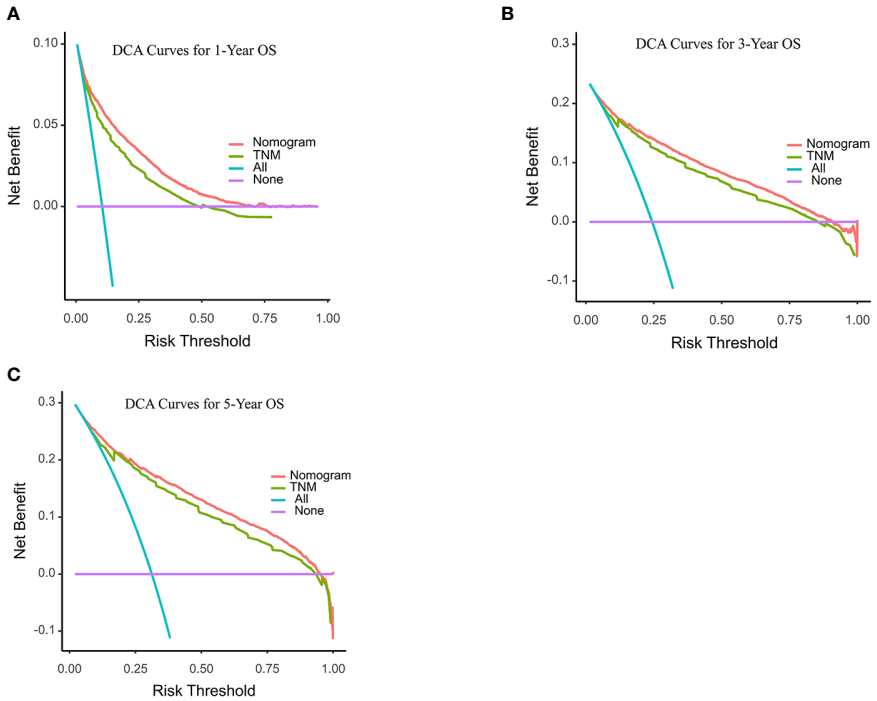

FIGURE 6
Decision curve analyses (DCA) of the nomogram and AJCC TNM staging system for 1-year **(A)**, 3-year **(B)**, and 5-year **(C)** overall survival. The x-axis represents the threshold probabilities, and the y-axis measures the net benefit. The horizontal line along the x-axis assumes that overall death occurred in no patients, whereas the solid purple line assumes that all patients will have overall death at a specific threshold probability. The Orange dashed line represents the nomogram. The green dashed line represents AJCC TNM staging system.

TABLE 4 External validation patient clinical characteristics information.

Variable	External validation (*n* = 228)	*p*
Age (years)		< 0.001
<31	3 (1.3)	
31-40	5 (2.1)	
41-50	20 (8.6)	
51-60	41 (17.8)	
61-70	72 (31.3)	
71-80	63 (27.3)	
81-90	24 (10.4)	
>90	0 (0.0)	
T.stage		< 0.001
T1	13(5.6)	
T2	12 (5.2)	
T3	173 (75.2)	
T4a	23 (10.0)	
T4b	7 (3.0)	
N.stage		< 0.001
N0	127 (55.2)	
N1a	22 (9.5)	
N1b	21 (9.1)	
N1c	34 (14.7)	
N2a	13 (5.6)	
N2b	11 (4.7)	
M.stage		< 0.001
M0	198(86.0)	
M1a	14 (6.0)	
M1b	16 (6.9)	
Summary.stage		< 0.001
Localized	22 (9.5)	
Regional	176 (76.5)	
Distant	30 (13.0)	
Chemotherapy		< 0.001
Yes	97 (42.1)	
No	131 (57.9)	
Liver metastasis		< 0.001
Yes	3 (1.3)	
No	225 (98.7)	
CEA		< 0.001
Normal	10,443(59.2)	
Positive	7,199(40.8)	
Survival status		
Alive	12,140(68.8)	
Dead	5,502(31.2)	

Risk stratification of the nomogram

According to the X-Tile software, patients with scores <197, 198 - 313, and > 313 points were divided into low-risk, intermediate-risk, and high-risk groups, respectively. Training set: 10,838 low-risk cases (61.43%), 5,021 medium-risk cases (28.46%), and high-risk 1,783 cases (10.11%). Internal validation set: 4,713 low-risk cases (62.33%), 2,097 medium-risk cases (27.73%), 751 cases (9.94%) were at high risk. External validation set: 146 cases of low risk (64.03%), 66 cases of medium risk (28.95%), and 16 cases of high risk (7.02%). Kaplan-Meier survival analysis for each risk group showed that the OS of the low-risk group was significantly better than that of the intermediate-risk group and high-risk group (P <0.001) (Figure 8), further validating the nomogram-based model to predict risk scores for patients with right-sided colon cancer has important clinical implications.

Discussion

The diagnosis and prognosis of colorectal cancer remain central and intricate topics in the medical field. Given the high incidence and mortality rate of colorectal cancer, numerous clinical research centers have pivoted towards harnessing both national and local databases for prognostic studies on this type of cancer (17, 18). Historically, prognosis models for colon cancer have encapsulated various types without distinctly differentiating between left and right-sided colon cancers. Contemporary literature, however, underscores a significant disparity in the overall survival rates between right and left-sided colon cancers, with the former exhibiting notably lower survival rates (19–23). This suggests that crafting a separate prognostic model for right-sided colon cancer might enhance the accuracy of prognosis. Presently, the clinical and prognostic value of right-sided colon cancer within the broader context of colorectal cancer has not garnered ample attention. Consequently, our research seeks to establish a specialized nomogram model for the prognosis of right-sided colon cancer, aiming to aid physicians in risk stratification.

While the AJCC staging system is regarded as the benchmark for predicting the prognosis of colorectal cancer patients, our findings indicate potential inadequacies in its post-operative prognostic predictions. Currently, nomograms, based on multifactorial regressions which amalgamate various indicators and utilize calibrated lines to illustrate the interrelation of

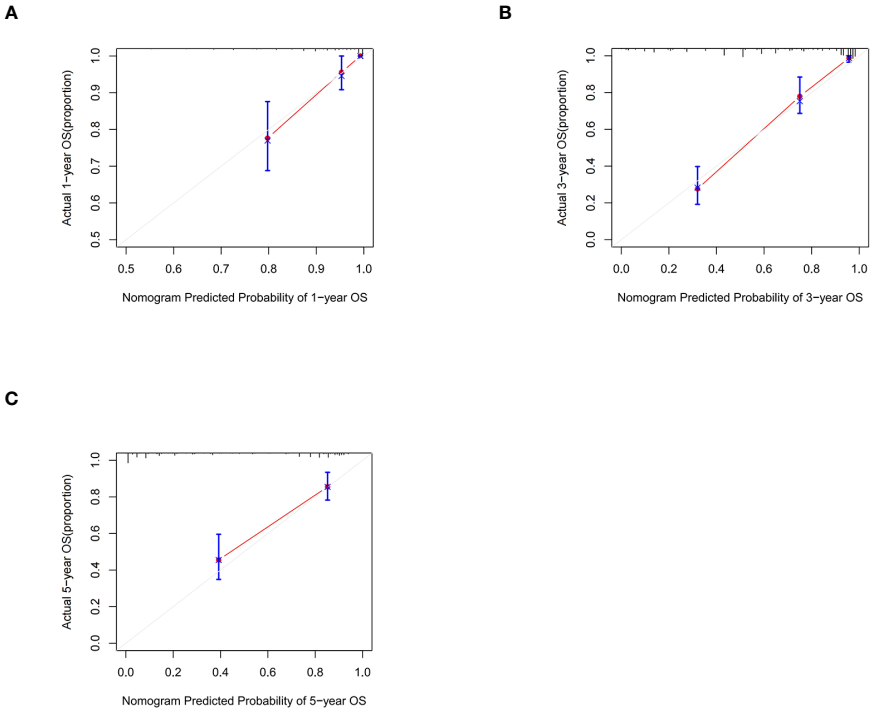

FIGURE 7
Calibration graphs forecasting the 1-, 3-, and 5-year overall survival (OS) of patients within the external validation set **(A)**, 1-year overall survival **(B)**, 3-year overall survival **(C)**. 5-year overall survival.

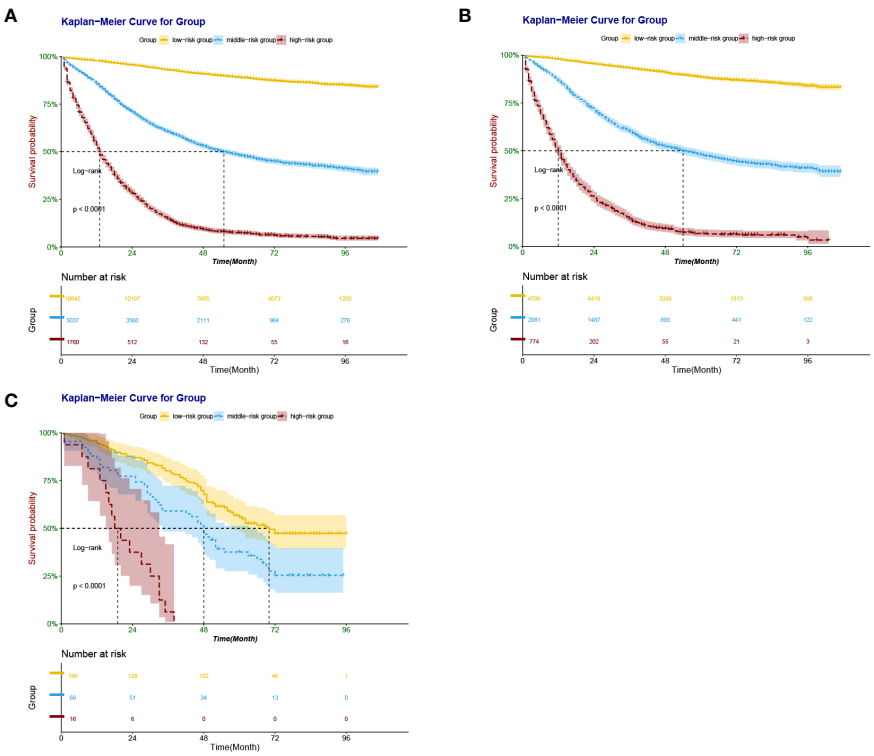

FIGURE 8
Kaplan–Meier survival curves derived from nomogram-based groups of patients with RCC after colectomy. The *p* value (<0.0001) was determined by the log-rank test. **(A)** Kaplan–Meier survival curves derived from nomogram-based groups of patients with RCC after colectomy in the training set. **(B)** Kaplan–Meier survival curves derived from nomogram-based groups of patients with RCC after colectomy in the internal validation set. **(C)** Kaplan–Meier survival curves derived from nomogram-based groups of patients with RCC after colectomy in the external validation set.

variables on a singular plane (24), dominate the clinical prognostic landscape. Due to their intuitive and user-friendly nature, nomograms play a pivotal role in shared decision-making between physicians and patients and are becoming increasingly prevalent in clinical settings. In fact, nomograms tailored for various tumors have showcased parity, and at times superiority, in prognostic evaluation compared to the traditional TNM staging (25, 26). However, it's noteworthy that as the number of predictive factors in a nomogram increases, its complexity can escalate. In such scenarios, LASSO regression analysis emerges as an efficacious instrument to eliminate inconsequential predictive factors. LASSO, a regression technique predicated on penalizing the absolute values of regression coefficients, can, with appropriate adjustments, compress certain coefficients to zero, thereby expunging non-essential or minimally impactful covariates (27, 28). Thus, LASSO not only maintains the predictive precision of nomograms but as data accrues, the accuracy of these models is poised to amplify.

In our study, we harnessed the predictive capabilities of machine learning to develop a nomogram based on the SEER database to forecast postoperative overall survival in right-sided colon cancer patients. This nomogram exhibited superior predictive accuracy compared to the conventional TNM staging system. Predictive factors incorporated in the model include age, chemotherapy status, CEA, AJCC 7th Edition T, N, and M staging, summary stage, and liver metastasis. Our univariate and multivariate analyses revealed that gender, tumor location, and histological type were not independent prognostic factors for cancer survival ($P > 0.05$). Furthermore, ethnicity was determined to be non-influential on postoperative OS. This consistency in external validation results, coupled with the addition of clinically relevant prognostic factors, ensures the model's applicability to the Chinese population.

Notably, the current AJCC staging guide omits age as a consideration. However, age stands as an independent predictor for both short-term and long-term postoperative mortality in cancer patients (29). Some studies have shown a rise in proximal colon tumors in patients aged <50 years and an association with expanding colon cancer screening practices, such as fecal occult blood tests and colonoscopies. Recent analyses indicate a decrease in colon cancer incidence among individuals aged 55-84 and a surge among those aged 20-55 (30–34). Lifestyle changes linked to Westernization, marked by shifts in dietary patterns over the past half-century, may explain these trends (35). In our study, patients aged <30 exhibited poorer outcomes than certain older cohorts, emphasizing that prevention and educational efforts should target younger demographics. The superior prognosis observed in the 40-60 age group can be attributed to their optimal physiological state. These findings advocate for the rationale behind initiating screenings at age 45 and routine screenings in individuals aged ≥50. As data on young right-sided colon cancer patients is sparse, further research is needed on personalized therapeutic strategies for this demographic. Patients aged >90 post-surgery have a markedly diminished 5-year OS compared to those aged <70, hinting at greater postoperative risks for the elderly, who also present with higher postoperative morbidity and mortality rates. These factors underscore the necessity for cautious therapeutic decisions, like surgical interventions, in elderly patients, and the imperative need for targeted management and continued research.

As an increasing number of researchers turn to the SEER and SEER-Medicare databases for outcome studies, we have identified several methods that amplify the potential of this data, deepening our understanding of right-sided colon cancer and enhancing patient care. The objective of future research is to refine staging and therapeutic techniques, thereby offering more personalized treatment options for right-sided colon cancer. To foster national improvements in care quality, it is essential to gain a profound insight into the care disparities among different regions and patient subgroups. Emphasizing primary prevention and early detection is particularly pivotal in addressing the challenges posed by an aging population and population growth.

Conclusion

Based on the extensive SEER database, we developed and validated a line graph, serving as a convenient and reliable tool for individualized postoperative survival prediction in patients with right-sided colon cancer. This model, utilizing readily accessible data from clinical practice, delivers compelling individualized survival forecasts. Subsequent validation highlighted the model's stellar performance in risk assessment. Consequently, our predictive tool empowers clinicians to accurately pinpoint high-risk patients, ensuring intensified follow-up and treatment strategies. Looking ahead, more prospective research is warranted to delve into survival prognostics for right-sided colon cancer patients.

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.

Author contributions

TQ: Data curation, Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing. CY: Methodology, Supervision, Writing – review & editing. YD: Formal analysis, Project administration, Writing – review & editing. MZ: Data curation, Methodology, Writing – review & editing. XW: Formal analysis, Project administration, Writing – review & editing. XS: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by Province Medical and Health Technology (2021KY1104), 2023 Jiaxing Key Discipline of Medicine-Thoracic Surgery (2023-ZC-014), Jiaxing Key Laboratory of Precision

Treatment for Lung Cancer, the National Natural Science Foundation of China (grant no. 82002982) and the Health Commission of Zhejiang Province (grant no. 2022ZB357).

Acknowledgments

We thank all participants at the Affiliated Hospital of Jiaxing University. We also thank the developers of the SEER program database.

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/fonc.2024.1330344/full#supplementary-material

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frontiers | Frontiers in Surgery

TYPE Original Research
PUBLISHED 27 March 2024
DOI 10.3389/fsurg.2024.1288061

OPEN ACCESS

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RECEIVED 03 September 2023
ACCEPTED 07 March 2024
PUBLISHED 27 March 2024

CITATION
Jakob D, Orth V, Gödde D, Zirngibl H and Ambe PC (2024) Microsatellite instability is highly prevalent in older patients with colorectal cancer.
Front. Surg. 11:1288061.
doi: 10.3389/fsurg.2024.1288061

Microsatellite instability is highly prevalent in older patients with colorectal cancer

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Background: Clinical guidelines suggest screening of colorectal cancer (CRC) for microsatellite instability (MSI). However, microsatellite instability—high (MSI-H) CRC is not rare in older patients. This study aimed to investigate the prevalence of MSI-H CRC in an unselected population in an age-based manner.
Material and methods: A retrospective analysis of data from patients undergoing radical surgery for CRC was performed. Only cases with results from MSI testing using immunochemistry (IHC) were analyzed. Age-based analyses were performed using two cut-off ages: 50 years. as stated in Amsterdam II guidelines, and 60 years. as outlined in the revised Bethesda criteria.
Results: The study population included 343 (146 female and 197 male) patients with a median age of 70 years (range 21–90 years). The prevalence of MSI-H tumors in the entire cohort was 18.7%. The prevalence of MSI-H CRC was 22.5% in the group ≤50 years vs. 18.2% in the group >50 years using the age limit in the Amsterdam II guidelines. MSI-H CRC was present in 12.6% of the group aged ≤60 years compared to 20.6% in the control group >60 years.
Conclusion: MSI screening of CRC based on age alone is associated with negative selection of a relevant number of cases. MSI-H CRC is also common in elderly patients, who may be negatively selected secondary to an age-based screening algorithm. Following the results of this study, screening based on clinical criteria should be omitted in favor of systematic screening as is already internationally practiced.

KEYWORDS

early onset colorectal cancer, colorectal cancer, microsatellite instability (MSI), mismatch repair, immunohistochemistry

Introduction

While the incidence of CRC seems to be decreasing in the general population over the last decades, the number of cases diagnosed at a young age has increased over the same period (1, 2). Generally, young age is defined by the Amsterdam II criteria as 50 years or younger (3, 4). Because the Amsterdam II criteria are very stringent, quite a number of MSI-H tumors went undetected. Thus the Amsterdam criteria were revised and the revised Bethesda criteria were defined (5). A central aspect of the revised clinical criteria was an increase of the age limit from 50 years to 60 years (5, 6). These clinical criteria were defined to identify individuals with high microsatellite instability (MSI-H) as a central feature of both hereditary nonpolyposis colorectal cancer (HNPCC) now known as "Lynch-like" syndrome and tumors within the spectrum of Lynch

syndrome (7, 8). Tumors in both Lynch syndrome and Lynch-like syndrome develop secondary to mutations involving the Mismatch Repair (*MMR*) genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* and possess a high degree of microsatellite instability (9–11). In both entities, CRC may develop at a very young age. The current German guidelines for the diagnosis and management of CRC recommend MSI testing in patients fulfilling the Amsterdam and Bethesda criteria (12). Thus, MSI testing is not routinely performed if these clinical characteristics are not met. More so, most clinicians tend to initiate MSI testing primarily when CRC is diagnosed at a young age (13, 14). Our clinical experience however indicates that MSI-H CRC may not be rare in elderly patients. We therefore intended to investigate the incidence of MSI-H CRC in an unselected population in an age-based manner.

Methods

We performed a retrospective analysis of data from a prospectively maintained colorectal cancer database at a university hospital. The study received approval from the ethics commission at Witten/Herdecke University. The study population included all consecutive cases of CRC undergoing oncologic resection between January 2015 and December 2020. MSI screening on cancer specimens was performed using IHC for the gene products of the most relevant *MMR-genes*; *MLH1*, *MSH2*, *MSH6*, and *PMS2* as published by Shia et al. (15). Only patients with available IHC findings were included for analysis. Age-specific groups were created using the ages defined in the Amsterdam II (50 years) and Bethesda (60 years) criteria. The control group included all patients above the defined cut-off ages. Data analysis was performed using statistical package for social sciences (SPSS), IBM version 25. Continuous variables are reported using absolute numbers and percentages, while central tendencies are reported using medians and ranges. Analytic statistics were done using the chi-square test. All calculations were done with a 95% confidence interval and p-values <0.05 were reported as statistically significant.

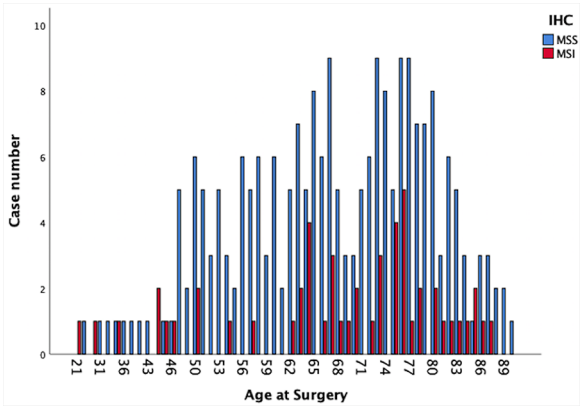

FIGURE 1
Distribution of the findings of IHC in the study collective.

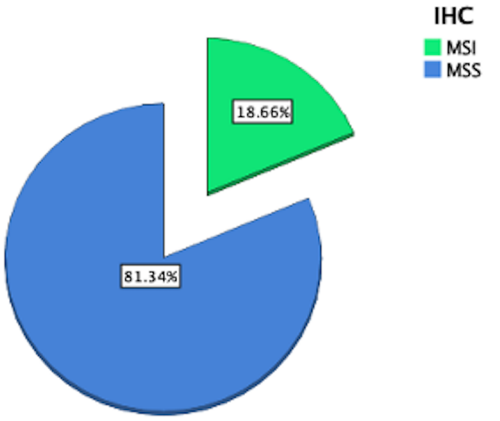

FIGURE 2
Prevalence of MSI-H tumors in the collective.

Results

The study population included 343 (146 female and 197 male) patients with a median age of 70 years (range 21–90 years). The tumor was in the right colon in 141 cases (41.1%), while the left colon including the rectum was involved in 202 cases (58.9%). Figure 1 demonstrates the distribution of IHC results for MSI in the study population, while the prevalence of MSI-H tumors is reported in Figure 2.

Table 1 represents the results of the first age-based analysis using the 50 years as cut-off as defined in the Amsterdam criteria, while the prevalence of MSI-H tumors for this is presented in Figure 3. The clinicopathological findings from the second analysis with 60 years as cut-off, based on the revised Bethesda criteria are presented in Table 2, while the corresponding prevalence of MSI-H tumors is demonstrated in Figure 4.

TABLE 1 Age-based analysis with cut-off at 50 years.

Characteristics	Age ≤ 50 years	Age > 50 years
	$N = 40$	$N = 303$
Sex		
Female	19 (47.5%)	127 (41.9%)
Male	21 (52.5%)	176 (58.1%)
Age		
Median	48 years	72 years
Range	21–50 years	51–90 years
Location of CRC		
Right colon	14 (35.0%)	127 (41.9%)
Left colon	26 (65.0%)	176 (58.1%)
UICC stages		
I–II	185 (61.1%)	38 (54.2%)
III	75 (24.8%)	22 (31.4%)
IV	43 (14.2%)	10 (14.3%)
MSI-status		
MSS	31 (77.5%)	248 (81.8%)
MSI	9 (22.5%)	55 (18.2%)

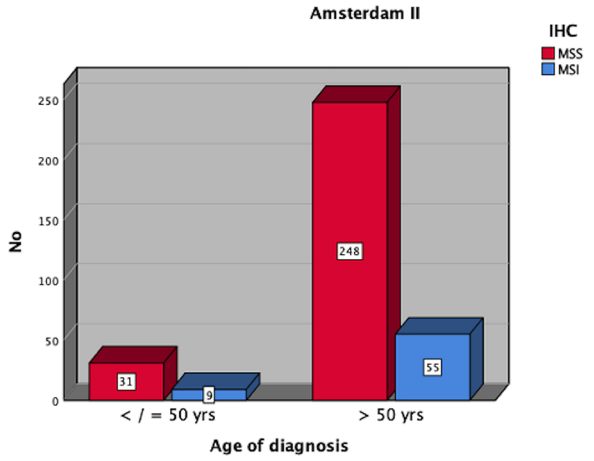

FIGURE 3
Distribution of MSI-H CRC amongst patients ≤50 vs. >50 years.

TABLE 2 Clinicopathological features based on age 60 years.

Characteristics	Age ≤ 60 years	Age > 60 years	*p*-Value
Sex	*N* = 96	*N* = 247	
Female	42 (43.7%)	104 (42.1%)	>0.05
Male	54 (56.3%)	143 (57.9%)	
Age			
Median	52 years	74 years	0.03
Range	21–60 years	61–90 years	
UICC Stages			
I–II	58 (61.7%)	152 (61.8%)	>0.05
III	23 (22.3%)	56 (22.8%)	
IV	15 (16.0%)	39 (15.4%)	
MSI-status			
MSS	84 (87.4%)	196 (79.4%)	>0.05
MSI	12 (12.6%)	51 (20.6%)	

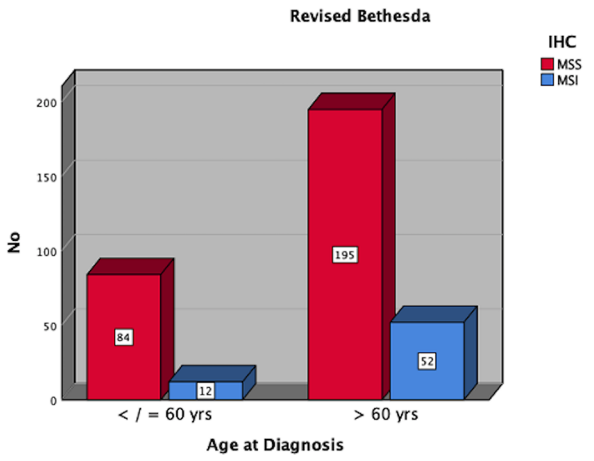

FIGURE 4
Distribution of MSI-H tumors in patients ≤60 vs. >60 years.

Discussion

Early onset CRC is defined in Amsterdam criteria as CRC before the age of 50 years and may be secondary to hereditary cancer predisposition. Another age limit (60 years) commonly used in the literature is defined revised Bethesda criteria. Both clinical criteria aimed at selecting individuals for microsatellite instability screening in the setting of CRC. However, MSI-H CRC is not a rare finding in older individuals (>60 years) with CRC. This study investigated the prevalence of MSI-H CRC in patients regarding the age at surgery using the two cut-off ages (50 and 60 years). The prevalence of MSI-H CRC in this study was 18.7%. The prevalence of MSI-H CRC in patients ≤50 years as defined in the Amsterdam II criteria was 22.5%, while MSI-H CRC was found in 12.6% of patients ≤60 years.

The prevalence of MSI-H CRC in this study was slightly higher in patients ≤50 years compared to controls (>50 years) 22.5% vs. 18.2%. This was not statistically significant. This finding must be interpreted with caution since numerically more cases of MSI-H CRC were found in the group >50 years compared to the younger cohort (9/40 vs. 55/303). A total of 55 cases of MSI-H CRC would have been undetected in this population if the Amsterdam II criteria alone had been used as the sole prerequisite for MSI testing.

Increasing the cut-off age to 60 years as spelled out in the revised Bethesda criteria was associated with a drop in the prevalence of MSI-H tumors from 22.5% in patients ≤50 years to 12.6% in the group ≤60 years The huge drop in the prevalence of MSI-H CRC amongst the two age groups is a simple effect of the number of cases associated with the age dynamic. Increasing the age from 50 to 60 years led to a marked increase in the size of the population from 40 to 96 cases. Although statistically not significant, the prevalence of MSI-H CRC was higher in the older group >60 years (20.6%) in comparison to the age group under 60 years (12.6%). This finding opposes the recommendation by Chou et al. to perform MSI screening for right-sided CRC in individuals ≤60 years not only regarding age but also with regard to the cancer location (16).

The findings of this study indicate that initiation of MSI screening in CRC based on clinically defined criteria bears a great risk of missing quite a large portion of potential cases with MSI-H CRC. Our findings are in line with the current literature regarding the poor performance of both the Amsterdam and the revised Bethesda criteria as selection tools for MSI screening (3, 4, 6). These findings should be seen as an argumentation to leave the dogma of fulfillment of clinical criteria and move on to systematic screening of colorectal neoplasia for MSI, especially since these clinical criteria were aimed at identifying individuals with possible germline mutations at risk for Lynch syndrome (17–19).

The results of this study indicate that the common practice of "red flag raising" and initiation of MSI-testing preferably in younger individuals with CRC leads to a high probability of undiagnosed cases with MSI-H CRC. This finding is in

accordance with the data published by Poynter et al. indicating that advanced age is a strong predictor for MSI-H CRC secondary to MLH1 methylation (20). More so, omitting MSI screening due to failure to fulfill clinical criteria may be detrimental to patients with stage II and III CRC regarding the need and choice of additive chemotherapy, especially regarding responsiveness to 5-FU-based regimes (21, 22). This may be a possible explanation for the previously reported poor outcome of CRC in young patients with advanced CRC (23).

A major limitation of this study is the retrospective design. Many cases needed to be excluded due to missing data. This led to a reduction in the study population. MSI in this study was investigated using immunohistochemistry only. Although there is a high concordance between PCR testing and IHC, there is still a possibility that some cases of MSI-H went undiagnosed via IHC alone. It is therefore fair to question whether the results recorded in this study may be reproducible in a larger population. More so, findings from genetic counselling and testing for possible germline mutations to diagnose or exclude Lynch syndrome in MSI-H cases were not generally performed and therefore could not be reported.

Conclusion

MSI screening of CRC based on age alone is associated with negative selection of a relevant number of cases. MSI-H CRC is also common in elderly patients, who may be negatively selected secondary to an age-based screening algorithm. Following the results of this study, screening based on clinical criteria should be omitted in favor of systematic screening as is already internationally practiced.

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 humans were approved by Ethics commission at Witten/Herdecke University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

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Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 21 May 2024
DOI 10.3389/fonc.2024.1381809

OPEN ACCESS

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RECEIVED 06 February 2024
ACCEPTED 07 May 2024
PUBLISHED 21 May 2024

CITATION
Cao L, Zhang L, Chen B, Yan L, Shi X and Tian L (2024) Application of multimodal standardized analgesia under the concept of enhanced recovery after surgery in laparoscopic radical colorectal cancer surgery.
Front. Oncol. 14:1381809.
doi: 10.3389/fonc.2024.1381809

Application of multimodal standardized analgesia under the concept of enhanced recovery after surgery in laparoscopic radical colorectal cancer surgery

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Aims: To observe the efficacy and safety of multimodal standardized analgesia in patients undergoing laparoscopic radical colorectal cancer surgery.

Methods: A prospective, double-blind, randomized study of patients who were admitted to our hospital between December 2020 and March 2022 with a diagnosis of colorectal cancer and who intended to undergo elective laparoscopic radical colorectal cancer surgery was conducted. The participants were randomly divided into two intervention groups, namely, a multimodal standardized analgesia group and a routine analgesia group. In both groups, the visual analogue scale (VAS) pain scores while resting at 6 h, 24 h, 48 h and 72 h and during movement at 24 h, 48 h and 72 h; the number of patient controlled intravenous analgesia (PCIA) pump button presses and postoperative recovery indicators within 3 days after surgery; the interleukin-6 (IL-6) and C-reactive protein (CRP) levels on the 1st and 4th days after surgery; and the incidence of postoperative adverse reactions and complications were recorded.

Results: Compared with the control group, the multimodal standardized analgesia group had significantly lower VAS pain scores at different time points while resting and during movement (P<0.05), significantly fewer PCIA pump button presses during the first 3 postoperative days (P<0.05), and significantly lower IL-6 and CRP levels on the 1st postoperative day (P<0.05). There was no statistically significant difference in the time to out-of-bed activity, the time to first flatus, the IL-6 and CRP levels on the 4th postoperative day or the incidence of postoperative adverse reactions and complications between the two groups (P >0.05).

Conclusion: For patients undergoing laparoscopic radical colorectal cancer surgery, multimodal standardized analgesia with ropivacaine combined with

parecoxib sodium and a PCIA pump had a better analgesic effect, as it effectively inhibited early postoperative inflammatory reactions and promoted postoperative recovery and did not increase the incidence of adverse reactions and complications. Therefore, it is worthy of widespread clinical practice.

KEYWORDS

laparoscopic radical colorectal cancer surgery, multimodal standardized analgesia, enhanced recovery after surgery, ropivacaine, parecoxib

1 Introduction

Colorectal cancer is a common malignant tumour of the digestive tract, and its incidence has gradually increased in recent years (1). Laparoscopic radical surgery is the main treatment method (2). Compared with traditional open surgery, laparoscopic colorectal cancer surgery has advantages such as less trauma, faster recovery, and oncological efficacy. In laparoscopic abdominal surgery, small incisions and artificial pneumoperitoneum can still lead to postoperative pain and thus affect the patients' mood and sleep quality as well as inhibit respiration, leading to complications such as pulmonary atelectasis and lung infections (3). Therefore, good postoperative analgesia is particularly important.

The rapid development of enhanced recovery after surgery (ERAS) concepts (4, 5) has led to an increase in its application in colorectal surgery, and pain management, as a very important concept of ERAS (6), requires standardized analgesia, preventive analgesia, multimodal analgesia and individualized analgesia management for postoperative patients (7). According to the guidelines for minimally invasive colorectal surgery, various analgesic methods are recommended, such as patient controlled intravenous analgesia (PCIA) combined with acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) or opioid agonists, as well as local anaesthetic incisional infiltration, ultrasound-guided transverse abdominis plane block, rectus abdominis muscle sheath block, or other analgesic techniques (7). However, at present, there is a lack of real-world research on the optimal multimodal standardized analgesia method for patients undergoing laparoscopic radical colorectal cancer surgery; such a lack has posed challenges to the clinical operation process (8, 9). Therefore, based on clinical practical needs, this study compared the short-term efficacy of ropivacaine combined with parecoxib sodium with that of a PCIA pump in laparoscopic radical colorectal cancer surgery to determine the best multimodal standardized analgesia method for surgery, with the aim of providing experience and inspiration for clinical practice.

2 Materials and methods

2.1 Patients

This prospective, double-blind, randomized study was approved by the Ethics Committee of Shaanxi Provincial People's Hospital. Patients who were admitted to our hospital between December 2020 and March 2022, were diagnosed with colorectal cancer, and who intended to undergo elective laparoscopic radical colorectal cancer surgery were enrolled according to the inclusion and exclusion criteria and then randomized by a computer-generated random allocation sequence into two interventional groups, namely, the multimodal standardized analgesia group and the routine analgesia group. The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all the patients.

The inclusion criteria were as follows: (1) aged ≥18 years. (2) diagnosed with colorectal adenocarcinoma by biopsy pathology, with no distant metastasis in relevant auxiliary examinations. (3) American Society of Anaesthesiologists (ASA) grade I ~ III and no history of psychiatric disease. (4) ECOG PS score: 0~1. The exclusion criteria were as follows: (1) required conversion to open approach during the laparoscopic surgery. (2) a history of previous abdominal surgery. (3) a history of allergy to any of the drugs included in the interventions. (4) underwent emergency surgery for intestinal obstruction, perforation or bleeding. (5) underwent intraoperative combined organ resection. (6) were transferred to the intensive care unit for treatment after surgery. (7) a history of drug therapy involving corticosteroids and cyclooxygenase inhibitors within 1 month before surgery. (8) serious diseases such as heart disease (congestive heart failure (NYHA grade II-IV) or coronary artery bypass surgery), liver disease (patients with a serum albumin concentration < 25 g/L or a Child–Pugh score ≥ 10) or kidney disease (patients with a creatinine clearance rate<30 ml/min or with a tendency towards fluid retention). All patients underwent laparoscopic radical colorectal cancer surgery after

enrolment, and the surgical procedures were completed in accordance with the "Guidelines for Laparoscopic Colorectal Cancer Radical Surgery (2018 Edition)" (10).

2.2 Anaesthesia protocol

After entering the operating room, electrocardiogram, blood pressure and blood oxygen saturation were routinely monitored. General anaesthesia was induced with 1~2 mg of intravenous midazolam, 0.2~0.3 μg/kg of sufentanil, 0.2 mg/kg of cisatracurium and 1~2 mg/kg of propofol. Then, tracheal intubation was performed, and mechanical ventilation was started after successful surgery. Anaesthesia was maintained with 0.1~0.2 mg/kg/minute of sevoflurane. The patients were maintained at a tidal volume of 6~10 ml/kg, respiratory rate of 12 breaths/minute, and end-tidal carbon dioxide of 35~45 mmHg. The same drugs for general anaesthesia induction and maintenance were used for both groups. All surgeries were performed by the same surgeons using the same equipment.

2.3 Intervention measures

The patients in the multimodal standardized analgesia group underwent the following before, during and after surgery: (1) preemptive analgesia: 40 mg parecoxib sodium was injected intravenously 30 minutes before anaesthesia induction; and (2) intraoperative analgesia: after closing the aponeurotic layer of the abdominal wall incision, 40 ml 0.5% ropivacaine hydrochloride was used for multipoint infiltration anaesthesia in the aponeurosis layer of each incision and subcutaneous tissue; and (3) postoperative analgesia: after the operation, the anaesthesiologist connected the patient-controlled intravenous analgesia (PCIA) pump to the patient. The formula for PCIA was 100 μg sufentanil + 16 mg ondansetron dissolved in normal saline to 100 mL. The parameter settings for PCIA were as follows: the loading dose was 2 mL, the background infusion dose was 2 mL/h, the single dose was 1 mL, and the lockout time was 20 minutes. Simultaneously, 40 mg parecoxib sodium was injected intravenously every 12 h for the first 3 days after the operation. Ondansetron (4 mg) was injected intravenously if the patient experienced nausea and vomiting. The button on the PCIA pump could be pressed if the pain worsened, and other adverse reactions were treated accordingly.

The patients in the routine analgesia group underwent the following only after surgery: postoperative analgesia: The PCIA was connected by the anaesthesiologist at the end of surgery (with the same formula as above). If the patient developed nausea and vomiting, 4 mg of ondansetron was intravenously injected. The button on the PCIA pump could be pressed when the pain worsened, and 40 mg of parecoxib sodium was injected intravenously for rescue analgesia. Corresponding treatment was administered when other adverse reactions occurred.

2.4 Clinical outcomes

According to the relevant published literature and guidelines (7, 11–13), we selected the following items as the clinical outcomes for our article.

1. Pain score: The visual analogue scale (VAS) pain scores while resting at 6 h, 24 h, 48 h and 72 h and during movement at 24 h, 48 h and 72 h (turning over, sitting up and getting out of bed) were recorded in both groups after the operation.
2. The number of PCIA pump button presses and postoperative recovery indicators: The total number of times the patient spontaneously pressed the button on the PCIA pump in the 3-day postoperative period was recorded. The time to out-of-bed activity and the time to first flatus were also recorded.
3. Relevant inflammation markers: Fasting peripheral venous blood specimens were taken from patients in both groups in the early morning of the 1st and 4th postoperative days, and interleukin 6 (IL-6) and C-reactive protein (CRP) levels were detected;
4. Incidence of adverse reactions and complications: The incidences of postoperative nausea and vomiting, skin itching, incision infection, and lung infection were recorded;

2.5 Statistical methods

SPSS 23.0 statistical software was used for statistical analysis. The Shapiro–Wilk test was used to test the normality of all variables. Normally distributed continuous variables are expressed as the mean ± standard deviation, and an independent sample *t* test was used for comparisons between the two groups. Nonnormally distributed continuous variables are expressed as medians (interquartile ranges) [M(Q1, Q3)], and the Wilcoxon rank sum test was used. Categorical variables are presented as frequencies and percentages, and the chi-square test or Fisher's exact test was used for comparisons between the two groups (when the theoretical frequency was less than 1). A P value <0.05 indicated a statistically significant difference.

3 Results

3.1 Clinical characteristics

Ninety-four patients were initially included in this study, and 10 patients were excluded for the following reasons: conversion to open surgery during laparoscopic colorectal cancer surgery (4 patients), taking nonsteroidal anti-inflammatory drugs to control pain within 1 month before surgery (2 patients), transferred to the intensive care unit after surgery (3 patients), and severe renal

insufficiency (1 patient). A total of 84 patients were ultimately included in the analysis, with 42 patients in each group. The mean age of patients in multimodal standardized analgesia group was 63.8. ± 11.1 years, including 27 males (64.3%), the mean body mass index (BMI) of patients was 23.3 ± 1.1 kg/m^2, and the mean operation time was 230.7 ± 49.6 minutes. The mean age of patients in the routine analgesia group was 66.4 ± 13.6 years, including 26 males (61.9%), the mean BMI of patients was 23.4 ± 1.1 kg/m^2, and the mean operation time was 240.2 ± 54.7 minutes. There was no statistically significant difference in age, sex, body mass index (BMI), ASA classification, surgical time, total incision length, tumour location, or tumour TNM stage between the multimodal standardized analgesia group and the routine analgesia group (P>0.05) (Table 1).

TABLE 1 Comparison of clinical characteristics between the two groups.

Baseline characteristics	the multimodal standardized analgesia group (n=42)	the routine analgesia group (n=42)	*P*-values
Age/years	63.8. ± 11.1	66.4 ± 13.6	0.338
Male/case (%)	27 (64.3)	26 (61.9)	0.821
BMI (kg/m^2)	23.3 ± 1.1	23.4 ± 1.1	0.896
Tumor location/case (%)			
Right hemicolon	7 (16.7)	5 (11.9)	0.533
Left hemicolon	3 (7.1)	1 (2.4)	0.608
Sigmoid colon	4 (9.5)	8 (19.0)	0.350
Rectum	28 (66.7)	28 (66.7)	1.000
TNM stages/case (%)			
Stage I	8 (19.0)	10 (23.8)	0.595
Stage II	18 (42.9)	22 (52.4)	0.382
Stage III	16 (38.1)	10 (23.8)	0.157
ASA classification/case (%)			
Classification I	7 (16.7)	8 (19.1)	0.776
Classification II	26 (61.9)	26 (61.8)	1.000
Classification III	9 (21.4)	8 (19.1)	0.786
Surgical time/min	230.7 ± 49.6	240.2 ± 54.7	0.400

3.2 VAS pain scores at different time points during the postoperative period

1. Comparison of VAS pain scores at different time points while resting: Compared with those in the routine analgesia group, the VAS pain scores in the multimodal standardized analgesia group were significantly lower at 6 h (P=0.024), 24 h (P=0.036), 48 h (P=0.042) and 72 h (P=0.035) after the operation (Table 2).
2. Comparison of VAS pain scores at different time points during movement: Compared with the routine analgesia group, the multimodal standardized analgesia group showed a significant decrease in VAS pain scores at 24 hours (P<0.001), 48 hours (P<0.001), and 72 hours (P=0.038) after surgery (Table 2).

3.3 The number of PCIA pump button presses and postoperative recovery indicators

According to Table 3, the number of button presses of PCIA in the multimodal standardized analgesia group was significantly less than that in the routine analgesia group (P<0.001), but there was no statistically significant difference in the time to first out-of-bed activity (P=0.152) or the time to first flatus (P=0.423) between the two groups.

3.4 Relevant postoperative inflammatory indicators

The IL-6 (P=0.003) and CRP levels (P<0.001) in the multimodal standardized analgesia group were significantly lower than those in the routine analgesia group on postoperative day 1, but the IL-6 (P=0.249) and CRP levels (P=0.068) on postoperative day 4 were not significantly different (Table 4).

3.5 Postoperative adverse effects and complications

In the multimodal standardized analgesia group, there were 5 cases of postoperative nausea, 2 cases of vomiting, 1 case of itchy

TABLE 2 Comparison of VAS pain scores between the two groups at different time points during the postoperative period.

Groups	resting				movement		
	6 h	24 h	48 h	72 h	24 h	48 h	72 h
The multimodal standardized analgesia group (n=42)	1.6 ± 0.8	1.5 ± 0.8	1.5 ± 0.7	1.3 ± 0.6	2.3 ± 0.8	1.9 ± 0.8	1.8 ± 0.8
The routine analgesia group (n=42)	3.8 ± 0.9	3.6 ± 0.9	3.0 ± 0.9	1.9 ± 0.7	4.6 ± 1.0	4.0 ± 1.0	3.2 ± 0.7
P values	0.024	0.036	0.042	0.035	<0.001	<0.001	0.038

TABLE 3 Comparison of the number of PCIA pump button presses and recovery indicators between the two groups.

Groups	the number of PCIA pump button presses (times)	time to first out-of-bed activity (h)	time to first flatus (h)
The multimodal standardized analgesia group (n=42)	1.46 ± 0.57	23.5 ± 4.9	48.1 ± 6.7
The routine analgesia group (n=42)	3.28 ± 0.89	33.3 ± 5.1	54.0 ± 6.4
P values	<0.001	0.152	0.423

skin, and 2 cases of incision infection, totalling 10 cases (24.4%). In the routine analgesia group, there were 4 cases of nausea, 1 case of vomiting, 1 case of incision infection, and 2 cases of lung infection, totalling 8 cases (18.6%). There was no statistically significant difference in the incidence of adverse reactions and complications between the two groups (P =0.595). See Table 5.

4 Discussion

Laparoscopic radical colorectal cancer surgery, as major cause of injury, can cause the body to release analgesic substances, leading to peripheral sensitization. Moreover, making the surgical incision directly stimulates nociceptive receptors, which can also cause peripheral nerve sensitization, leading to a decrease in the body's pain threshold, causing significant postoperative pain (14), thus increasing the risk of postoperative complications and affecting early postoperative activities and rehabilitation exercises (7). In addition, if acute postoperative pain is not effectively managed, it may progress to chronic pain that is difficult to control, seriously affecting patient postoperative quality of life.

Contrary to traditional methods, ERAS is a new concept in which a series of optimization measures can be applied during the perioperative period to avoid complications and surgical stress and promote the postoperative recovery of patients (15, 16). Perioperative pain management plays a very important role in the process of ERAS implementation. Multimodal analgesia and standardized analgesia are the core measures for ERAS pain management. Multimodal analgesia refers to the combined application of analgesic drugs with different mechanisms of action and/or multiple analgesic methods that act on different stages and targets of pain to achieve more satisfactory analgesic effects and minimize adverse drug reactions while reducing the impact of pain and drugs on the immune system, cardiovascular system, endocrine system, and nervous system and reducing the occurrence of postoperative complications (17). Standardized analgesia refers to the standardized treatment of perioperative pain, regular recording and evaluation of analgesic effects, timely handling of adverse reactions and various problems that arise during analgesic treatment, and reducing the occurrence of postoperative pain-related complications (7). However, perioperative pain management is receiving increasing amounts of attention. However, relevant studies have shown that the effectiveness of perioperative pain treatment is still unsatisfactory. Two studies in the United States in 2014 showed that 50-70% of patients still experienced moderate-to-severe pain after surgery (18–20). According to a 2017 study investigating the current status of perioperative pain management in 847 hospitals in China by Zhang et al., multimodal analgesia has not been widely popularized for perioperative pain treatment in China, and although postoperative analgesic pumps are widely used in clinical practice, the technical application rate is not high, and a standardized pain management model has not been established (18).

In this study, the VAS score of the multimodal standardized analgesia group was significantly lower than that of the control group, and the number of PCIA pump button presses was significantly lower in the former group, indicating that the multimodal standardized preemptive analgesia method (intravenous injection parecoxib sodium 40 mg at 30 minutes before anaesthesia induction) + intraoperative analgesia (intraoperative ropivacaine for multipoint infiltration anaesthesia) + postoperative analgesia (postoperative administration of parecoxib at regular intervals and PCIA after surgery) had an absolute advantage in terms of analgesic effect compared to the routine analgesia group. First, parecoxib sodium is a new type of nonsteroidal anti-inflammatory drug that selectively inhibits

TABLE 4 Comparison of relevant postoperative inflammatory indicators between the two groups.

Groups	IL-6 (pg/ml)		CRP (mg/L)	
	postoperative day 1	postoperative day 4	postoperative day 1	postoperative day 4
The multimodal standardized analgesia group (n=42)	36.0 ± 9.0	14.1 ± 4.5	30.8 ± 7.6	16.3 ± 3.7
The routine analgesia group (n=42)	41.8 ± 8.6	18.9 ± 4.4	37.5 ± 7.6	18.9 ± 2.8
P values	0.003	0.249	<0.001	0.068

TABLE 5 Comparison of postoperative adverse effects and complications between the two groups.

Groups	nausea	vomit	pruritus	incision infection	lung infection	total
The multimodal standardized analgesia group (n=42)	5 (11.9)	2 (4.8)	1 (2.4)	2 (4.8)	0 (0.0)	10 (23.8)
The routine analgesia group (n=42)	4 (9.5)	1 (2.4)	0 (0.0)	1 (2.4)	2 (4.8)	8 (19.0)
P values	0.725	0.557	0.314	0.557	0.152	0.595

cyclooxygenase-2 (COX-2), which is hydrolysed *in vivo* to valdecoxib, which can inhibit the expression of COX-2 in the periphery and reduce the production of prostaglandins to exert anti-inflammatory and analgesic effects. It can inhibit central COX-2 expression to inhibit pain hypersensitivity, improve the pain threshold and exert an analgesic effect. This product takes effect quickly and has a powerful analgesic effect. Its application before and after surgery can significantly reduce incision pain and visceral pain in laparoscopic colorectal cancer surgery patients (7, 14). Second, as a long-lasting amide-type local anaesthetic, ropivacaine is safe, effective, and has long-lasting effects. At the end of the procedure, infiltration anaesthesia is applied to the myofascial layer of the wound and the subcutis, which provides analgesia by blocking the branch nerves in the myofascial layer of the wound and around the skin. When used in small doses, this product mainly blocks the sensory nerves rather than the motor nerves, effectively alleviating postoperative pain without affecting early ambulation (21).

IL-6 is one of the main proinflammatory factors in the acute phase of the inflammatory response and plays an important role in regulating the body's response to injury, infection development, etc. CRP is an acute response protein that acts similarly to IL-6 and can reflect the degree of the inflammatory response in the body. The levels of IL-6 and CRP increase rapidly under stressful conditions, such as during surgery, and can affect a patient's postoperative recovery if they are in a state of high expression after the operation (22). In this study, the IL-6 and CRP levels in the multimodal standardized analgesia group were significantly lower than those in the routine analgesia group on the first postoperative day, possibly because parecoxib sodium can control the inflammatory response of the body at an early stage and reduce the release of inflammatory factors in the postoperative period (23), thus reducing postoperative pain in patients, which is consistent with the findings of current studies (24). In terms of the time to first flatus, although the difference between the two groups was not statistically significant, the time in the former group was still shorter, which may be attributed to the rapid recovery of gastrointestinal function prompted by the shorter time to out-of-bed activity after good analgesia and the increase in the amount of activity.

The overall incidence of adverse reactions and complications, as well as the incidences of nausea, vomiting, skin itching, incision infection and lung infection, were not significantly different between the multimodal standardized analgesia group and the routine analgesia group, indicating that the multimodal standardized analgesia method was safe and feasible and did not increase the incidence of postoperative complications and adverse reactions in patients.

This study has several limitations. (1) This was a single-centre study, and the clinical outcomes might be affected by the medication preferences observed by clinicians to some extent, which might cause some bias in the research results. (2) Only CRP and IL-6 were selected to determine postoperative inflammatory conditions, without considering changes in commonly used clinical inflammatory indicators such as white blood cell count, neutrophil count, and procalcitonin level, which might have an impact on the results. (3) The sample size was small, causing some limitations in the assessment of the impact on clinical outcomes.

5 Conclusions

In conclusion, the multimodal standardized analgesia method with ropivacaine combined with parecoxib sodium and a PCIA pump explored in this study has a better analgesic effect on patients undergoing laparoscopic radical colorectal cancer surgery and can effectively inhibit early postoperative inflammatory reactions and promote postoperative recovery without increasing the incidence of adverse reactions and complications. At the same time, the method is simple to apply, easy to master, highly feasible and clinically applicable.

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 humans were approved by Shaanxi Provincial People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. LZ: Writing – original draft. BC: Writing – original draft. LY: Writing – original

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Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research received two fundings: Shaanxi Provincial People's Hospital Science and Technology Development Incubation Funding (2022YJY-55) and Shaanxi Provincial Administration of Traditional Chinese Medicine Research Project (2023-JC-005).

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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frontiers | Frontiers in Immunology

TYPE Original Research
PUBLISHED 10 June 2024
DOI 10.3389/fimmu.2024.1388272

OPEN ACCESS

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RECEIVED 19 February 2024
ACCEPTED 27 May 2024
PUBLISHED 10 June 2024

CITATION
Luenstedt J, Hoping F, Feuerstein R, Maurer B, Berlin C, Rapp J, Marx L, Reichardt W, von Elverfeldt D, Ruess DA, Plundrich D, Laessle C, Jud A, Neeff HP, Holzner PA, Fichtner-Feigl S and Kesselring R (2024) Partial hepatectomy accelerates colorectal metastasis by priming an inflammatory premetastatic niche in the liver. *Front. Immunol.* 15:1388272. doi: 10.3389/fimmu.2024.1388272

Partial hepatectomy accelerates colorectal metastasis by priming an inflammatory premetastatic niche in the liver

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Background: Resection of colorectal liver metastasis is the standard of care for patients with Stage IV CRC. Despite undoubtedly improving the overall survival of patients, pHx for colorectal liver metastasis frequently leads to disease recurrence. The contribution of this procedure to metastatic colorectal cancer at a molecular level is poorly understood. We designed a mouse model of orthograde metastatic colorectal cancer (CRC) to investigate the effect of partial hepatectomy (pHx) on tumor progression.

Methods: CRC organoids were implanted into the cecal walls of wild type mice, and animals were screened for liver metastasis. At the time of metastasis, 1/3 partial hepatectomy was performed and the tumor burden was assessed longitudinally using MRI. After euthanasia, different tissues were analyzed for immunological and transcriptional changes using FACS, qPCR, RNA sequencing, and immunohistochemistry.

Results: Mice that underwent pHx presented significant liver hypertrophy and an increased overall metastatic load compared with SHAM operated mice in MRI. Elevation in the metastatic volume was defined by an increase in *de novo* liver metastasis without any effect on the growth of each metastasis. Concordantly, the livers of pHx mice were characterized by neutrophil and bacterial infiltration, inflammatory response, extracellular remodeling, and an increased abundance of

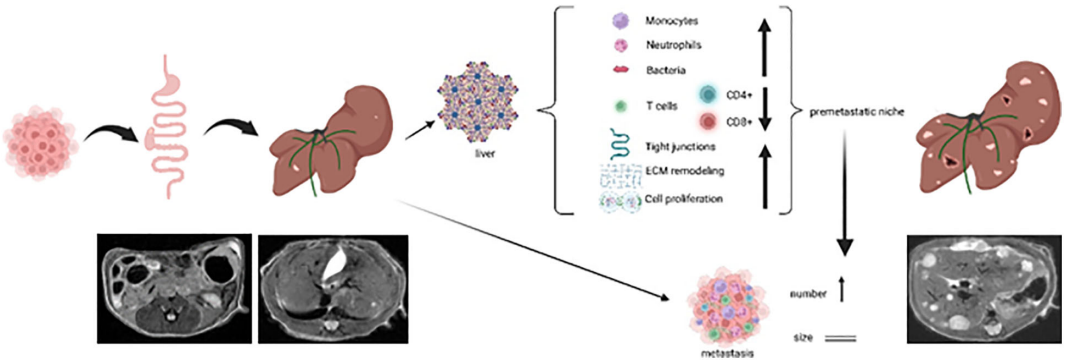
10.3389/fimmu.2024.1388272

tight junctions, resulting in the formation of a premetastatic niche, thus facilitating metastatic seeding.

Conclusions: Regenerative pathways following pHx accelerate colorectal metastasis to the liver by priming a premetastatic niche.

KEYWORDS

colorectal cancer, liver metastasis, partial hepatectomy, premetastatic niche, tight junctions



GRAPHICAL ABSTRACT

1 Introduction

Colorectal cancer (CRC) ranks second among the cancer-associated deaths worldwide (1). While early CRC is associated with a rather good prognosis after tumor resection, distant metastasis is an interdisciplinary challenge and reduces 5-year-survival (5-ys) to only 11% (2). The liver is the most frequent and clinically relevant site of metastasis. In cases of isolated liver metastasis (LM), complete resection of hepatic metastases in combination with adjuvant chemotherapy can raise the 5-ys to 35.5%, with even long-term survivors (3). These results have led to more rigorous surgical approaches in resecting LM, even though complete (R0) resection shows a relapse of disease in up to 60% of patients, with the liver as the most probable site of recurrence (4, 5). Along with the regenerative capacity of the liver, this leads to an increasing number of patients with stage IV CRC undergoing repetitive surgical liver metastasectomies (6). The regeneration of the liver after partial hepatectomy (pHx) and the underlying molecular mechanisms have been studied extensively, revealing that IL-6 (7) and multiple growth factors (TNFα, TGFβ, EGF and VEGF) are key regulators of regeneration and proliferation in the residual liver (8, 9). All of these, as well as many downstream targets (e.g. β-Catenin, Stat3), have been linked to a generally unfavorable prognosis in cancer patients. IL-6 and the above-mentioned growth factors have also been described in the context of the premetastatic niche, a concept that describes tissue alterations facilitating the engraftment of circulating tumor cells in the target organ, thus leading to successful implantation of metastases (10, 11). This raises the question of the effects of pHx on metastatic disease, which has been addressed in several animal studies. The published studies rely on animal models of CRC liver metastasis, in which hematogenous seeding is achieved via portal vein or splenic injection. Therefore, these models are rather artificial and exclude the crucial influence of

Abbreviations: 5-ys, 5 year survival; APTAK, murine colorectal cancer organoid organoids deficient for APC, Trp53 and Tgfbr2 and display a Kras gain of function mutation (G12D mutant) together with a constitutively activated Akt1; CD, cluster of differentiation; cm, centimeter; CRC, colorectal cancer; Ctrl, control; DEG, differentially expressed genes; DNA, deoxyribonucleic acid; EMT, epithelial-to-mesenchymal transition; FACS, fluorescent activated cell sorting; Figure, Figure; g, gram; HE, hematoxylin/eosin; IHC, immunohistochemistry; i.p., intraperitoneal; LM, liver metastasis; MDSC, myeloid derived suppressor cells; mm, millimeter; MRI, magnetic resonance imaging; µm, micrometer; µl, microliter; pHx, partial hepatectomy; PMN, premetastatic niche; PO, preoperative; POD, postoperative day; qPCR, quantitative Real Time polymerase chain reaction; RNA, ribonucleic acid; ROI, region of interest; Suppl., supplementary; TJ, tight junction; UICC, union for international cancer control; VEGF, vascular endothelial growth factor.

the microenvironment of the primary tumor on CRC metastasis as well as the significant changes that cancer cells undergo before entering the bloodstream (e.g. epithelial-mesenchymal transition (EMT)) (12–15). As the liver is often the tumor manifestation defining the patients's prognosis, in several cases of synchronous metastasis of CRC, resection of LM is performed prior to the resection of the primary tumor. This liver-first approach urges clinicians to understand the effects of pHx in the presence of the primary tumor. To analyze the missing aspects, we developed a reproducible mouse model of orthograde colorectal liver metastasis and characterized the impact of partial hepatectomy on the immunological compartments in primary CRC, LM and healthy liver, and on tumor progression in depth.

2 Methods

2.1 Organoid culture

APTAK organoids were kindly gifted by Florian Greten, Georg Speyer Haus, Frankfurt. These cells are murine colorectal carcinoma cells holding the following mutational features: Deletions in the *Apc*-, *Trp53*- and *Tgfbr2*-gene, a myristoylated Akt-1 with constitutively activated signaling and a $Kras^{G12D}$-mutation (16). The APTAK organoids were maintained in Advanced DMEM-F12 (Gibco/Thermo Fisher Scientific, Waltham, MA, USA) supplemented with penicillin (100 U/ml)/streptomycin (100 µg/ml) (Gibco/Thermo Fisher Scientific), HEPES 10 mmol/L (Invitrogen/Thermo Fisher Scientific), Glutamax 2 mM (Invitrogen/Thermo Fisher Scientific), N2 1× (Gibco/Thermo Fisher Scientific), B27 1× (Gibco/Thermo Fisher Scientific), and N-acetylcysteine 1 mmol/L (Sigma-Aldrich, St. Louis, MO, USA) and supplemented with hygromycin (200 µg/ml, Invitrogen/Thermo Fisher Scientific) and puromycin (2 µg/ml, InvivoGen, San Diego, CA, USA) (hereafter referred to as basal medium). The organoids were split every 3–5 days at a 1:10 ratio and cryoconserved for long-term storage.

2.2 Animal studies

All animal studies were performed using 8–12 weeks old C57Bl6/J-mice (purchased from Charles River, Wilmington, MA, USA) at the pathogen-free barrier facility of the CEMT, University Medical Center Freiburg. The experiments were planned and carried out in accordance with the institutional guidelines and all experiments were approved by the regional board (Regierungspräsidium Freiburg, G21/001).

2.3 Orthotopic organoid transplantation mouse model

We adapted the subserosal orthotopic organoid implantation technique described by Fumagalli et al. (17). APTAK organoids cultured in Cultrex RGF basement membrane extract (BME) Type 2 (R&D Systems, Minneapolis, MN, USA) were dissociated into single cells by mechanical disruption and washed with cold PBS. After determining the cell number with the cell counter TC20 (BioRad, Hercules, CA, USA), the appropriate cell number was resuspended in collagen I/5x neutralization buffer (vol/vol-ratio 1:4), and collagen domes of 100.000 cells/10 µl were plated on a 6-well plate. After 30 min polymerization at 37°C, basal medium was added and cells were incubated over night until implantation. Mice analgesia was performed with intraperitoneal (i.p.) injection of 0.1 mg/kg bodyweight (BW) buprenorphine (Temgesic, Schering-Plough, Kenilworth, NJ, USA). Anesthesia was induced by 2.5 Vol % Isoflurane (Isoflurane Piramal, Piramal, Mumbai, India) with the SomnoSuite® Low-Flow Anesthesia System (Kent Scientific Corporation, Torrington, CT, USA). The unconscious mice were positioned on a heating pad with all legs fixed and the abdomen was shaved while anesthesia was maintained by continuous application of isoflurane via mouthpiece. After disinfection of the skin, a median laparotomy of approximately 1 cm was performed on the lower abdomen. The cecum was mobilized using two cotton swabs and placed on a wet gauze. Under the microscope, a 2 mm incision of the serosal layer was made and a deep subserosal pocket was created in which the organoid-collagen-graft was fully placed. After covering the graft with the serosal layer, an anti-adhesion layer (Seprafilm, Baxter, Deerfield, IL, USA) was placed on top. The cecum was then replaced in the abdominal cavity and the abdominal wall and skin were closed in two layers using 6–0 Vicryl (Ethicon/Johnson&Johnson, New Brunswick, NJ, USA) suture. The duration of the surgical procedure was approximately 10–15 minutes.

2.4 Magnetic resonance imaging

MR imaging was performed using a 9.4 tesla small bore animal scanner (BioSpec 94/21, Bruker Biospin, Karlsruhe Germany) and a dedicated mouse quadrature-resonator (Bruker). The mice were anesthetized under spontaneous breathing conditions using Isoflurane. Heart and respiration rates were continuously monitored and maintained at a constant level. Gating was used to reduce motion and blood flow artifacts during the scan. The MRI protocol consisted of a localizer and a T2-weighted spin echo RARE (Rapid Acquisition with Relaxation Enhancement) sequence. This sequence was performed to delineate the tumor and eventual metastasis from the surrounding healthy tissue. The RARE sequence in axial orientation featured a field-of-view (FOV) of 28 mm (1), a matrix size of 280 x 280 pixels, and an in-plane resolution of 100 x 100 µm (1). The slice thickness was 0.75 mm (TR/TEeff/FA: 300 ms/36 ms/180°). The number of slices was adjusted to the measured volume (on average 30) to ensure complete coverage of the abdomen. The Bruker ParaVision 6.0.1 software was used for imaging and images were analyzed using the NORA software supplied by the Medical Center of the University of Freiburg. The volumes of all hepatic lobes and metastases were assessed individually by manually marking the respective lobes/LMs as regions of interest (ROIs) in each section.

2.5 Ultrasound

During isoflurane anesthesia mice were placed on a heating pad and the abdomen was shaved. Prewarmed ultrasound gel was applied to the abdomen and a VEVO 3100 (Fujifilm/VisualSonics, Toronto, Canada) ultrasound together with a small animal transducer was used for ultrasound imaging.

2.6 Partial hepatectomy

For distribution among the control-, SHAM-, and pHx-groups, we assessed the preoperative hepatic tumor load using MRI. Animals displaying an approximately similar number and volume of LM in the imaging were allocated equally among the different protocols to reduce the influence of cage-specific phenotypes. After general analgesia and anesthesia with buprenorphine and isoflurane as described above, mice were shaved and placed on a heating pad. After disinfection, a median laparotomy of approximately 2 cm, starting at the xiphoid, was performed and retractors were placed on both sides of the abdominal wall and under the xiphoid. The falciforme ligament and the membrane between the medial and left hepatic lobes were dissected. A 3–0 Vicryl (Ethicon/Johnson&Johnson) suture was placed around the base of the medial lobe and tightened with 3 knots, after which the ischemic lobe was cut approximately 0.1 cm distal to the suture (Supplementary Figure 1A). The resected lobe was placed in cooled PBS Buffer on ice until further analysis. The abdominal cavity was flushed with prewarmed saline, and the abdominal wall and skin were closed using 6–0 Vicryl (Ethicon/Johnson&Johnson) stitches. The pHx procedure took approximately 15 min. SHAM mice underwent laparotomy, including dissection of the falciforme ligament and the membrane between the medial and left lobes without resection of the lobe. Control animals received general anesthesia without any surgical procedures.

2.7 Tumor dissociation

Animals were euthanized by cervical dislocation. Subsequently, the abdomen was opened and each lobe of the liver was resected directly at the vena cava. The lobes were weighed and all visible liver metastases were dissected while the organ was sliced. The entire cecum was resected and the tumor tissue was separated from the healthy intestine. We collected samples for RNA isolation (stored in RNAprotect buffer (Qiagen, Netherlands)) and for protein isolation from all tissues mentioned. Healthy liver tissue was minced and dissociated using the Liver Dissociation Kit, mouse (Miltenyi Biotec, Bergisch Gladbach, Germany) according to the manufacturer's protocol. The primary tumor and LM were minced into <1 mm pieces and dissected using the Tumor Dissociation Kit, mouse (Miltenyi Biotec) according to the manufacturer's instructions. The single cell suspension was filtered through a 100 µm cell strainer and ACK lysis buffer (Gibco/Thermo Fisher Scientific) was added to lyse erythrocytes during a 1.5 minutes incubation.

2.8 Flow cytometry

Cells were transferred to 100 µl FACS buffer (PBS + 0,5% BSA), incubated with TruStain FcX PLUS (anti-mouse CD16/32) antibody (BioLegend, San Diego, CA, USA) for 15 min and then stained with the respective fluorescent antibodies for 60 min. Cells were then washed with FACS buffer (for extracellular staining) and fixed with 1x Fixation/Permeabilization buffer for 60 min. For intracellular staining, we used the eBioscience™ Foxp3/Transcription Factor Staining Buffer Set (Invitrogen/Thermo Fisher Scientific) according to the manufacturer's instructions. All FACS antibodies used were supplied by BioLegend and used undiluted with 1 µl/100 µl cell suspension. FACS was performed using Beckman Coulter Gallios (Beckman Coulter, Brea, CA, USA) or BD LSRFortessa (Becton Dickinson, Franklin Lakes, NJ, USA). Data were analyzed using Kaluza Software (Beckman Coulter). Cellular aggregates were excluded using SSC-W.

2.9 T cell stimulation

Equal amounts of single cells from the tumor/liver dissociation were seeded in RPMI-Medium (+ 1% Pen/Strep + 1% HEPES + 5 µl beta-mercaptoethanol) on a 12-well plate overnight. The cells were then stimulated by adding Cell Activation Cocktail (BioLegend) for 3 hours, followed by addition of Brefeldin A (BioLegend) for 2 hours. The cells were then harvested and stained for FACS analysis, as described above.

2.10 RNA isolation and cDNA synthesis

Tissue samples for RNA isolation were stored in RNAprotect Buffer. The tissue was shredded in 350 µl RLT buffer (Qiagen, Venlo, Netherlands) + 1% beta-mercaptoethanol. Further RNA isolation was carried out using the RNeasy Mini Kit (Qiagen) according to the manufacturer's instructions. RNA concentrations were measured using a NanoDrop™ spectrophotometer (Thermo Fisher Scientific). For cDNA synthesis RNA was transcribed using ProtoScript II First Strand cDNA Synthesis Kit (New England Biolabs, Ipswich, MA USA) according to the manufacturer's instructions. cDNA was finally diluted to 3 ng/µl for qPCR experiments.

2.11 DNA isolation

For quantification of bacterial DNA, we isolated DNA from tissue samples using the DNeasy Blood & Tissue Kit (Qiagen) according to the manufacturer's instructions, and concentrations were assessed using a NanoDrop™ spectrophotometer (Thermo Fisher Scientific).

2.12 Quantitative real-time PCR

Quantitative Real-Time PCR was performed using QuantiTect SYBR Green RT PCR mastermix (Qiagen) with 7.5 ng template cDNA and 5 pmol of each primer (purchased from Eurofins Genomics, Ebersberg, Germany; primer sequences supplied the supplements). qPCR was carried out on a Roche LightCycler 480 (Roche, Basel, Switzerland) with each sample-gene combination in triplicates. The protocol consisted of a 10 min activation step at 95°C followed by 50 cycles of 45 s amplification at 60°C and inactivation at 95°C for 15 s. 18S was used as a housekeeping gene, Cp values were calculated using the LightCycler480 software (Roche), and the relative expression of target genes was calculated by comparative method after normalization to 18S-expression.

2.13 Bacterial 16S qPCR

In order to quantify bacterial infiltration, we performed qPCR with amplification of the bacterial V6 region using five different primers (see Supplements). Each sample was measured in triplicates using the QuantiFast SYBR® Green PCR Kit (Qiagen). 100 ng DNA was mixed with 500 nM primers. By diluting the DNA of *Bifidobacterium actinocoloniiforme* (DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, DSM22766) in 10-fold series we generated a standard curve using the Threshold cycle (Ct) values. To quantify the sample bacterial DNA, we correlated the average Ct-values to the standard curve of log values from *the Bifidobacterium actinocoloniforme*.

2.14 Bulk RNA sequencing

RNA sequencing was performed at Genewiz, Germany, using the standard Illumina protocol to create raw sequence files (.fastq files). Poly(A) mRNA was used to prepare cDNA libraries, which were then sequenced as 2x 150 bp paired end using the Illumina NovaSeq instrument (Illumina, San Diego, CA, USA).

2.15 RNA seq analysis

Raw sequencing files were uploaded to the galaxy web platform (https://usegalaxy.eu) (18) and quality was assessed using FASTQC. Owing to good quality and no adaptor content, trimming was not necessary. Data were mapped to the murine reference genome (GRCm39) provided by GENCODE (www.gencodegenes.org, downloaded September 2021) using the STAR aligner (19) in standard settings for paired sequencing data. Reads were assigned to counts using featureCounts software (20) and the gene annotations also provided by GENCODEs (downloaded September 2021). Paired-end settings were used for featureCounts software, and a quality score of >10 was required for counting. Data were imported in R 4.0.2 (https://www.r-project.org), and differentially expressed gene analyses were conducted using DESeq2 (21). A batch effect was removed using the limma:: removeBatchEffect() function (22). Differentially expressed genes were defined as padj <0.05 and abs(log2 FC) >1. The Ensembl gene ID was converted to MGI symbols using the biomaRt package (23). The fgsea package (24) conducted Gene Set Enrichment Analysis (GSEA) by ranking all genes with at least >10 counts according to the log2 FC, which were previously shrunken by the apeglm logarithm (25) before. Gene sets were accessed from MsigDB (26) and downloaded on the 26th of May 2023. For visualization, ggplot2 (27), ggraph and ComplexHeatmaps (28) were used.

2.16 Protein isolation

Tissue samples were shredded in RIPA buffer containing phosphatase and proteinase inhibitors (Phosstop (Roche), protease inhibitor cocktail, sodium orthovanadate, and PMSF (Santa Cruz, Santa Cruz, CA, USA) on ice. Three cycles of freezing and thawing were applied using liquid nitrogen, and the suspension was centrifuged at maximum speed for 10 min. The supernatant containing the protein lysate was transferred to a new tube. Protein concentration was measured using a Pierce BCA-Kit (Thermo Fisher Scientific) and an Azure Ao Microplate Reader (Azure Biosystems, Dublin, CA; USA).

2.17 Western blot

Protein samples were aliquoted with 4x Laemmli Buffer (BioRad) and denatured at 95°C for 3 min. An equal amount of protein was loaded on a 12–20% Mini-Protean TGX precast gel (BioRad) together with a color-coded prestained broad range protein ladder (Cell Signaling Technology, Danvers, MA, USA). After SDS-electrophoresis, the proteins were blotted onto a PVDF membrane using the trans-blot turbo transfer system (BioRad) according to the manufacturer's instructions. The membrane was then blocked with 5% BSA/TBST for 60 min at RT and incubated with the respective primary (Anti-S100A8, Anti-MMP9, Anti-Claudin-2, Anti-Occludin, and Anti-ZO-1) and secondary (anti-rabbit IgG) antibodies according to the manufacturer's instructions (a detailed description of the antibodies used is supplied in the Supplements). For detection, the Immobilon Crescendo Western HRP substrate (Merck Millipore, Burlington, MA, USA) was added to the membrane and imaging was carried out using a ChemiDoc BioRad imager (BioRad).

2.18 Immunohistochemistry

Tissue samples were fixed in 4% PFA for 24 hours, dehydrated and embedded in paraffin. Sections of 3 µm were cut, rehydrated, and heat induced epitope retrieval was carried out with citrate or TE-Buffer (Zytomed Systems, Berlin, Germany). Sections were then blocked with 2.5% BSA and avidin-biotin-block (Zytomed Systems) according to the manufacturer's instructions. Sections were then incubated with the primary antibody overnight and biotinylated secondary antibody for 1 h according to the manufacturer's instructions (see a detailed description of the antibodies used in Supplements). Positive staining was visualized using DAB (Zytomed

Systems), and the sections were counterstained with hematoxylin before dehydration and mounting with ROTI® Histokitt (Carl Roth, Karlsruhe, Germany). Slides were digitalized using a Zeiss Axio Scan Z.1 Microscope Slide Scanner (Zeiss, Jena, Germany).

2.19 Immunofluorescence

Slides were treated until secondary antibody incubation as described in the *Immunohistochemistry* section, and then incubated with the Vector® TrueVIEW® Autofluorescence Quenching Kit (Biozol, Eching, Germany) to reduce autofluorescence. After washing, nuclear staining was performed using NucBlue™ Fixed Cell Stain ReadyProbes™ (Thermo Fisher Scientific). Sections were then mounted with VECTASHIELD Vibrance Antifade Mounting Medium (Biozol) and scanned using a Zeiss Axio Scan Z.1 Microscope Slide Scanner (Zeiss).

2.20 Statistics

For statistical analysis, we used a one-way analysis of variance (ANOVA) test with Tukey's *post-hoc* analysis when comparing multiple samples or a two-tailed Students-t-test for two variables. Statistical significance was set at p-values <0.05, and significance levels are represented in the graphic as follows: *** = p<0.001, ** = p<0.01, * = p<0.05, n.s. = not significant. All statistical analyses were performed using GraphPad Prism.

3 Results

3.1 Orthograde CRC metastasis mouse model - implantation of APTAK organoids frequently leads to orthograde liver metastases of CRC

To establish a mouse model of orthograde CRC metastasis we used murine CRC tumor organoids deficient for *Apc*, *Trp53* and *Tgfbr2* and that display a *Kras* gain of function mutation (G12D mutant) together with a constitutively activated Akt1 (hereafter referred to as APTAK organoids) (29). We combined this APTAK mouse model with a partial hepatectomy model to monitor the effect of pHx on the background of orthograde colorectal liver metastasis (Figure 1A). APTAK organoids were surgically implanted under the serosal layer of the distal cecum, leading to carcinomas with luminal contact after 2

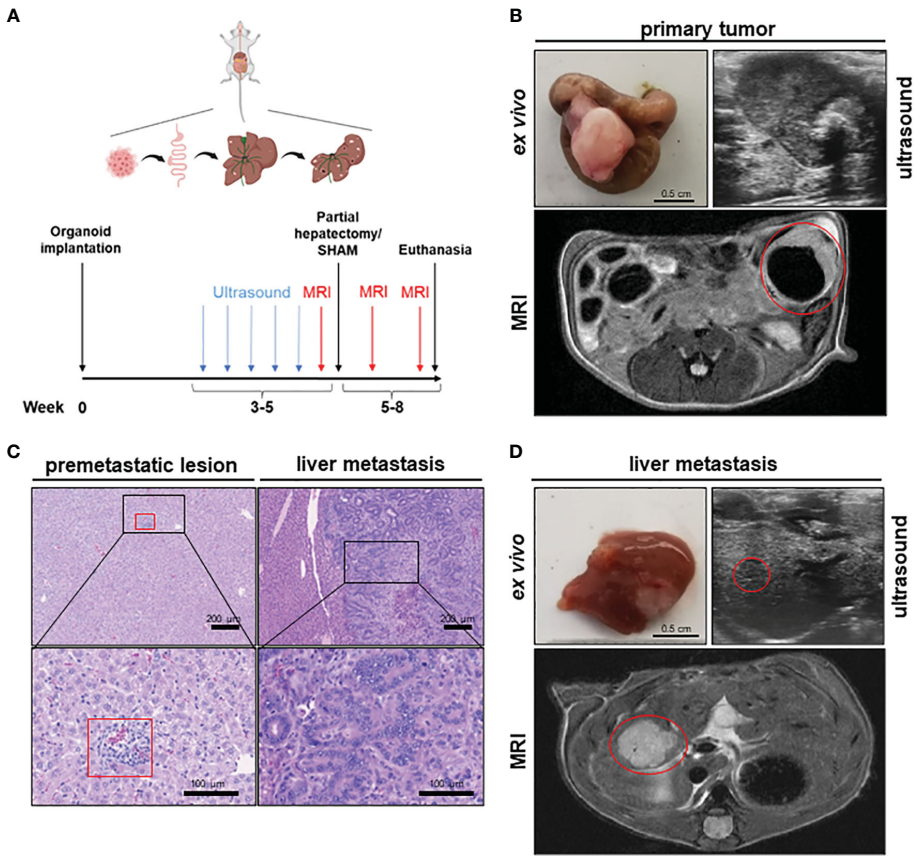


FIGURE 1
A novel mouse model to study the effects of partial hepatectomy in orthotopic metastasized colorectal carcinoma. **(A)** Overview of experimental layout (top) and timeline for procedures (bottom); **(B)** Representative images of primary tumor ex vivo (scale bar = 0.5 cm) and T2-weighted transversal MRI of early primary tumor (red circle) and locally advanced primary tumor in ultrasound; **(C)** Representative HE-staining of liver with premetastatic lesion (red square) and of advanced liver metastasis (LM) (scale bars in left panels = 200 µm and in right panels =100 µm); **(D)** Representative images of liver and LM ex vivo (scale bar = 0.5 cm) and of T2-hyperintense LM (red circle) in the medial hepatic lobe (max. diameter 7 mm) in transversal T2-weighted MRI and in ultrasound of the same liver metastasis (red circle).

weeks (Figures 1B–D). These tumors caused cellular aggregates that appeared in the liver after 3–4 weeks (microscopically detectable in hematoxylin/eosin (HE)-sections) (Figure 1C) and macroscopically visible metastases after 5–6 weeks (Figures 1C, D). To further characterize the early-appearing cellular accumulations in the liver, we performed an immunohistochemistry (IHC) of liver sections. While the liver metastases and primary tumors displayed plenty of EpCam-positive cells, we did not find any EpCam-positive epithelial cells in the microscopically visible perivascular cellular aggregates (Supplementary Figure 1A). Hence, we adapted the term premetastatic lesions.

To objectify the metastatic load in the liver, magnetic resonance imaging (MRI) was performed prior to liver resection. Detectable liver metastases in MRI appeared after 4–5 weeks as T2-hypointense lesions (Figure 1D), with the smallest distinguishable measuring 0.2 mm in diameter. To measure the time to metastasis and general tumor burden, mice were screened weekly for detectable liver metastases with ultrasound starting 3 weeks after implantation. In comparison to MRI, detection of LM in ultrasound was delayed with visible lesions starting at >1 mm in diameter (Figure 1D). After resection of the medial lobe (Supplementary Figure 1B), mice were screened again for metastases on postoperative day (POD) 7 and 14 in MRI. The animals were then euthanized and their organs were harvested for further analysis. Therefore, we set up a valuable orthograde CRLM mouse model suitable for analyzing pHx, which resembles the human situation.

3.2 Medial lobe resection induces significant hypertrophy of the residual liver

In order to verify the hypertrophic effect on the residual liver and to evaluate the effect of pHx on the metastatic load we performed volumetric analysis of the MR images prior to surgery and 7 and 14 days postoperatively (Figure 2A). Following pHx, the mice developed significant hypertrophy of ~50% of the residual right and left lobes compared to control and SHAM-operated mice both in weight (Figure 2B) and volume measured in MRI (each $p<0.001$) (Figure 2C, Supplementary Figure 1C). The hypertrophy was already seen in MRI on POD7 but further increased until POD14. The total volume of healthy liver tissue in pHx mice on POD14 was comparable to that in both control groups (Supplementary Figure 1D). We could conclude that 1/3 partial hepatectomy in our model is sufficient to generate significant hypertrophy, consistent with the effects of a major hepatectomy in humans.

3.3 Partial hepatectomy increases *de-novo* metastasis without affecting growth of present metastasis

As pHx has been linked to a potentially prometastatic effect in injection models of colorectal liver metastasis before (12–14), we were curious about the impact of resection in our model of orthograde metastasis. Regarding the metastatic burden in the animals, we found no difference in the total metastatic volume within the liver on POD7 between control, SHAM, and pHx mice. On POD14, on the other hand, an increase in the metastatic volume in the residual right and left lobes was observed in the hepatectomy group compared to that in both control groups (Figure 2D, Supplementary Figure 1E). The same effect was observed when the metastases in the medial lobe of the control groups were included in the analysis (Supplementary Figure 1G). The increase in total metastatic volume was explained by an increase in the total number of metastases rather than by accelerated growth of the present metastases, and the number of metastases was elevated after pHx compared to the two other groups, analogous to the total metastatic volume (Figure 2E, Supplementary Figure 1F). Regarding the size of each liver metastasis individually over the postoperative period, we found no difference in the volume increase between pHx, SHAM, and control mice (Figure 2F). Consistently, at transcriptional level, we found a significant induction of cell proliferation represented by *Ki67*-expression within the healthy liver after pHx compared to SHAM and control mice, both in quantitative real-time polymerase chain reaction (qPCR) and immunohistochemistry (IHC) with $p<0.05$ (Figures 2G, H). However, proliferation in liver metastases was not altered following hepatectomy (Figures 2I, J). The detected general decrease in *Ki67*-expression in all three models (Figure 2J) compared to preoperative levels can be explained by the increase in necrotic tissue in larger metastases over time. In summary, pHx increased the number of *de novo* metastases without affecting the proliferation and growth of each metastasis. Therefore, we assumed that one of the major implications of pHx is priming of the liver for *de novo* metastatic implantation.

3.4 Partial hepatectomy induces an inflammatory phenotype in liver and LM

It is well established that inflammation and the tumor microenvironment (TME) heavily influence CRC carcinogenesis and metastasis (30), therefore we analyzed the effect of pHX on the TME composition of primary tumors (PT) and liver metastases (LM), and immune cell compartments in healthy liver tissues. After generating single-cell suspensions of all three tissues, immune cell compositions were analyzed using fluorescence-activated cell sorting (FACS). Regarding innate immune cells, we found an increased number of neutrophils both in healthy livers and metastases after pHx, as well as a moderate increase in monocyte count (Figure 3A, Supplementary Figure 2A). Comparing the abundance of these cell types at different time points after resection revealed that the accumulation in the liver did not occur before POD5 (Figure 3B). These changes were not accompanied by a general increase in neutrophil or monocyte abundance in the peripheral blood (Supplementary Figure 2A). As surgical stress has been linked to an increase in myeloid-derived suppressor cells (MDSC) in tumors, we characterized the MDSC subsets in the liver and peripheral blood in depth. We did not observe a significant difference in the abundance of both polymorphonuclear (PMN-MDSCs) and monocytic MDSCs (M-MDSCs) in either tissue after pHx. However, a change in the PMN-MDSC subtypes towards a monocytic phenotype [described by Veglia et al. (31)] was observed: pHx caused an increase in tumor-

10.3389/fimmu.2024.1388272

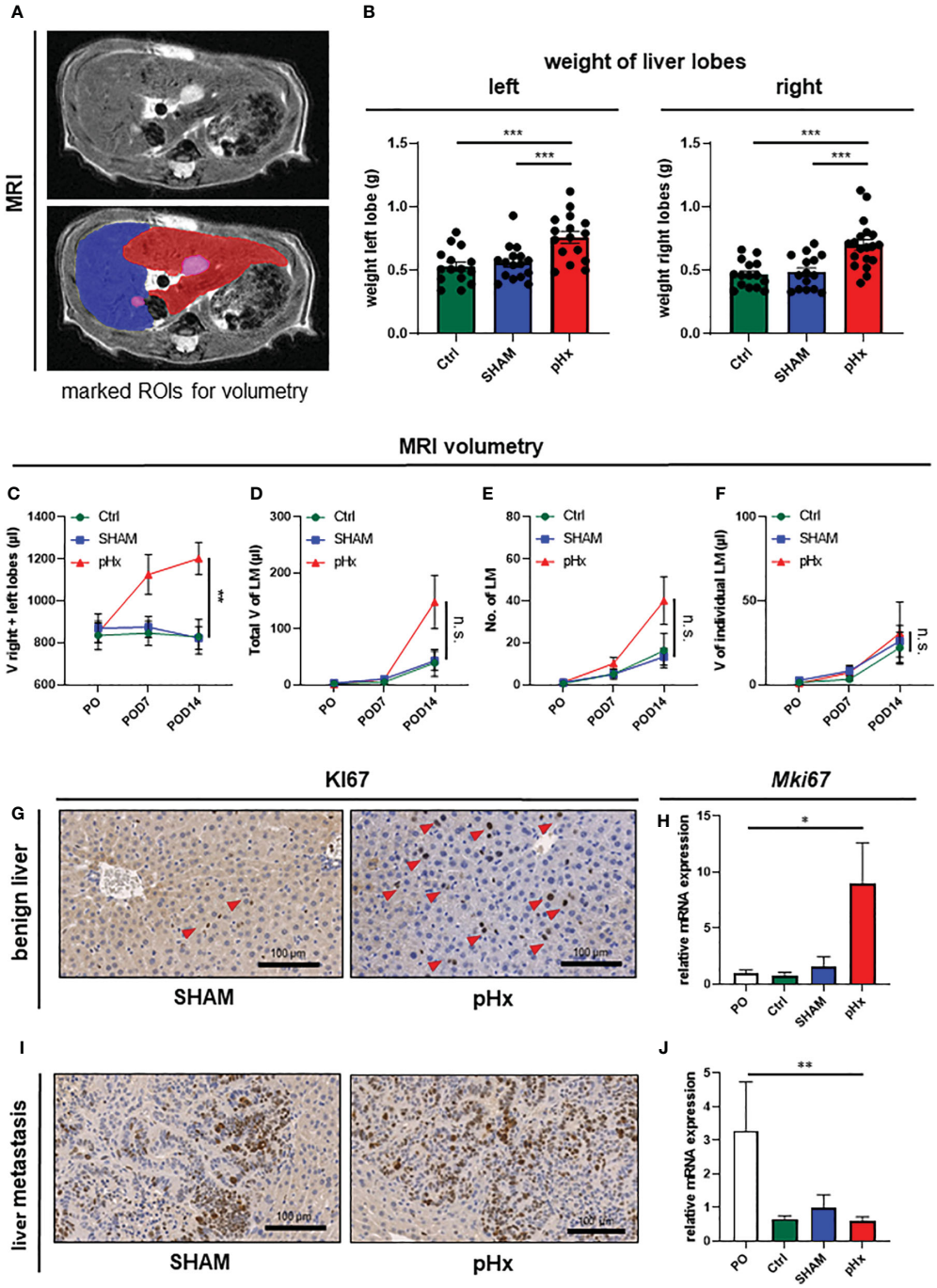


FIGURE 2
Medial lobe hepatectomy induces hypertrophy of the residual liver and increases overall metastatic volume and number without affecting the individual growth of each metastasis. **(A)** Representative MRI of liver and LM following pHx (POD7) in native T2-weighted MRI (top) and with marked regions of interest (ROI) (bottom): blue: right upper hepatic lobe, red: left hepatic lobe, pink: LM; **(B)** Boxplots showing the weight in grams of left and right liver lobes after euthanasia of Ctrl group (n=15/15), SHAM group (n=16/15) and pHx group (n=16/19); **(C)** Time course analysis of the combined volume of healthy left and right lobes in µl measured in MRI of Ctrl (n=5), SHAM (n=6) and pHx (n=9) group; **(D)** Time course analysis of total volume of liver metastases in left and right lobes in µl measured in MRI for Ctrl (n=7), SHAM (n=15) and pHx (n=19) group; **(E)** Time course analysis of the number of LM in left and right lobes assessed in MRI for Ctrl (n=7)), SHAM (n=14) and pHx (n=15) group; **(F)** Time course analysis of the individual growth in volume of LM in MRI for Ctrl (n=7), SHAM (n=14) and pHx (n=12) group; **(G)** Representative immunohistochemistry of Ki67 of healthy liver following SHAM- and pHx-surgery. Nuclear counterstaining was performed with hematoxylin, red arrows point to Ki67^{+} cells; **(H)** Boxplot representing the relative expression of *MKi67* in healthy liver tissue analyzed by qPCR in PO (n=14), Ctrl (n=4), SHAM (n=10) and pHx (n=12) group; **(I)** Immunohistochemistry of Ki67 of liver metastasis. Nuclear counterstaining was performed with hematoxylin; **(J)** Boxplot representing the relative expression of *Mki67* in liver metastasis analyzed by qPCR for PO (n=5), Ctrl (n=3), SHAM (n=8) and pHx (n=14) group. (Scale bars = 100 µm, bar plots represent mean ± standard error of the mean (SEM), p-values calculated via one-way ANOVA Tukey test, * = p<0.05, **, p <= 0.01 *** = p<0.001).

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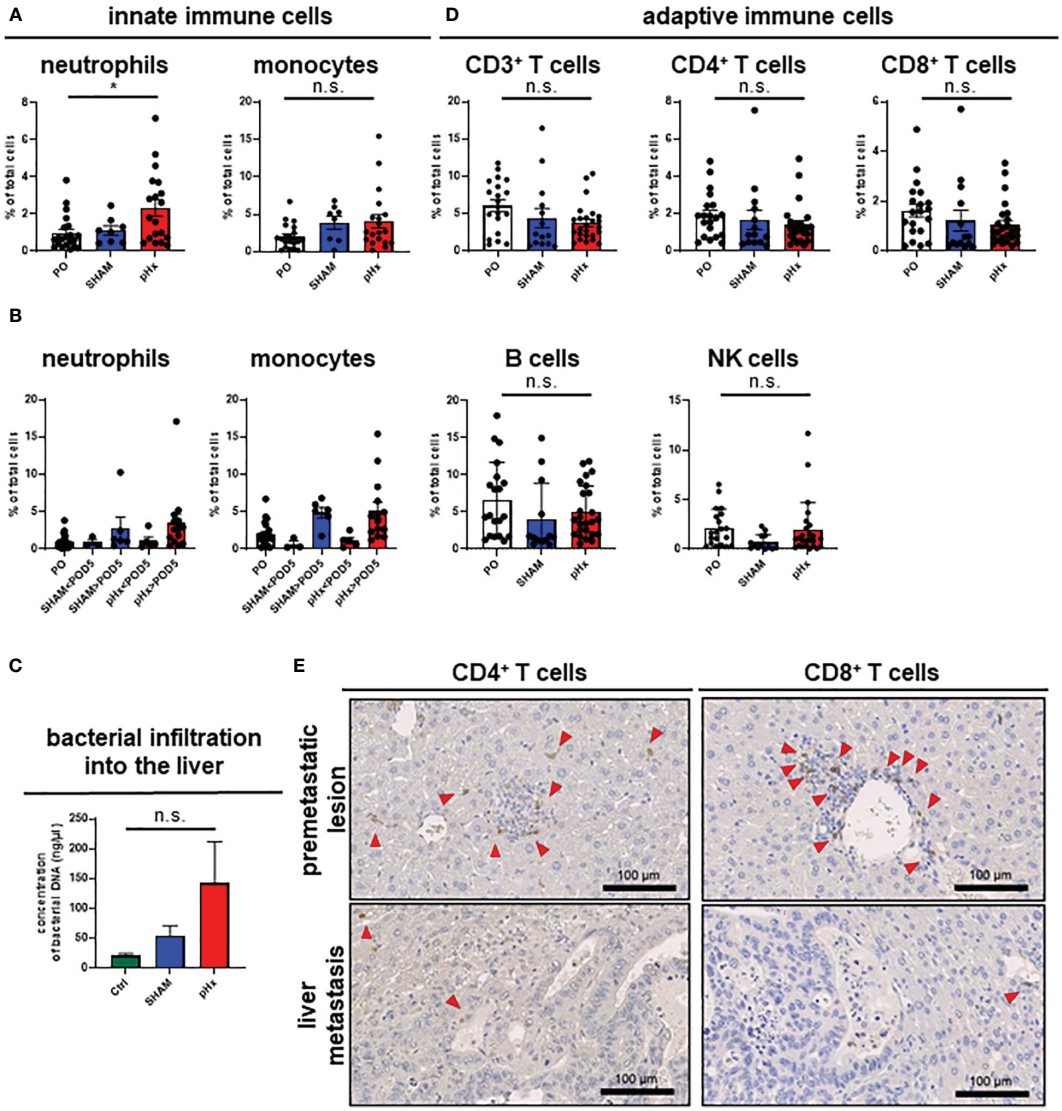

FIGURE 3
pHx induces neutrophil accumulation and increases bacterial abundance in the residual liver. **(A)** Flow cytometric analysis with staining of different populations of innate immune cells in healthy liver tissue (neutrophils: CD45+/CD11b+/Ly6G+/CD64-, monocytes: $CD45^+/CD11b^+/Ly6G^-/CD64^+$) for PO (n=21), SHAM (n=8) and pHx (n=19) group, **(B)** Time course of infiltration of the liver with innate immune cells before POD5 (range POD3–5) and after POD5 (range POD7–14) for PO (n=21), SHAM<POD5 (n=3), SHAM>POD5 (n=6), pHx<POD5 (n=5) and pHx>POD5 (n=14) group; **(C)** Concentration (ng/µl) of bacterial DNA in healthy liver measured with qPCR for Ctrl (n=5), SHAM (n=5) and pHx (n=7) group; **(D)** FACS analysis of different populations of adaptive immune cells in healthy liver tissue following pHx (NK cells: $CD45^+/CD3^-/NK1.1^+$, T cells: $CD45^+/CD3^+/NK1.1^-$, B cells: $CD45^+/CD3^-/B220^+$) for PO (n=20), SHAM (n=14) and pHx (n=25) group; **(E)** Representative immunohistochemistry of the distribution of $CD4^+$ and $CD8^+$ T cells in healthy liver and accumulation in premetastatic lesions (top) with absence in macroscopic metastasis (bottom). Red arrows point to the cells of interest. (Scale bars = 100 µm, bar plots represent mean ± SEM). n.s. non significant.

associated $CD14^{high}$ PMN-MDSCs in the liver, while decreasing $CD14^{low}$ cells (Supplementary Figure 2B). As the microbiome is an important constituent of the TME of CRC and affects CRC pathogenesis (30), we analyzed bacterial infiltration in the liver after pHx. Along with the increased infiltration of myeloid cells, we found an increased presence of bacteria within the liver following pHx (Figure 3C) as analyzed by qPCR, whereas bacterial infiltration of the LM was not altered by pHx (Supplementary Figure 2C). Taken together, pHx induces an inflammatory composition with an elevated abundance of innate immune cells in the residual liver as a delayed effect, which may be supported by increased bacterial infiltration.

3.5 pHx slightly abates T cell abundance with no effect on T cell exhaustion, cytotoxicity, and activation

Having shown that pHx surgery alters innate immune cell responses, we wondered whether pHx also affects adaptive

immunity in CRLM. In our pHx mouse model, we could show that the numbers of cells of the adaptive immune system (T cells, B cells and NK cells) in the liver or LM did not change significantly after the respective surgery. However, a trend towards a decrease in $CD4^+$ and $CD8^+$ T cell abundance in the liver (Figure 3D) and especially in metastases (Supplementary Figure 2D) following pHx was observed in FACS analysis. To further investigate the role of T cells in this metastasis model, we performed IHC staining for $CD4^+$ and $CD8^+$ T cells in liver sections. We found that both $CD4^+$ and $CD8^+$ T cells were scarce in healthy liver tissue, accumulated around premetastatic lesions, and were completely depleted in macrometastases (Figure 3E). However, not only the absolute abundance of adaptive immune cells impacts tumorigenesis and metastasis, but also the function of the adaptive immune cells heavily influences tumor progression. Therefore, we functionally characterized the $CD8^+$ T cells for their functionality in depth. First, we analyzed T cell cytotoxicity, exhaustion, and activation of $CD8^+$ T cells in the liver in the different intervention groups using FACS. While we observed a general increase in exhaustion markers (PD-1, Tcf1) on $CD8^+$ T cells along tumor progression in accordance with the present literature, pHx did not affect the expression of exhaustion markers compared to SHAM or control samples (Supplementary Figure 2E). Furthermore, we do not detect any changes in T cell cytotoxicity (granzyme B) and activation (CD38) after pHx (Supplementary Figure 2E).

3.6 pHx induces a prometastatic transcriptomic program including cell cycle progression, epithelial-mesenchymal transition, angiogenesis and hypoxia in the liver

As the livers of mice undergoing pHx shows veritable changes in the immune cell compartments, we wondered whether these changes lead to an impairment of the initiation of the metastatic process in the livers. To analyze the underlying transcriptional alterations in the healthy livers, we performed bulk RNA sequencing from healthy livers of four PO- and four pHx-mice. In total, 1083 upregulated and 289 downregulated differentially expressed genes (DEGs) were identified comparing the livers of PO and pHx groups after batch effect removal (Figures 4A, B). In order to define metastasis-associated pathways regulated after pHx, we performed Gene Set Enrichment Analysis (GSEA) with Hallmark gene sets, revealing numerous enriched pathways impacting metastasis (Figure 4C), such as the Hallmarks E2F targets and G2M checkpoint. Both gene sets were enriched in the pHx group and encompass important transcripts that regulate cell-cycle progression (Figure 4D). In addition to an increased proliferative activity, we observed an enrichment of genes involved in epithelial-mesenchymal transition (Figure 4C). The most striking enriched gene sets regarding a potential influence on metastatic seeding were the Hallmark terms angiogenesis, hypoxia, and inflammatory response (Figures 4E–G), which are interconnected pathways that potentially mediate the prometastatic effect of the surgical procedure (Figure 4H). Therefore, we showed that pHx may facilitate the efficient seeding of LMs due to a prearrangement of prometastatic factors in the liver.

3.7 Partial hepatectomy induces genes of the premetastatic niche in residual liver tissue enabling *de novo* metastasis

As we have shown that several genes affecting premetastatic niche formation are increased in the transcriptomic analysis of pHx livers, we analyzed the formation of this special metastasis-favoring niche in pHx treated animals on transcriptomic and proteomic level in depth The residual liver following pHx is defined by an increased abundance of inflammatory cells and increased proliferation. Inflammatory tissue has been described to be more susceptible to metastatic seeding (32) and inflammation is an essential component of the premetastatic niche (10). To further investigate the effects of pHx, we focused on pathways that facilitate engraftment of circulating tumor cells in the organ. Several genes that regulate hepatic hypertrophy after liver resection have also been described in the context of the formation of a premetastatic niche in the liver for metastatic tumors (7, 8, 10). By analyzing the transcriptional profile of the healthy liver tissue via qPCR, we found a significant induction of several genes associated with the premetastatic niche in the hepatectomy mice compared to preoperative levels, as well as to control mice (e.g., the inflammatory genes *S100A9* or *IL-6*, growth factors such as *VEGF* and *TGF-β* or *MMPs* as markers of extracellular remodeling) (Figure 5A). These changes in gene expression are specific for partial hepatectomy and not a general effect of surgical trauma, as they were not observed after SHAM surgery (Figure 5A). Several of the described genes can be directly linked to neutrophil invasion, either as they attract neutrophils [e.g. *IL-6* (33) *or TIMP1* (34)], or as a result of neutrophil activity [e.g. *S100A9* (35), *Fibronectin* (36), *LOX* (37), *HIF-1α* (38) *or MMP2/9* (39)]. Transcriptional regulation was confirmed at protein level via western blot, where we could also find an upregulation of representative proteins involved in the premetastatic niche (e.g., S100A8 (interaction partner of S100A9, together forming the heterodimer calprotectin) and MMP9) (Figures 5B, C). Furthermore, the intrahepatic localization of MMP9 and S100A8 was detected by IHC of liver sections, showing an increased presence of both proteins around perivascular premetastatic lesions (Figures 5D, E). Hence, we conclude that prometastatic transcriptional changes along with the inflammatory cellular composition occur in defined sectors within the macroscopically healthy liver and lead together to the formation of premetastatic niches in the liver.

3.8 pHx induces tight junction formation in the liver which may impact tumor cell seeding

One effect of hepatectomy during liver regeneration is an increased formation of tight junctions (TJ) (40). As some members of the zonula occludens proteins are thought to enable

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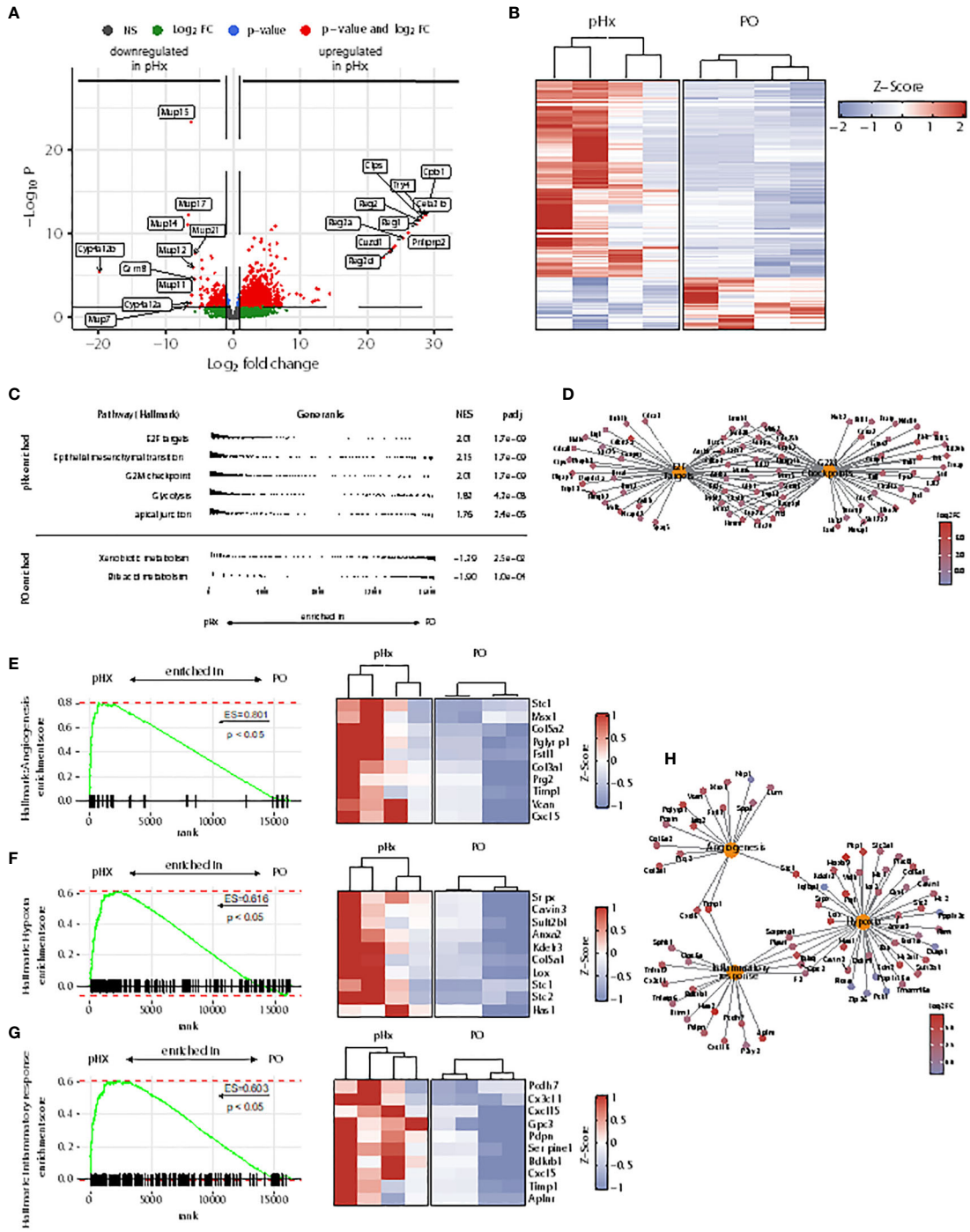

FIGURE 4
Partial hepatectomy is associated with upregulation of gene sets associated with metastasis in the liver. **(A)** Volcano plot of differently expressed genes (DEGs) in RNA sequencing from healthy liver tissue of 4 pHx and 4 PO samples. The 10 DEGs with the highest or lowest log2 fold change were labeled; **(B)** Heatmap from all DEGs with a base count mean of > 10 visualized by Z-scores; **(C)** Overview of 5 most enriched and 2 most depleted hallmark terms in gene set analysis (GSEA) following pHx; **(D)** Cnet plot visualizing all DEGs related to hallmarks E2F targets and G2M checkpoint and their overlap; **(E-G)** GSEA for hallmarks angiogenesis **(E)**, hypoxia **(F)** and inflammatory response **(G)** and heatmap of the respective 10 leading edge genes (right) visualized by Z-scores; **(H)** Cnet plot of DEGs related to hallmarks angiogenesis, hypoxia, and inflammatory response.

intrahepatic extravasation of circulating tumor cells, we analyzed the expression of the genes *Claudin-2* and *-5* as well as *Occludin* and *ZO-1* in liver tissues in this mouse model. We found that *Claudin-2, Claudin-5, Occludin* and *ZO-1* gene expression was increased following pHx compared to PO, Ctrl or SHAM samples in qPCR (Figure 6A) and on proteomic level the expression of the tight junction proteins Claudin-2, Occludin und ZO-1 was elevated following pHx in western blot (Figure 6B). This finding was supported by RNA sequencing data that showed enrichment of the apical junction gene set (Figure 6C). Additionally, we analyzed

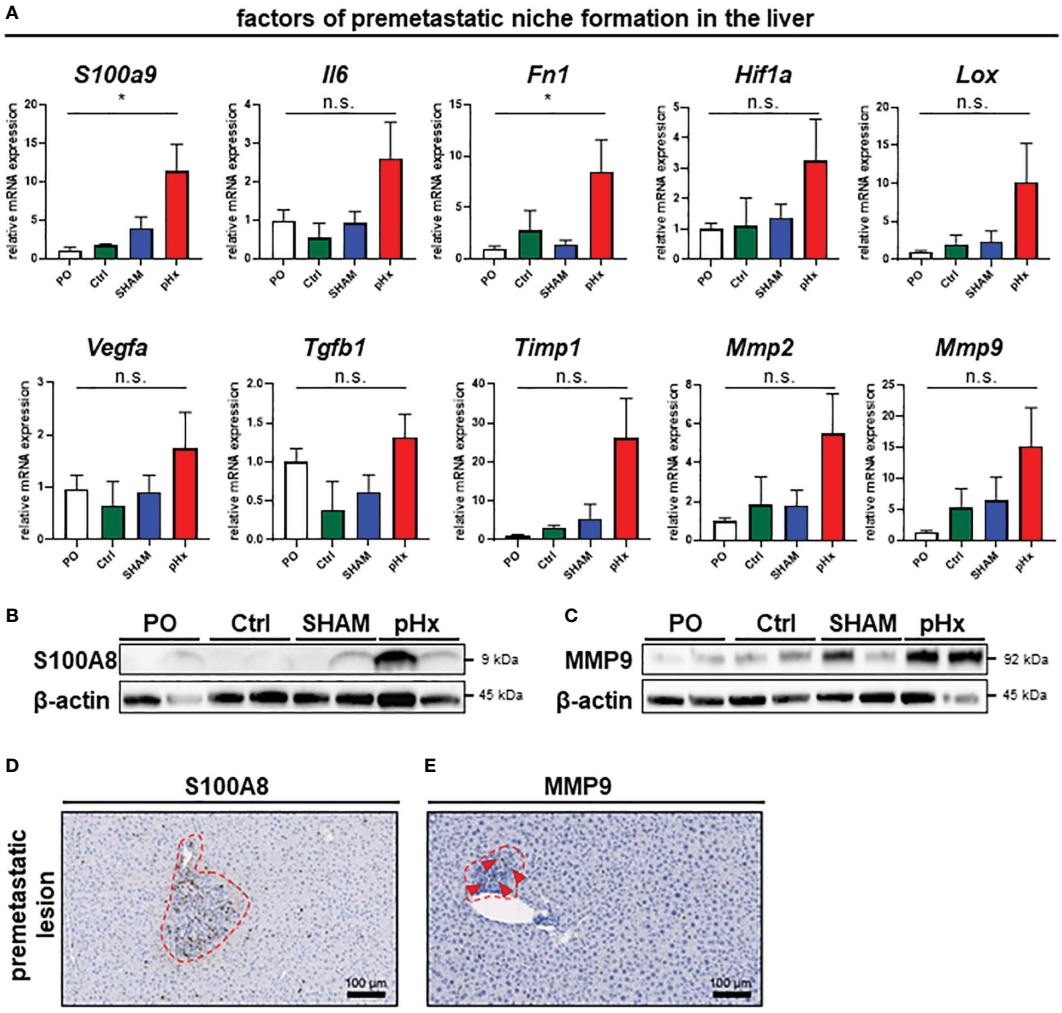

FIGURE 5
Partial hepatectomy induces premetastatic niche (PMN) formation in the liver. **(A)** Relative mRNA levels (normalized on preoperative values) of the PMN-associated genes *S100a9*, *Il6*, *Fn1*, *Hif1a*, *Lox*, *Vegfa*, *Tgfb1*, *Timp1*, *Mmp2* and *Mmp9* in healthy liver tissue analyzed by qPCR for PO (n=26), Ctrl (n=4), SHAM (n=17) and pHx (n=26) groups; **(B, C)** Western Blot analyses of the expression of the premetastatic niche factors S100A8 and MMP9 from healthy liver (top). β-actin was used as loading control; **(D, E)** Representative IHC stainings of liver sections (bottom) of S100A8 and MMP9, red square marking perivascular premetastatic lesions (scale bars = 100 µm). (Bar plots represent mean ± SEM, p-values calculated via one-way ANOVA Tukey test, * = p<0.05, n.s. non significant.

the expression of several TJ genes in primary tumors and healthy intestines, as they are linked to a worsened prognosis in several tumors and have been shown to drive colorectal carcinogenesis and EMT (41). We found that a similar upregulation of Claudin-5, Occludin and ZO-1 was observed in the healthy intestine both on transcriptomic and proteomic level (Figures 6D, E). Furthermore, an upregulation of *Occludin* in primary tumors was detected (Figure 6F). As tight junctions are formed in the interactions of several cell types, we stained proteins using immunofluorescence of sections of primary tumors and attached healthy ceca for intestinal localization. In the healthy intestine, TJ proteins Claudin-2, E-cadherin and ZO-1 were located at the membrane of epithelial cells with emphasis on the luminal side of the crypts (Figure 6G). In tumor tissue, we found TJ proteins with no spatial orientation and partially within the cytoplasm of the cells, indicating depolarization of the cells (Figure 6G), in accordance with the literature.

3.9 *De novo* metastasis in pHx could be primarily attributed to premetastatic niche formation in the liver as pHx has no impact on epithelial-mesenchymal transition in primary tumors

Since we observed an increase in *de novo* metastases in our model, we were curious if pHx has an impact on the metastatic potential in the primary tumor. While we detected a trend towards increased *Ki67*-expression in primary tumors (Supplementary Figures 3A, B), the expression of genes involved in EMT revealed no significant changes in the expression of *Ctnnb1*, *Vimentin*, *Snai1* and *2* or *Zeb1* (Supplementary Figure 3C). Additionally, the expression of EMT genes was measured in liver metastases. The expression levels of *Ctnnb1*, *Snai1* and *2* or *Cdh1* were not influenced by pHx (Supplementary Figure 3D).

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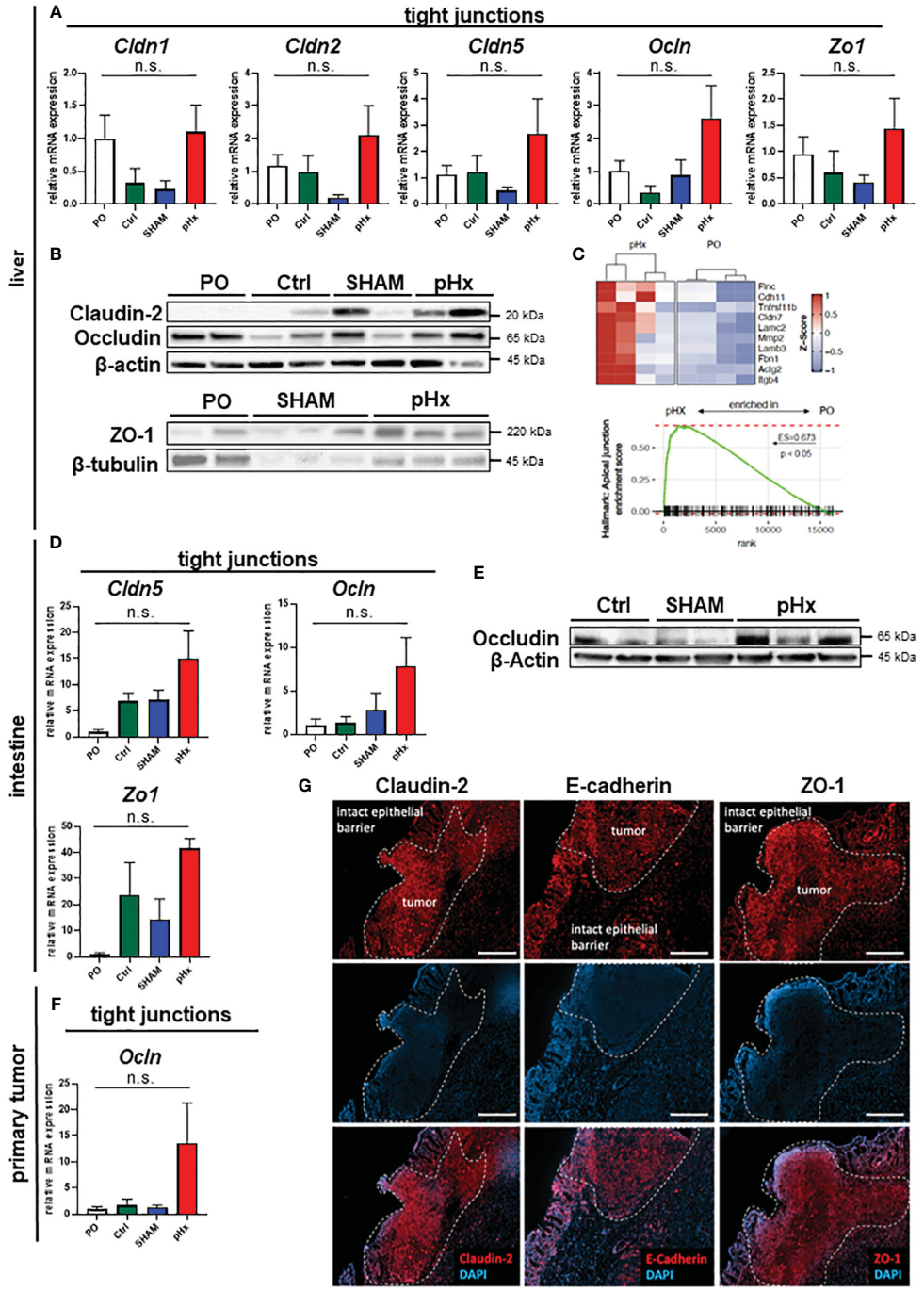

FIGURE 6
pHx induces tight junction formation in the liver which may impact tumor cell seeding. **(A)** Relative expression of tight junction (TJ) genes *Cldn1*, *Cldn2*, *Cldn5*, *Ocln* and *Zo1* in healthy liver analyzed with qPCR for PO (n=17), Ctrl (n=4), SHAM (n=12) and pHx (n=20) groups; **(B)** Western Blot of selected tight junction proteins Claudin2, Occludin and ZO-1 in the liver. β-actin and β-tubulin were used as loading control; **(C)** Gene Set Enrichment Analysis of bulk RNA sequencing from healthy livers for the hallmark apical junction with heatmap of the 10 leading genes involved according to Z-scores; **(D)** Relative gene expression of *Cldn5*, *Ocln* and *Zo1* in healthy cecum analyzed with qPCR for PO (n=4), Ctrl (n=4), SHAM (n=4) and pHx (n=6) groups; **(E)** Representative Western Blot analysis of protein expression of Occludin in the cecum. β-actin was used as loading control; **(F)** Relative expression of *Ocln* in primary tumors analyzed with qPCR for PO (n=9), Ctrl (n=4), SHAM (n=7) and pHx (n=17) groups; **(G)** Immunofluorescence stainings of tight junction proteins (Claudin-2, E-cadherin, and ZO-1) in healthy epithelium and primary CRC (scale bar = 100 µm). Counterstaining of the nuclei was performed with DAPI. The white dashed lines mark the border between intact and benign epithelial cells and the primary tumors. (Bar plots represent mean ± SEM, n.s. non significant).

In summary, we have demonstrated that pHx causes various changes in the cellular and transcriptional composition of the residual liver in a mouse model of orthograde colorectal liver metastasis that can be recapitulated as inflammation, extracellular remodeling, and tight junction formation. The transformation in the residual liver favors further metastatic seeding, while the impact on the primary tumor seems to be insignificant, and ultimately results in an elevated metastatic burden following pHx (see Graphical Abstract).

4 Discussion

In this study we present a novel immuno-competent model for studying orthograde CRC liver metastasis and the influence of surgery on tumor progression. Several studies have described the potential negative effects of surgery on different tumors. Tsuchiya et al. found an acceleration of metastatic growth of intravenously injected CRC cells after surgery (13) and Harun et al. found an increased growth of liver metastasis following partial hepatectomy after splenic injection of CRC cells (14). In a study by Brandt et al. (12) tumor cells were directly injected into the remaining liver following different hepatectomies, and they described increased metastatic load depending on the extent of resection. All studies were based on tumor cell injection, excluding important features of the full path of regular *in vivo* metastatic disease. Solid tumors are characterized not only by the primary malignant cells, but especially in CRC the tumor microenvironment and microbiome have a major impact on tumor progression and metastasis. Therefore, an injection model of tumor cells cannot mimic the course of disease in humans. Studying orthotopic metastatic CRC in rodents is difficult because most models do not develop metastasis or are limited by luminal obstruction of the primary tumor. The combination of subserosal organoid implantation into the cecal wall with the aggressive mutational features of the APTAK-organoids offers the possibility to study the influence of pHx in a model of orthograde metastasis, together with immunological effects that highly resemble the human situation in CRC patients. On molecular level the APTAK tumors resemble the CMS4 subtype of human CRC patients (16).

Assessment of the intrahepatic tumor load *in* and *ex vivo* is difficult as the macroscopically visible lesions only represent a small part of the overall metastases and histological analyses usually do not include the entire organ. MRI offers the unique possibility of objectifying the metastatic volume in this model (as even small liver metastases are easily distinguishable in imaging) *in vivo* and at several time points. Yet, microscopic metastases cannot be detected in the MRI. In contrast to previously published results, resection of the medial liver lobe did not accelerate the growth of each metastasis, but rather increased *de novo* metastasis, suggesting priming of the residual liver for metastatic seeding.

The concept of the premetastatic niche (PMN) has attracted the attention of oncological research in recent decades. Following the seed and soil hypothesis of tumor metastasis, priming of the target organ by the tumor is regarded as a promising therapeutic approach for preventing metastasis. The niche is defined by extracellular remodeling via MMPs, inflammation with accumulation of neutrophils, macrophages, regulatory T cells, and bone-marrow derived cells (BMDCs), reprogramming of cancer-associated fibroblasts, and increased angiogenesis (10). Niche formation is induced by several tumor-derived secreted factors that overlap with important regulators of liver regeneration following major hepatectomy (9). The here presented descriptive data strongly suggests that this overlap promotes further metastasis following partial hepatectomy. These premetastatic niches can be detected as inflammatory spots within the liver, dominated by neutrophil and lymphocyte accumulation, and characterized by an increased turnover of the extracellular matrix, without the presence of (malignant) epithelial cells. The central effect of pHx on the residual liver appears to be increased inflammation, as many of the regulated PMN genes are either the cause or effect of the inflammatory phenotype. The extent of the inflammatory response to hepatectomy was also recently described to define successful or failed liver regeneration following hepatectomy (42) and therefore plays a crucial role in short- and long-term results of colorectal LM resection.

We also showed that this response is accompanied by an overall increase in bacterial presence following pHx, which might sustain the inflammation itself. Moreover, hepatic inflammation is not an early, but rather a delayed response, that occurs several days after surgery. Hence, a measurable effect on the metastatic burden was only detected in the MRIs performed on POD14.

Furthermore, liver regeneration is characterized by increased expression of tight junction genes, which help to establish a new hepatic structure (40). Several TJ proteins can be associated with poorer prognosis of cancer patients or accelerated metastasis (41, 43). TJs are thought to mediate direct cell-cell-interactions between hepatocytes and circulating tumor cells, easing the engraftment of new metastases in the liver, but have not yet been described as regulators of the PMN. We found an induction of TJ formation in the healthy liver following pHx, which might attribute to the increase in *de novo* metastases in our model, and could be added to the concept of the PMN. Astonishingly, we also demonstrated that upregulation of TJ proteins can also be observed in the healthy intestine. In the intestine, TJ proteins are involved in colorectal carcinogenesis as regulators and targets of important EMT cascades (e.g., Wnt- or Notch-signaling) and in regulating the cell cycle, inflammation, invasion, and metastasis. CRC itself is characterized by an overexpression of different Claudin genes and by loss of polarization with translocation of TJ proteins to the cytoplasm, which can be seen in the immunofluorescence of primary tumors (44). Transcriptional changes in the intestine also emphasize the crucial effect of hepatectomy on distant organs.

Following metastatic growth in this model, we found that the premetastatic niche is defined by accumulation of neutrophils and both $CD4^+$ and $CD8^+$ T lymphocytes. Although nearly all immunocytes were excluded during metastatic growth independent of the procedure, indicating immune evasion of the metastasis, we noted a tendency towards reduced T cell count, both for $CD8^+$ and $CD4^+$ T cells in FACS analyses of livers and LMs after pHx. T cell abundance and function in primary tumors are important for tumor progression and patient prognosis, as indicated by the prognostic value of the immunoscore for different cancer entities (45). Especially cytotoxic $CD8^+$ T cells appear to define tumor progression in patients, but their effect has so far only been described in primary tumors and not in metastatic sites. During tumor progression or chronic infection, T cell function is weakened, leading to T cell exhaustion (46). This is thought to be one of the crucial features for successful checkpoint-inhibition in anti-tumor therapies. It has been shown that in several cancers that are usually responsive to PD-1-inhibition, the presence of liver

metastasis aggravates the effect of such treatment (47, 48). Therefore, we were curious about the effect of pHx on T cell function. We observed an overall increase in the expression of exhaustion markers on $CD8^+$ T cells during tumor progression, consistent with previous murine and human data, but no significant effect of hepatic resection on T cell exhaustion. Our results indicate a possible negative effect of pHx on metastatic CRC in the absence of systemic treatment. As most Stage IV-patients receive systemic therapy prior to the resection of LM, the validation of our findings in humans is difficult, as chemotherapy may prevent or delay intravasation of tumor cells, as well as priming of a premetastatic niche, for example by VEGF-inhibition. These therapeutic modulations should be studied in the future. The clinical benefit of resecting colorectal LM is undoubted, and the combination of modern systemic therapies and more aggressive surgical procedures in UICC Stage IV CRC has achieved significant improvements in the prognosis of patients in the last decades. Nevertheless, a recurrence rate of >50% needs to be addressed in order to reduce the burden of repetitive hepatectomies for patients. Targeting the premetastatic niche in the context of liver surgery appears promising at first sight, but most of the involved pathways are also indispensable for liver regeneration following pHx. Our descriptive data call for a closely timed systemic therapy around pHx (especially in the context of a liver-first approach), to prevent novel metastasis in the vulnerable regenerative period.

In summary, we present a murine model of orthograde CRC metastasis in which pHx causes increased *de novo* metastasis and a generally higher intrahepatic tumor burden by priming a premetastatic niche dominated by inflammation, angiogenesis, and overexpression of tight junctions in the residual liver.

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 below: https://www.ncbi.nlm.nih.gov/geo/, GSE253251.

Ethics statement

The animal study was approved by Regierungspräsidium Freiburg, Freiburg, Germany. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

JL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. FH: Data curation, Formal analysis, Investigation, Validation, Writing – original draft, Writing – review & editing. RF: Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. BM: Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. CB: Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing. JR: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. DP: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing, Conceptualization, Data curation. LM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. WR: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. DV: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. DR: Conceptualization, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. CL: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. AJ: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. HN: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. PH: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. SF-F: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. RK: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was financed by the collaborative research center 850 (CRC850) of the German Research Foundation to SFF and RK. JL and CB were supported by the IMM-PACT-Programme for Clinician Scientists, Department of Medicine II, Medical Center – University of Freiburg and Faculty of Medicine, University of Freiburg, funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – 413517907.

Acknowledgments

We thank the Lighthouse Core Facility, Medical Center University Freiburg for assistance with flow cytometry and qPCR

and the AMIR Core Facility (DFG-RIsources No RI_00052), for support in preclinical MR and Ultrasound Imaging. The Graphical Abstract was created with BioRender.com. Jost Luenstedt and and Christopher Berlin were funded by the IMM-PACT-Programme for Clinician Scientists, Department of Medicine II, Medical Center – University of Freiburg and Faculty of Medicine, University of Freiburg, fundedby the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – 413517907.

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/fimmu.2024.1388272/full#supplementary-material

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frontiers | Frontiers in Oncology

TYPE Clinical Trial
PUBLISHED 12 September 2024
DOI 10.3389/fonc.2024.1411353

OPEN ACCESS

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RECEIVED 02 April 2024
ACCEPTED 26 August 2024
PUBLISHED 12 September 2024

CITATION
Yang F, Yuan Y, Liu W, Tang C, He F, Chen D, Xiong J, Huang G and Qian K (2024) Effect of prehabilitation exercises on postoperative frailty in patients undergoing laparoscopic colorectal cancer surgery.
Front. Oncol. 14:1411353.
doi: 10.3389/fonc.2024.1411353

Effect of prehabilitation exercises on postoperative frailty in patients undergoing laparoscopic colorectal cancer surgery

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Background: To improve perioperative frailty status in patients undergoing laparoscopic colorectal cancer surgery (LCCS), we explored a new intensive prehabilitation program that combines prehabilitation exercises with standard enhanced recovery after surgery (ERAS) and explored its impact.

Methods: We conducted a prospective randomized controlled trial. Between April 2021 to August 2021, patients undergoing elective LCCS were randomized into the standardized ERAS (S-ERAS) group or ERAS based on prehabilitation (group PR-ERAS). Patients in the PR-ERAS group undergoing prehabilitation exercises in the perioperative period in addition to standard enhanced recovery after surgery. We explored the effects of this prehabilitation protocol on frailty, short-term quality of recovery (QoR), psychological status, postoperative functional capacity, postoperative outcomes, and pain.

Results: In total, 125 patients were evaluated, and 95 eligible patients were enrolled and randomly allocated to the S-ERAS (n = 45) and PR-ERAS (n = 50) groups. The Fried score was higher in the PR-ERAS group on postoperative day (7 (2(2,3) vs. 3 (2,4), P = 0.012). The QoR-9 was higher in the PR-ERAS group than in the S-ERAS group on the 1st, 2nd, 3rd, and 7th postoperative days. The PR-ERAS group had an earlier time to first ambulation (P < 0.050) and time to first flatus (P < 0.050).

Conclusion: Prehabilitation exercises can improve postoperative frailty and accelerate recovery in patients undergoing LCCS but may not improve surgical safety. Therefore, better and more targeted prehabilitation recovery protocols should be explored.

Clinical trial registration: www.clinicaltrials.org, identifier NCT04964856.

KEYWORDS

frailty, laparoscopic colorectal cancer surgery, colorectal cancer, enhanced recovery after surgery, prehabilitation exercises

1 Introduction

Frailty is a condition in which the body is unable to compensate and carries a high risk of disability, falls, hospitalization, and death. The core features of frailty include weakness, decreased endurance, and delayed performance (1). Patients with preoperative coexisting frailty had significantly more postoperative complications, longer lengths of hospital stay, and significantly slower recovery (2, 3). Frailty has been identified as a major obstacle to colorectal cancer (CRC) treatment in older patients (4).

Bed rest can cause muscle atrophy, insulin resistance, and disorders of fatty acid metabolism (5, 6). In addition, bed rest increases the risk of deep vein thrombosis and lung infections. Studies have confirmed that preoperative physical exercise effectively improves perioperative frailty (7, 8). Preoperative functional exercise can improve patients' cardiopulmonary function and ability to cope with the stress of surgery and anesthesia, reduce the incidence of postoperative cardiovascular and cerebrovascular accidents, surgery-related complications (9, 10), and postoperative hospitalization time. In addition, preoperative functional exercise can improve patients' postoperative survival rate and quality of life, and enhance patients' postoperative regulation of blood fat and blood glucose (11).

Enhanced recovery after surgery (ERAS) is beneficial for early recovery after laparoscopic colorectal cancer surgery (LCCS), and reduces complications, readmission, and mortality (12, 13). However, its effectiveness does not appear to be significant (14), and a large systematic review concluded that ERAS does not reduce major complications after LCCS (15). CRC patients experience more psychological stress than general patients because they face the dual stress of surgery and cancer, therefore, surgeons should focus not only on the patient's physical illness but also on their psychological state. Doctors can understand patients' psychological status by assessing their anxiety, depression, and sleep status during hospitalization.

LCCS is one of the standard treatments for CRC. It requires intestinal resection and intestinal anastomosis, patients cannot eat normally immediately after surgery and need to combine enteral nutrition and parenteral nutrition to meet their nutritional needs, which not only prolongs the length of postoperative hospitalization and increases nutritional risk, but also deteriorates the patient's hospital experience and increases psychological stress. A meta-analysis found that nutritional pre-rehabilitation alone or combined with an exercise significantly reduced the length of hospital stay for colorectal surgery patients (14). Another meta-analysis suggested that prehabilitation of colorectal cancer patients with postoperative recovery and reduced complication rates were beneficial (16). However, it is controversial whether it can improve postoperative functional capacity (17, 18), and the effect of either prehabilitation exercise or ERAS on postoperative prognosis is not satisfactory. Additionally, few studies have combined prehabilitation exercises and ERAS to examine their effects on postoperative outcomes. Both ERAS and prehabilitation exercises have been shown to improve the prognosis of patients undergoing LCCS. However, the main assessments have been length of hospital stay, postoperative complications, and functional recovery. To evaluate the effects of prehabilitation exercises combined with ERAS on postoperative vulnerability, psychological status, functional recovery, and postoperative complications in patients, we explored a new intensive prehabilitation protocol for prehabilitation exercises combined with standard ERAS. We also investigated the effects of this prehabilitation protocol on frailty, short-term recovery quality, psychological status, postoperative functional capacity, postoperative outcomes, and pain.

2 Patients and methods

2.1 Study design

This single-center, prospective, randomized controlled trial was conducted at the First Affiliated Hospital of Chongqing Medical University between April 2021 and August 2021. To report this trial, we adhered to the Consolidated Standards of Reporting Trials Statement (CONSORT). Patient enrolment was initiated after written informed consent was obtained. This study was reviewed and approved by the Medical Ethics Committee of Chongqing Medical University.

2.2 Patients

Patients were recruited from a treatment group at the Department of Gastrointestinal Surgery. Inclusion criteria for the patients were as follows: Patients undergoing elective LCCS, aged >18 years and ≤100 years, with an American Society of Anesthesiologists (ASA) score is between I and III, who could clearly understand and voluntarily participate in the study and sign an informed consent form. Exclusion criteria were as follows: Emergency surgery; those with a history of cognitive dysfunction; an ASA score ≧IV; those with a history of spontaneous pneumothorax, coagulation dysfunction, acute and systemic infectious diseases, and moderate or higher fever; pregnant women; those with a history of drug abuse; those who were judged by the physician in charge to be unsuitable for ERAS-exercise; those with other severe cardio-pulmonary diseases that would affect the 6-minute walking distance (6MWD); and those who failed to provide informed consent.

2.3 Sample size calculation

The sample size was estimated based on the difference in frailty between the two groups at discharge. The mean population difference between the experimental and control groups was expected to be 0.6 with a standard deviation of 0.8. It was assumed that the ERAS exercise group had a better attenuation of frailty than in the control group. The test level (α) for this parameter was set at 0.050, and a two-sided two-sample unequal variance t-test was used with $\beta = 0.9$. As the experimental group: control group ratio was 1:1, with 38 cases required for each group,

48 cases in each of the experimental and control groups were selected to account for a 20% shedding rate. Allocation was performed in the preoperative clinic. The diagnosis was confirmed on the day of admission and surgery was scheduled. This study used a simple randomization method. A random sequence was generated by a random number table generated by SPSS software (version 25.0), odd numbers were assigned to the PR-ERSA group and even numbers to the S-ERSA group. The table of random numbers is kept by statisticians independent of the research team and inaccessible to researchers before and during grouping. The grouping information was sealed in opaque and sequentially coded envelopes, and it was not until the subjects met the inclusion criteria and decided to participate in the study that the grouping was revealed by this statistician who opened the envelopes on the spot in the presence of the researcher and the subjects.

2.4 Patient characteristics and perioperative management

The following information was collected from the patients before surgery: Sex, age, body mass index (BMI), history of smoking and drinking, occupation, education level, preoperative hemoglobin and albumin levels, preoperative diagnosis, preoperative American Society of Anesthesiologists (ASA) grading, New York Heart Association (NYHA) grading, Nutritional Risk Screening 2002 (NRS-2002) score, and activities of daily living (ADL) scores. We discussed the surgical plan for each patient the day before surgery and then performed a colectomy or rectectomy according to the scheduled operation plan. We used a midline incision for specimen extraction from the right colon lesions, a transverse incision for the left colon lesions, and a left lower abdominal oblique incision for the rectal lesions. In rectal resection, if the risk of anastomotic leakage was high, we performed a temporary ileostomy and reversed the ileostomy 2-3 months later. No nasogastric tube was inserted, and abdominal drainage was not routinely placed unless the risk of anastomotic leakage high. After patient-controlled intravenous analgesia (PCIA) removal, the patient may receive additional non-selective NSAIDs (flurbiprofen ester) if necessary.

After informed consent was obtained and surgery was scheduled, patients were randomized into the PR-ERAS and standardized enhanced recovery after surgery (S-ERAS) groups. For patients in the PR-ERAS group, prehabilitation exercises twice a day based on a standardized enhanced prehabilitation protocol for the S-ERAS group (Supplementary Material 1) were designed with formatted exercise instructions.

2.5 Prehabilitation exercises

Once the patient's elective surgery was scheduled, a rehabilitation therapist provided the patient with details of the exercise on a video. The patients performed prehabilitation exercises at home if they could not be temporarily admitted for surgery, and once they were admitted to the hospital, they performed prehabilitation exercises at the bedside. The prehabilitation exercise lasted until the day before the operation. Since the patients in this study were all cancer patients, in order to avoid the risk of cancer progression increased by long waiting time, the colorectal cancer surgery was completed as scheduled, and the duration of preoperative prehabilitation exercise was not extended. The exercise program consisted of three elements: Upper limb exercises, breathing exercises, and lower limb exercises (Table 1). The prehabilitation exercises include slow, non-weight-bearing movements of the limbs, thorax and abdomen, each lasting 10 to 15 minutes. These exercises do not cause a large increase in heart rate and respiratory rate, so they are light-intensity.

Patients in the PR-ERAS group were encouraged to perform this exercise twice, in the morning and afternoon, with 10-15 repetitions of each movement. The rehabilitation therapist provided each patient with a diary to record the exercise duration and type. The rehabilitation therapist advised each patient to follow the exercise program and supervised their exercise through WeChat or phone every day. Therefore, the light-intensity exercise was performed under close supervision and was individualized according to each patient's tolerance. The patients were also encouraged to perform postoperative rehabilitation exercises with the help of a rehabilitation therapist. If the patient complained of any discomfort, such as a heart rate >100/min, severe weakness, chest tightness, or dizziness, the prehabilitation exercise program was suspended and a rehabilitation therapist was consulted to decide whether to resume prehabilitation exercises based on the patient's condition. Supplementary Figure S1 shows details of the prehabilitation exercises.

2.6 Outcome assessments

The primary outcome of this study was the Fried's Frailty Phenotype (FP) scores(1), the scores from 0 to 5 (1 point for each component; 0 = best to 5 = worst) and represent robust (0), prefrail

TABLE 1 Prehabilitation exercise regimens.

Exercise programs	Types of Movement
Upper limb exercises	Hands squeeze and relaxation
	Elbow flexion and extension
	Arms raised flat in front and spread upward
	Horizontal elbow flexion and chest expansion, then spread arms
Breathing exercises	Deep inhalation to expand the thorax, lip reduction and exhalation
	Deep inhalation to expand the abdomen, slow exhalation
	Deep inhalation, exhale 3 times, expectorate
Lower limb exercises	Ankle flexion and extension
	Ankle rotation
	Quadriceps contraction and relaxation

(1-2), and frail (3-5) health status. It include following five components: (1) unintentional weight loss of ≥4.5 Kg or ≥5% of body weight in the prior year; (2) slowness, with the slowest 20% of the population walking 5 meters, adjusting for gender and standing height; (3) weakness, with dominant grip strength in the lowest 20% at baseline, adjusted for gender and body mass index; (4) low physical activity level, according to the Minnesota leisure time physical activity questionnaire, with a weighted score of the kilocalories consumed per week calculated for each participant, and (5) poor endurance and energy according to self-reported exhaustion, identified by two questions from the CES–D scale. The FP scores were assessed on the day of the elective surgery and on the seventh postoperative day. Secondary outcomes included perioperative functional capacity, which was assessed using the 6-minute walking distance (6MWD) (19) test on the day of scheduled surgery and on postoperative day 7. In addition, we measured the Borg Dyspnea Scale score before and after each test to assess the degree of dyspnea (20). The quality of recovery (QoR-9) score (21) evaluated both physical and mental well-being by assessing five dimensions: Emotional state, physical comfort, psychological support, physical independence, and pain at the first, second, third, and seventh postoperative days. The patient's mood state was assessed using the Hospital Anxiety and Depression Scale (HADS) questionnaire (22). The HADS is a fourteen items scale, with seven of the items related to anxiety and seven to depression. It was assessed on the day of surgery and seven days after surgery. Patient sleep status on the scheduled day of surgery and on the seventh postoperative day was assessed using the Sleep Self-Rating Scale (SRSS). The Visual Analog Pain Scale (VAS) is a unidimensional measure of pain intensity and consists mainly of a 100 mm straight line (23). The patient marked the corresponding position on this line. Each patient was asked to provide the VAS scores at rest and during exercise at 24 hours, 48 hours, 72, hours and 7 days postoperatively. Before surgery, we assessed the patients' nutritional status and ability to live using the Nutritional Risk Screening 2002 (NRS-2002) (24) and Activities of Daily Living Scale (ADL), respectively.

Postoperative pneumonia and surgical complications (anastomotic leak, surgical site infection, incision infection, hemorrhage, lymphorrhea, ileus, and gastroparesis) were the secondary outcomes. Recovery parameters, such as time to ambulation, time to pass gas, time to first defecation, time to fluid intake, time to pull out the catheter, postoperative hospital stay, reoperation, and readmission, were compared between the two groups.

2.7 Statistical methods

SPSS software (version 25.0; IBM Corporation, Armonk, N.Y., USA) was used for the statistical analysis. Continuous variables were expressed as mean ± standard deviation and range (interquartile range), according to the normality of the data. The Kolmogorov-Smirnov test was used to determine the normal distribution of continuous variables. Continuous variables were compared using the independent Student's t-test or Mann–Whitney U test, depending on the normality of the data. Categorical variables, such as sex, ASA Grading, type of surgery, and presence and incidence of complications, were expressed as frequencies and percentages. The chi-squared test was used to compare categorical variables. Statistical significance was set at $P < 0.05$.

3 Results

3.1 Basic characteristics and postoperative pain

Between May 2021 and December 2021, 125 patients were evaluated for inclusion in the study, following the process shown in Figure 1. A total of 24 patients were excluded because they either did not meet the inclusion criteria or refused to participate. During the trial, one patient in the PR-ERAS group was lost to follow-up before admission and one patient did not exercise as planned, which was considered a protocol violation. Four patients in the S-ERAS group were lost, and 95 patients were included and randomized into the PR-ERAS (n = 50) and S-ERAS (n = 45) groups. The duration of prehabilitation exercise in the PR-ERAS group was 13.2 ± 4.8 days. None of the patients in the PR-ERAS group had their surgery delayed or cancelled because of exercise, and no injuries or falls occurred. The increase in walking time (s) (1.55(0.9,2.1) vs. 2 (1.6,2.8), P=0.011) of the PR-ERAS group was shorter than that of the S-ERAS group, and the drop in grip strength (Kg) (3.35 (1.8,5.7) vs. 5.5(4.2,8.7), P<0.001) decreased less, and the difference was statistically significant. But the difference in other baseline clinical variables between the two groups was not statistically significant (Table 2). No statistical differences were found in the

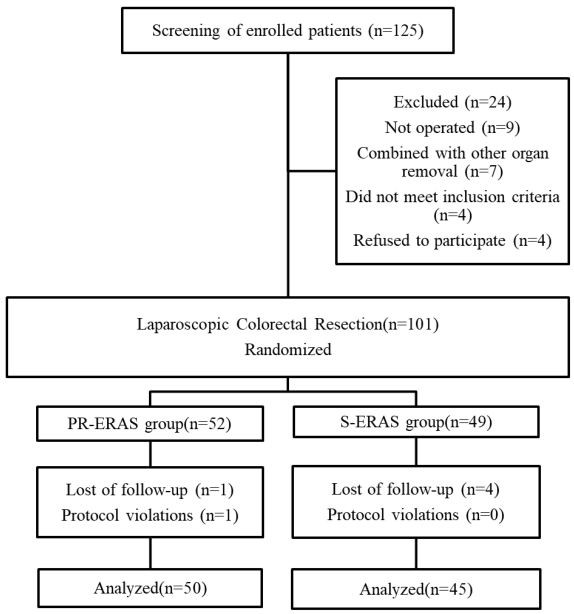

FIGURE 1
Study flow diagram. ERAS, Enhanced recovery after surgery; PR-ERAS, Enhanced recovery after surgery based on prehabilitation; S-ERAS, Standardized enhanced recovery after surgery.

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postoperative pain between the two groups (Table 3). No patients converted to open surgery, and there was no preoperative pain.

3.2 Fried's frailty phenotype scores and frailty status

Before the scheduled surgery, the frailty score, frailty status, and five criteria were similar between the two groups. On postoperative day 7, the difference in the FP scores between the PR-ERAS and S-ERAS groups was statistically significant (P=0.012), with median and quartiles of 2(2,3) and 3(2,4), respectively. Among its five criteria, only the walking time (s) (6.5(5.9,6.9) vs. 7.3(6.7,8.3), P=0.016) and grip strength (Kg) (23.1 ± 7.5 vs. 19.6 ± 6.6, P=0.016) were smaller in the PR-ERAS group than in the S-ERAS

TABLE 2 Baseline clinical variables.

	PR-ERAS group (n=50)	S-ERAS group (n=45)	P
Age (year)	60 ± 10	64 ± 12	0.084
Male	34 (68)	24 (53.3)	0.143
BMI (Kg/m^2)	22.7 ± 2.4	23.0 ± 2.9	0.644
Smoking	26 (52)	16 (35.6)	0.107
Drinking	22 (44)	14 (31.1)	0.196
Preoperative hemoglobin (g/L)	128 ± 20	124 ± 23	0.452
Preoperative albumin (g/L)	42 ± 4	41 ± 6	0.193
ASA Grading (I/II/III)	1/31/18	3/19/23	0.126
NYHA Grading (I/II/III)	5/43/2	3/33/9	0.054
TNM stage (I/II/III/IV)	13/26/19/2	12/20/10/3	0.854
From enrolment to admission (day)	9 ± 4.6	7.9 ± 2	0.154
From admission to surgery (day)	4.3 ± 1.8	4.9 ± 2.7	0.147
From enrolment to surgery (day)	13.2 ± 4.8	12.8 ± 3.2	0.638
Highly educated	7 (14)	9 (20)	0.435
Main comorbidity[a]	19 (38)	19 (42.2)	0.675
No. of daily medication	0 (0,1)	0 (0,1)	0.214
Type of colectomy (right/left/ sigmoid/rectal)	8/3/5/34	11/7/6/21	0.173
Ostomy	17 (50)	7 (33.3)	0.226
Laparoscopic surgery	50 (100%)	45 (100%)	NA
Hospitalization expenses	70293 (64010,75526)	72067 (68691,78733)	0.061
NRS2002	3 (2,4)	3 (2,4)	0.681
ADL	100 (100,100)	100 (100,100)	NA
Increase in walking time (s)	1.55 (0.9,2.1)	2 (1.6,2.8)	0.011
Drop in grip strength (Kg)	3.35 (1.8,5.7)	5.5 (4.2,8.7)	<0.001

Variables are presented as n (%), mean ± standard deviation, or median (interquartile range). PR-ERAS, enhanced recovery after surgery based on prehabilitation; S-ERAS, Standardized enhanced recovery after surgery; BMI, body mass index; ASA, American Society of Anesthesiologists; NYHA, New York Heart Association; NRS-2002, Nutritional Risk Screening 2002; ADL, activities of daily living. [a]Include hypertension, diabetes mellitus, coronary atherosclerotic heart disease, chronic obstructive pulmonary disease, cerebral infarction, and asthma. NA, Not Applicable.

TABLE 3 Postoperative pain.

	PR-ERAS group (n=50)	S-ERAS group (n=45)	P
VAS at rest			
24 hours after surgery	0 (0,1)	0 (0,1)	0.929
48 hours after surgery	0 (0,1)	0 (0,1)	0.455
72 hours after surgery	0 (0,0)	0 (0,0)	0.264
the day of discharge	0 (0,0)	0 (0,0)	0.134
VAS during exercise			
24 hours after surgery	2 (2,3)	2 (2,3)	0.737
48 hours after surgery	2 (1,2)	2 (2,2)	0.216
72 hours after surgery	1.5 (1,2)	2 (1,2)	0.093
the day of discharge	1 (1,1)	1 (1,1)	0.928
Number of PCIA presses	43.1 ± 11	44.9 ± 10.9	0.438
Dosage of PCIA (mL)	2 (1,5)	3 (1,5)	0.905
Rescue analgesia	15 (30)	13 (28.8)	0.906

Variables are presented as n (%), mean ± standard deviation, or median (interquartile range). VAS, Visual Analog Pain Scale; PCIA, patient-controlled intravenous analgesia.

group, and the differences were statistically significant, while the others were statistically similar (Figure 2).

3.3 Short-term recovery quality and psychosocial status

Prehabilitation exercises had significant improvement on postoperative recovery. The QoR-9 scores in the S-ERAS group on the first postoperative day (14(13,16) vs. 14(13,14) P=0.036), second day (15(14,16) vs. 15(13,16) P=0.021), third day (17(15,17) vs. 16(15,17) P = 0.042), and seventh day (18(17,18) vs. 17(16,18) P = 0.005) were all better than in the S-ERAS group, and the differences were statistically significant (Figure 3). The preoperative sleep and psychological status were similar between the groups. However, postoperative HADS scores were lower in the PR-ERAS group than in the S-ERAS group (p=0.047), and the median and interquartile ranges for the two groups were 2 (2–15) and 14(4–17), respectively (Figure 4). However, the difference in SRSS scores between the two groups was not statistically significant (Figure 5).

3.4 Perioperative functional capacity

The PR-ERAS and S-ERAS groups showed similar preoperative and postoperative 6MWD results. We performed Brog scoring

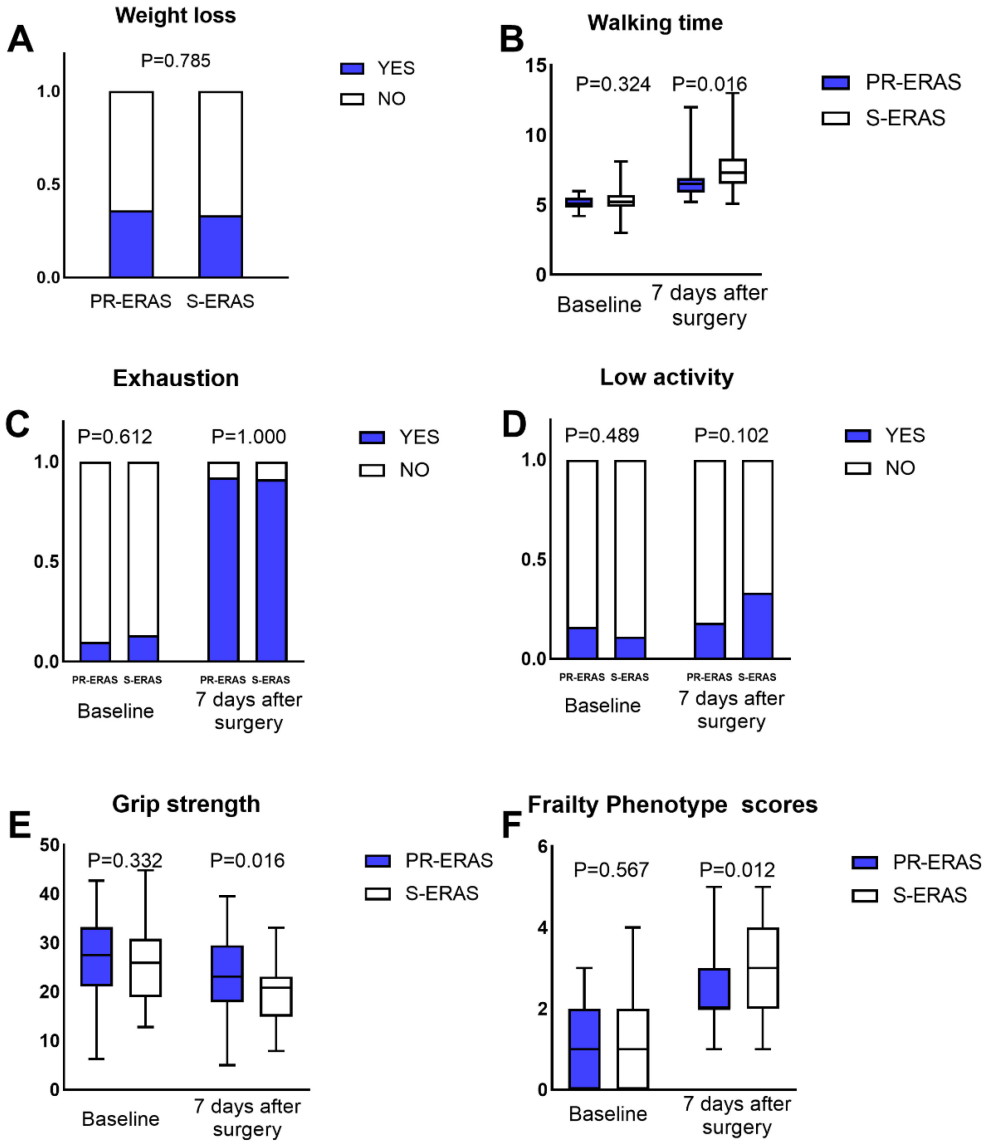

FIGURE 2
Fried's Frailty Phenotype (PF) scores and its five criteria. The walking time, grip strength and PF scores expressed as the median (range), the weight loss, exhaustion and low activity expressed as percentages. Only the differences in walking time, grip strength and PF scores were statistically significant, the others were statistically similar. ERAS, Enhanced recovery after surgery. **(A)** Weight loss; **(B)** Walking time; **(C)** Exhaustion; **(D)** Low activity; **(E)** Grip strength; **(F)** Frailty Phenotype scores.

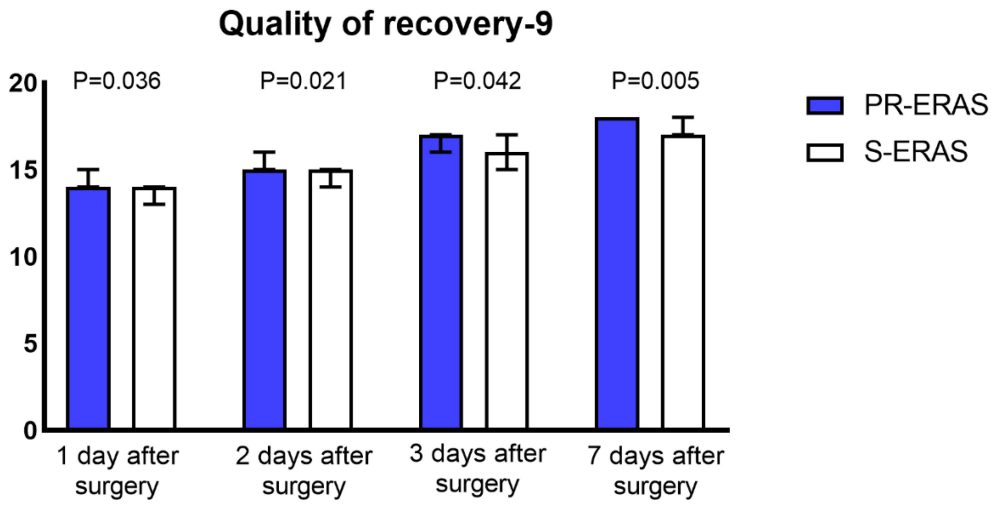

FIGURE 3
Quality of recovery (QoR-9) scores. The differences in all four comparisons were statistically significant.

before and after both trials, and only the PR-ERAS group had a lower Brog score after 6MWD postoperatively than in the S-ERAS group (0.5(0,1) vs. 1(0.5,1), respectively, P=0.028), which was a statistically significant difference, while the results were similar at all other times (Table 4).

3.5 Surgical outcomes and postoperative complications

Compared to S-ERAS, the PR-ERAS group had earlier time to first ambulation (Hour) (13(10,15) vs. 15(12,20) P=0.006) and time to first flatus (Hour) (14(8.5,25) vs. 18.5(14,40) P=0.039). The rates of intraoperative blood loss, intraoperative blood transfusion, postoperative pneumonia, and other complications were statistically similar between the groups (Table 5).

3.6 Subgroup analysis of PR-ERAS group

Considering the difference in surgical procedures (colectomy and proctectomy) and the different ostomy rates in PR-ERAS group, subgroup analysis was performed in the PR-ERAS group. The NRS2002 score, PF score, 5 criteria in PF score, HADS score, SRSS score, QoR-9 score, 6MWD score and borg score were compared between different groups of patients. There is no statistical difference was observed in subgroup analysis. (Supplementary Tables S1, S2)

4 Discussion

Based on the results of this study, we suggest that adding prehabilitation exercises to a standardized enhanced recovery

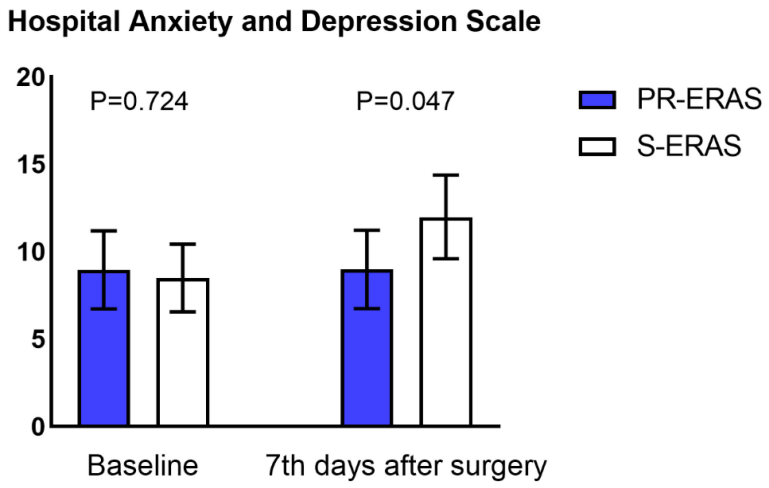

FIGURE 4
Hospital Anxiety and Depression Scale (HADS). Only the difference on postoperative day 7 was statistically significant.

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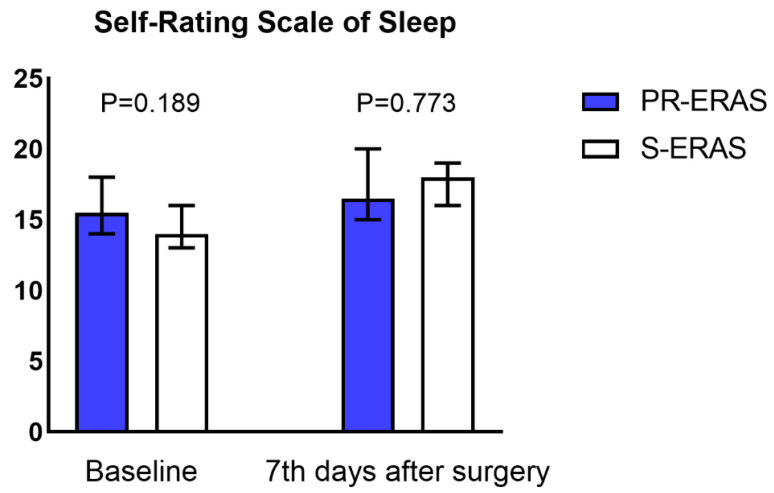

FIGURE 5
Sleep Self-Rating Scale (SRSS). The differences in both assessments were not statistically significant.

program may further improve postoperative frailty status, increase the quality of short-term postoperative recovery, accelerate postoperative recovery, and partially improve postoperative psychosocial status. However, it may not improve postoperative functional capacity or reduce the incidence of postoperative complications.

To our knowledge, no study has evaluated the effect of prehabilitation exercises combined with ERAS on frailty status after LCCS. Physical exercise may lead to inadequate gastrointestinal perfusion and gastrointestinal damage and symptoms such as nausea, vomiting, and abdominal pain (25). Therefore, we monitored the patients for gastrointestinal discomfort during the preoperative exercise. Fortunately, no gastrointestinal discomfort was reported among the patients who followed the prehabilitation exercises, nor did anyone suffer from complications such as falls and injuries. This suggests that

TABLE 4 6MWD and borg score when scheduled surgery and 7 days after surgery.

	PR-ERAS group (n=50)	S-ERAS group (n=45)	P
When scheduled surgery			
6MWD	430 (400,500)	420 (335,480)	0.124
Borg score before 6MWD	0 (0,0)	0 (0,0)	0.134
Borg score after 6MWD	0 (0,0.5)	0 (0,0.5)	0.091
7 days after surgery			
6MWD	267.5 (230,300)	250 (180,300)	0.191
Borg score before 6MWD	0.5 (0,1)	1 (0.5,1)	0.028
Borg score after 6MWD	0 (0.5,1)	0 (0.5,1)	0.426

6MWD, 6-minute walking distance.

TABLE 5 Surgical outcomes.

	PR-ERAS group (n=50)	S-ERAS group (n=45)	P
Intraoperative blood loss (mL)	30 (20,50)	2 (20,50)	0.496
Intraoperative blood transfusion	0	2 (4.4)	0.222
Operation time (min)	154 (140,170)	150 (134,170)	0.383
Time to ambulation (h)	13 (10,15)	15 (12,20)	0.006
Time to first flatus (h)	14 (8.5,25)	18.5 (14,40)	0.039
Time to first defecation (h)	26.5 (10.5,40)	38 (16,60)	0.121
Time to fluid intake (h)	4 (4,4)	4 (4,4)	0.948
Time to pull out urinary catheter (h)	36 (19,61)	37.5 (19,59)	0.702
Admitted to ICU	0	3 (6.6)	0.103
Pneumonia	1 (2)	3 (6.6)	0.342
Surgical complications[a]	7 (14)	9 (20)	0.435
Postoperative hospital days (d)	5 (4,6)	5 (4,7)	0.363
Reoperation	3 (6)	1 (2.2)	0.619
Readmission within one month	3 (6)	3 (6.6)	1
Death within one month	0	1 (2.2)	0.474

ICU, Intensive care unit. [a]Include anastomotic leak, hemorrhage, lymphorrhea, ileus, gastroparesis, incision infection, and abdominal infection.

prehabilitation exercises are safe and effective for improving frailty and enhancing the quality of short-term recovery after LCCS. Our prehabilitation protocol is easy, and there was a video to guide patients, they can do it alone. The main role of rehabilitation therapists is to supervise patients to complete prehabilitation exercises and corrective actions, so the patient costs little.

FP scores consist of shrinking, weakness, poor endurance and energy, slowness, and low physical activity level, where patients without features were considered robust, meeting 1-2 features was defined as prefrail, and those with three or more critical features were considered vulnerable (1). Frailty is reversible and can be improved with reasonable interventions. Previous studies have shown promising effects on frailty status through trials of non-pharmacological interventions, such as physical exercise (26). The effects observed are similar to those found in this study. In addition, bed rest can adversely affect musculoskeletal and cardiovascular systems and increase the risk of frailty (27). We designed the prehabilitation exercises to include three light-intensity exercises combined with isometric exercises (breathing exercises and hand grips), dynamic exercises (shoulder abduction and ankle exercises), and resistance exercises (quadriceps contraction and relaxation, curls, and lumbar exercises). These exercises are effective in improving frailty, cardiorespiratory function, emotions, and cognition (26, 28–30). The effect of different mobility exercises is different, and patients with different states of frailty may have different optimal mobility training, where patients with pre-frailty may be suitable for moderate-intensity exercises, while patients with severe frailty may only be able to perform simple prehabilitation exercises (31, 32). In addition, the type of exercise intervention may need to be tailored to the patient's wishes and their environment (33). Currently, the optimal exercise program is unknown, and different exercise programs should be designed for different populations. One of the findings of this study was that the prehabilitation program improved the grip strength of patients after surgery, but did not improve the incidence of postoperative complications, which is similar to the conclusion of a previous study (34).

Another salient finding of this study was that prehabilitation exercise significantly improved the quality of short-term recovery after LCCS according to QoR-9 score. The QoR-9 assesses physical and mental health through five dimensions: Emotional state, physical comfort, psychological support, physical independence, and pain. Although we did not analyze the differences in each of the five dimensions in detail, the quality of recovery in the PR-ERAS group was significantly better than that in the S-ERAS group in all four postoperative assessments, confirming the advantage of prehabilitation exercises. In addition, prehabilitation exercises accelerated the recovery of gastrointestinal function after LCCS and promoted early bed removal, the result that further affirms the role of prehabilitation in improving the quality of patients' short-term postoperative recovery. Similar to the findings of this study, previous research has found that physical exercise has beneficial effects on physical and psychosocial health (35), with particularly positive effects on depressive symptoms (36). HADS screens patients for anxiety and depression while in the hospital, and our study found that prehabilitation exercises improved patients' anxiety and depression in the hospital. Patients in PR-ERAS group have faster time to ambulation and time to first flatus than S-ERAS group, which means patients in PR-ERAS group have faster postoperative recovery. Therefore, it can improve the patient's postoperative experience. The factors influencing anxiety and depression may be multifaceted and related to individual personality traits, disease duration, and severity of the speed of disease recovery. Therefore, it is possible that this outcome was also influenced by the patient's early recovery. There is evidence that physical activity improves cognitive function and reverses some effects of chronic disease (37), thereby improving surgical outcomes. But cognitive function was not assessed in this study, so we don't know whether our prehabilitation exercise program will improve patients' cognitive function. The focus of this study was on the effect of prehabilitation exercise on postoperative short-term outcomes in patients undergoing colorectal cancer surgery. Therefore, this study did not explore the effect of our prehabilitation protocol on patients' long-term outcomes, including oncological features. We will follow the patients in this study for a period of 5 years and will demonstrate the effect of the prehabilitation protocol on the long-term outcome of patients undergoing colorectal cancer surgery in future studies. Previous studies have found that unsupervised outpatient prehabilitation program does not improve postoperative outcomes after elective pancreaticoduodenectomy (38). Therefore, increased compliance of prehabilitation programs is important, it can improve patient prognosis (39), and clinicians should consider not only the safety and efficacy of the protocols but also patient compliance when developing prehabilitation protocols. It is also necessary to develop appropriate prehabilitation protocols for patients according to the types of surgery. In addition, prehabilitation protocols need to be adjusted according to the physical and psychological conditions of patients, patients with good general condition can consider moderate intensity rehabilitation protocols, while patients with poor general condition should focus on light intensity prehabilitation protocols. Increased communication with patients, providing repeated education, and improved nutrition can also promote post-LCCS rehabilitation.

The present study has some limitations: Firstly, the patients were followed up with for a short period of time after surgery, it is best to wait 6-8 weeks to better observe the expected results, but most of the observations in this study lasted only until the 7th day after surgery, there were no indicators of intermediate postoperative outcomes. Secondly, due to the short follow up time, this study did not include the long-term outcomes of the patients, and we will present the long-term outcomes of the patients in future studies, including the oncological data. Thirdly, although the present study was able to demonstrate the benefit of prehabilitation exercises on the improvement of postoperative frailty, the sample size was small, and the prehabilitation protocol we explored may not be the most appropriate for patients undergoing elective LCCS. Fourthly, all patients in this study undergoing minimally invasive surgery, so the

impact of the present prehabilitation protocol on postoperative frailty and the quality of recovery after open colorectal resection is debatable. Finally, power analysis was performed only for primary outcome, but not for other secondary outcomes.

5 Conclusion

In patients scheduled for LCCS, ERAS in combination with prehabilitation exercises, improves postoperative frailty status, enhances the quality of recovery, and accelerates the recovery of gastrointestinal function. However, it did not improve elective postoperative functional capacity or reduce the incidence of complications. Therefore, it is necessary to develop a more suitable prehabilitation protocol for patients undergoing LCCS. Additionally, improvements in compliance with prehabilitation programs and the discovery of individualized prehabilitation protocols need to be emphasized.

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 humans were approved by Medical Ethics Committee of The First Affiliated Hospital of Chongqing Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

FY: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. YY: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. WL: Data curation, Writing – review & editing. CT: Methodology, Supervision, Writing – review & editing. FH: Methodology, Supervision, Writing – review & editing. DC: Data curation, Writing – review & editing. JX: Methodology, Supervision, Writing – review & editing. GH: Project administration, Resources, Supervision, Writing – review & editing. KQ: Project administration, Resources, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by the Chongqing Medical University Future Medical Youth innovation team development support program (Grant number 03030299QC-W0007), the study on the role of a new PPARγ transcription cofactor STK38L in adipogenic differentiation of human adipocytes (Grant number cstc2021jcyj-msxmX0286), Major projects in the field of health, Science and Technology Department of Hubei Province (Grant number 2022BCE024) and Enshi Prefecture Science and Technology Bureau, selenium-citing special (D20230071).

Acknowledgments

The authors would like to thank the medical staff of the Department of Gastrointestinal Surgery of the First Affiliated Hospital of Chongqing Medical University, they diligently use the new intensive prehabilitation protocol in their day-to-day work. We would like to thank Editage (www.editage.cn) for English language 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1411353/full#supplementary-material

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frontiers | Frontiers in Surgery

TYPE Review
PUBLISHED 19 November 2024
DOI 10.3389/fsurg.2024.1400814

OPEN ACCESS

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RECEIVED 14 March 2024
ACCEPTED 28 October 2024
PUBLISHED 19 November 2024

CITATION
Mikalonis M, Avlund TH and Løve US (2024) Danish guidelines for treating acute colonic obstruction caused by colorectal cancer—a review.
Front. Surg. 11:1400814.
doi: 10.3389/fsurg.2024.1400814

Danish guidelines for treating acute colonic obstruction caused by colorectal cancer—a review

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Acute onset of colonic obstruction caused by colorectal cancer occurs in approximately 14% of Danish patients with colon cancer(1). Given that colorectal cancer is a common cancer with about 4,500 new cases annually, acute onset will occur in a reasonably large number of patients in Danish emergency departments, and all surgeons should be familiar with the treatment principles. A revised guideline from the Danish Colorectal Cancer Group is currently underway, and this status article reviews the latest knowledge and recommendations.

KEYWORDS

colorectal cancer, colonic obstruction, emergency, guidelines, surgery

Introduction

Bowel obstruction as a first symptom is observed in approximately 14% of Danish patients with colon cancer according to previous Danish Colorectal Cancer Group (DCCG) annual reports (1). Understanding the treatment options for acute colonic cancer obstruction is crucial for timely intervention and improved patient outcomes.

Traditionally, emergency surgery has been performed to treat patients with acute colonic obstruction. Emergency surgery for colon cancer is still associated with high 30- and 90-day mortality rates. Changing from emergency to elective surgery for the treatment of acute colonic obstruction without perforation seems to be desirable. This approach will enable preoperative staging, optimization and planning of the procedure. Patients with metastatic cancer without signs of bowel perforation can be spared surgery.

Another feared complication associated with high morbidity and mortality rates is colonic perforation. The risk of perforation of the coecum in patients with colonic ileus increases with radiological findings of a coecum diameter ≥12 cm, and urgent decompression is recommended (2).

These guidelines address the management of large bowel obstruction in patients with colorectal cancer. The overall purpose of these guidelines is to provide uniform, high quality evidence-based cancer treatment across Denmark. These guidelines are primarily intended to support clinical work and the development of clinical treatment quality, which is why the primary target group in the Danish health care system is health care professionals (surgeons, oncologists, primary health care physicians, policy-makers).

Recently, updated ASCRS guidelines provide similar management recommendations for patients with right-sided and left-sided colonic obstruction as well as for those with colonic perforation (3).

Materials and methods

A literature review was performed using PubMed articles from 2010–2022 with the search string "Intestinal Obstruction" [Mesh]) OR ("bowel obstruction" OR "obstruction" OR "colon obstruction" OR "intestinal obstruction"). Available literature from the PubMed, Cochrane and Embase electronic databases was used for the section on the treatment of perforation. The search strategy was as follows: (Colon cancer OR Rectal cancer OR colorectal cancer) AND Perforation AND surgery AND acute AND emergency. Only articles in English were searched for. Any potential conflicts were resolved through discussion after the screening results were revealed, and if any disagreements persisted, the systematic review coordinator made the final decision. The same reviewers conducted a full-text screening of the selected articles. The Oxford 2009 Levels of Evidence were used to determine levels of evidence and levels of recommendation.

Results and discussion

Diagnostics

In acute colonic obstruction, a computed tomography (CT) scan of the abdomen with IV contrast should be performed (B).

The diagnosis of colonic ileus can be made by CT scan, which has a high sensitivity (91%) and specificity (91%) (4) [2B]. CT scans can be used to identify the anatomical localization of the obstruction and assess the severity of the ileus based on the diameter of the cecum. In addition, CT scans with intravenous contrast can often clarify the cause of ileus, identify signs of ischemia and help surgeons determine the stage of a potential tumor. This allows the treatment strategy and its timing to be planned more effectively (5) [4]. CT scans can be supplemented with contrast enema to further clarify the completeness of the stenosis. Therefore, CT scan appears to be superior to conventional x-ray imaging (6) [2B].

Acute surgical treatment

The treatment strategy for colonic obstruction should be determined by a colorectal surgeon. Surgical resection should be performed with the participation of a colorectal surgeon (B).

If possible, treatment of colonic obstruction should be performed during the day and with the participation of a colorectal surgeon. The morbidity, mortality and anastomotic leakage rates are likely to be lower when surgery is performed by an experienced colorectal surgeon (7–11) [2A–B]. Long-term survival after emergency colorectal resection for cancer is also likely related to surgeon subspecialization (7, 8, 12) [2A–B]. A Swedish registry study failed to demonstrate differences in survival between patients treated by emergency surgeons and those treated by colorectal surgeons but the registry study still showed an increased rate of permanent stomas in patients operated on by emergency surgeons (13) [2B].

The following treatment modalities for colonic obstruction are equivalent in terms of survival: stenting, colonic stoma placement and resection with or without primary anastomosis (A).

The treatment strategy for obstructing colorectal cancer depends on the patient's clinical condition and tumor location. Emergency surgery for colon cancer is still associated with high 30- and 90-day mortality rates. In a Swedish report from 2014, the 30- and 90-day mortality rates were 8.2 and 14.9%, respectively (14) [2B], while the Danish 30-day mortality, in emergency setting, in a DCCG theme report from 2018 was 12%.

In the case of acute resection, both morbidity and mortality are higher than those of elective resection (14) [2B], and there is a greater risk of colostomy (15) [1B]. Changing from emergency to elective surgery for the treatment of acute colonic obstruction without perforation seems to be desirable. This approach will enable preoperative staging, optimization and planning of the procedure. Patients with metastatic cancer without signs of bowel perforation can be spared surgery.

Colonic stenting for left-sided malignant colonic obstruction

There are a large number of publications on short-term outcomes after decompression via self-expandable metallic stenting in the colon accounting for the feasibility of procedure. According to a 2017 meta-analysis of 448 patients from seven randomized trials comparing stenting as a bridge to surgery and emergency colon resection for left-sided colorectal cancer, the stent group had lower rates of permanent stoma and lower morbidity. Patients receiving primary anastomosis in the stent group accounted for 71.7% vs. 55.3% in acute resection group (RR 1.27 95pct. CI (0.98–1.64). There was no difference in mortality or anastomotic leakage rate (16) [1A]. Similar results have been reported from other meta-analyses of randomized trials (17–20) [1A].

A retrospective study comparing results after self-expanding metallic stents vs. stoma decompression exhibited financial savings and shorter hospitalization times in the stent group but no difference in the clinical success rate in terms of obstruction resolution (21) [3B]. A recent randomized English study of colon cancer patients presenting with colonic obstruction requiring stenting showed no difference in morbidity, mortality, or 3-year disease-free survival (DFS) between patients treated with stents and patients treated with acute resection or stoma placement (22) [1B]. However, another recent meta-analysis of randomized trials showed significantly lower permanent stoma rates in the stenting group than in the acute resection group. Moreover, significantly lower morbidity but not significantly lower mortality was shown (23) [1A].

According to a Cochrane meta-analysis, stent-related complications were described as acceptable (stent-related perforation 5.8%, stent migration 2.1% and stent obstruction 2.1%) (24) [1A]. A more recent Danish study reported a stent perforation rate of 8.9 (25) [2B]. In a systematic review of 82 studies (2,287 patients), Datye et al. (26) [3A] failed to observe a significant difference in perforation rates between patients who underwent stenting in a palliative setting and patients who underwent bridging to surgery. The overall perforation rate was

4.9%, approximately half of which occurred in the first 24 h. The risk factors for perforation were chemotherapy, radiotherapy and glucocorticoid therapy. The mortality rate among patients with perforation was 16.2%. The degree of obstruction should be taken into account when evaluating perforation risk. A retrospective review of 130 patients reported that the perforation rate is associated with the angle of stenosis (27) [2B], a factor that should also be considered before stent placement. Three randomized trials from 2008–2011 described asymptomatic perforation rates ranging from 6%–27% (28–30) [1A], which has raised concerns about the long-term outcomes of the placement of a metallic stent as a bridge to surgery. In addition to the risk of perforation, colon cancer stenting may theoretically have other oncological disadvantages due to pressure on the tumor. A 2021 meta-analysis by Balciscueta et al. found an increased incidence of perineural ingrowth and lymphatic vessel ingrowth in patients who underwent stenting as a bridge to surgery compared to that in patients who underwent urgent resection (31) [2A]. The same author's 2020 meta-analysis found increased local recurrence rates in patients with stent-related perforation but no difference in 3- or 5-year survival (32) [2A]. On the other hand, another retrospective study from Italy showed no difference in perineural ingrowth between stented vs. primarily resected tumors (33) [2B]. Other recent studies also failed to demonstrate lower long-term survival with stenting than with emergency surgery. Two Spanish studies showed no difference in 3-year DFS (34, 35) [2B]. Thus, the data are inconclusive, and no conclusion can currently be drawn on long-term survival.

Colonic stenting for right-sided malignant colonic obstruction

Recent retrospective studies have shown similar morbidity and mortality for right-sided stenting vs. emergency surgery, as well as a lower rate of stoma formation (36) [3B]. A systematic review of 14 cohort studies from 2015 reported less overall morbidity and mortality for stenting than for emergency resection of acute right-sided colonic obstruction and a lower rate of stoma formation (37) [2A]. This was confirmed in new meta-analyses from 2022 (38) [2A] and 2021 (39) [2A]. Stenting of colonic tumors proximal to the splenic flexure can thus be performed at centers where expertise is available.

The optimal timing of surgery after stenting has not been well described, but evidence suggests that surgery should be performed as soon as possible after the patient's condition has stabilized and the necessary assessment has been performed. The ESGE guidelines recommend surgery approximately 14 days after stent placement (40). This finding is supported by a Danish study that showed that increased recurrence rates were associated with long intervals between stent placement and surgery (41) [2B].

Decompressing stoma

A meta-analysis of 8 studies comparing temporary stoma placement vs. emergency surgical resection found no difference in 30-day morbidity or mortality, which was approximately 7% for both groups. There were fewer permanent stomas in the decompressing stoma group (42) [2A]. Due to concerns about long-term outcomes after stenting as a bridge to surgery, there has been a focus on this topic in recent years. A 2016 cohort study comparing stents vs. stomas as a bridge to resection found fewer required procedures and lower long-term morbidity (primarily due to herniation) in the stent group (43) [2B] but otherwise comparable outcomes. A more recent meta-analysis from 2022 comparing stents vs. stomas showed no difference in 3-year overall survival (OS), perioperative mortality or permanent stoma rates. However, there were fewer Clavien–Dindo 1–2 complications in the stent group but similar Clavien–Dindo 3–4 complications in both groups, and there was no difference in the permanent stoma rate (44). Another meta-analysis from 2021 comprising 48 studies, including 8 randomized studies, examined 5-year OS with stenting or stoma placement as a bridge to surgery. A significantly higher 5-year OS was associated with stoma placement than with stenting, but conversely, stoma placement was associated with a longer hospitalization time (45). Therefore, decompressing stoma placement cannot be dismissed as a good alternative to stenting as a bridge to surgery. This should especially be considered in patients with long remaining life expectancies.

Emergency resection

For right-sided colonic obstruction (acute obstructing tumors orally to the splenic flexure) without feculent peritonitis, right-sided hemicolectomy with primary ileocolic anastomosis can be safely performed in selected patients. In Denmark, the leakage rate after acute colonic resection is 2.8%, according to the DCCG annual report from 2012 (1) [2C]. The anastomotic leakage rate has been reported to be between 2.5 and 5.2% in retrospective studies of acute right-sided colon resection (46, 47) [2B]. For left-sided colonic obstruction (acute obstructing tumors in or anally to the splenic flexure), primary resection can be performed with an anastomosis with manual emptying of the dilated colon orally to the tumor. In a systematic review, Kam et al. reported a significantly higher anastomotic leakage rate (7%) in patients who underwent antegrade lavage than in those who underwent manual emptying (1%). There was a significantly higher 30-day mortality after antegrade irrigation (7.2% vs. 1%) (48) [2A]. Hartmann's operation is a preferred surgical strategy for patients at high risk of anastomotic leakage. Colectomy can be performed for severely distended and damaged colons or in the presence of synchronous colon tumors (49) [2A].

In palliative treatment of colonic obstruction, stenting is the first choice where technically feasible (B).

With stent placement, patients with metastatic disease avoid a stoma and the following reduced quality of life. Meisner et al. (50) [2B] demonstrated a 98.4% technical success rate, 87.8% clinical success rate and low complication rate (perforation 5.1%, migration 5.5%) in a prospective multicenter study of stenting in a palliative setting. The mortality rate was less than 2% (two patients died—one after 24 days and one after 34 days). The risk of perforation seems to be an unresolved issue. A Dutch randomized trial comparing acute resection with stenting for palliation of mechanical ileus in patients with metastatic colon cancer was stopped early due to a high rate of stent-related

perforations (6 perforations out of 11 stents placed) (28) [1B]. This perforation rate has however not been reported in general.

Bevacizumab treatment has previously been reported to be a risk factor for bowel perforation, and a retrospective study from 2015 suggested a higher risk of perforation with stent treatment in patients treated with this drug (51) [3A]. The most common problem with stent as palliation is migration. Stent migration has an incidence of up to 10.5% (52) [2A]. Migration can be related to treatment with palliative chemotherapy (as the response triggered by treatment can result in tumor shrinkage) or to stent type and diameter. Migration rates are expected to increase with longer survival due to more effective palliative chemotherapy. However, a study comparing palliative treatment with stoma vs. stent treatment suggested a greater likelihood of discharge to home with stent treatment (53) [2B]. In a randomized trial between stents and stomas, the hospital length of stay was shorter, and the quality of life was higher in stent-treated patients (54) [1B]. Stenting is therefore a recommended choice for the palliative treatment of stenosing colon cancer.

Patients with colorectal cancer and colon perforation are frequently severely septic. The initiation of medical treatment for hypotension, metabolic acidosis and infection is recommended as soon as possible, as the severity of sepsis has a major impact on patient mortality and morbidity (C).

Primary oncologic resection of the bowel is recommended as the first surgical choice. If the patient's physiological condition, comorbidities and tumor location put them at high risk of anastomotic leakage, primary resection and stoma placement are recommended. A double lumen stoma (loop or split stoma) is recommended because it increases the possibility of closure (B).

Colonic perforation, a complication of obstructive colorectal cancer, is associated with high morbidity and mortality (55) [4]. The incidence of perioperative mortality was reported to be between 5% and 19% in a retrospective US study (56) [2b]. Perforation can be categorized as perforation of the colon proximal to the obstructing tumor site due to distention or perforation of the tumor itself. In the case of perforation of the tumor itself, abscess formation and local peritonitis may occur. Furthermore, studies suggest that tumor perforation is an independent risk factor for the development of peritoneal carcinomatosis (57, 58) [3b-3a].

Perforation of the colon proximal to the tumor frequently results in fecal peritonitis and severe septic conditions, which require urgent surgical intervention to control contamination and septic shock (59) [3b]. Sepsis severity has a major impact on postoperative mortality in patients with colorectal cancer and colon perforation (60) [3b]. It is therefore important to treat patients' hypotension, metabolic acidosis and systemic inflammatory response as soon as possible. In the UK, a targeted intervention with "sepsis packages" has been shown to significantly reduce mortality (61).

There are various surgical options for patients with tumor perforation. Oncologic resection is recommended. The choice between primary anastomosis or stoma should depend on the degree of contamination, the patient's physiological condition, sepsis, comorbidity [American Society of Anesthesiologists (ASA) score] and tumor location. There is generally a higher risk of anastomotic leakage in acute surgery (59, 62) [3a]. Stoma placement should therefore be chosen for patients who are at high risk of postoperative anastomotic leakage and is expected in a higher proportion of emergency patients. Risk factors for anastomotic leakage include age, male sex, an American Society of Anesthesiologists (ASA) score >3, smoking status, diabetes status and a serum ALB concentration <4 g/dl (63) [2c]. Double-lumen stoma (loop or split stoma) is preferred, as it makes later stoma reversal more likely (56, 58, 59) [3b]. The fact that stomas that develop during emergency surgery have a lower probability of being closed should be taken into account (56) [3b]. For perforation of the coecum in the presence of right-sided colon tumors, right-sided hemicolectomy with ileocolic anastomosis or ileostomy is recommended. In the case of cecal perforation and a tumor located in the left colon, subtotal colectomy is recommended. If the perforation was in the left colon and the tumor was in the same location, left-sided hemicolectomy with primary anastomosis was recommended. Alternatively, Hartman's operation can be performed (58, 59) [3b].

Author contributions

MM: Writing – original draft, Writing – review & editing. TA: Writing – original draft, Writing – review & editing. UL: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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