Techniques in Coloproctology (2025) 29:119
https://doi.org/10.1007/s10151-025-03163-x

ORIGINAL ARTICLE

Propensity score-matched analysis of risk factors for prolonged postoperative ileus after TME in rectal cancer

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Received: 3 November 2024 / Accepted: 17 April 2025

Abstract

Background Prolonged postoperative ileus (PPOI) is a common complication following total mesorectal excision. Early detection and prompt intervention are crucial for the treatment of rectal cancer.

Methods We conducted a retrospective study. After applying propensity score matching, we collected and compared the clinical characteristics of 164 patients in both the PPOI group and the non-PPOI group using univariate analysis. Significant factors identified were then evaluated in a multivariable logistic regression analysis. Moreover, we analyzed the clinical features and treatment strategies.

Results The incidence of PPOI after laparoscopic TME was 18.3% in our trial. Univariate analysis revealed significant differences in several factors between the two groups, including prophylactic anaerobic antibiotic therapy ($p < 0.001$), preoperative bowel obstruction ($p = 0.006$), preoperative nutritional support therapy ($p < 0.001$), and the type of stoma ($p < 0.001$). However, further multivariable logistic regression analysis indicated that prophylactic anaerobic antibiotic therapy was not an independent risk factor for PPOI. Among the patients who experienced PPOI, the majority, 135 patients (82.3%), presented with Clavien–Dindo grades I–II. Overall, 81.7% and 85.4% of patients received oral probiotics and vancomycin treatment, respectively. Only 48 patients (29.3%) required gastric tube insertion, while 27 patients (16.5%) needed a transnasal ileus tube due to ineffective drug treatment.

Conclusions Our study suggests that selecting the appropriate preoperative nutritional support strategy and type of stoma is crucial in reducing the incidence of PPOI. When PPOI occurs, a multi-stage treatment protocol may be beneficial for recovery.

Keywords Rectal cancer · Prolonged postoperative ileus · Total mesorectal excision · Clinical features · Risk factors

Introduction

Rectal cancer is a common tumor in the digestive system. Total mesorectal excision (TME) surgery has become the standard treatment for resectable rectal cancer, leading to improved oncological outcomes [1]. The adoption of minimally invasive surgical techniques and enhanced recovery after surgery (ERAS) protocols in colorectal surgical practice reduce the surgical stress response and enhance postoperative care [2, 3]. However, many short-term postoperative complications continue to impact patient recovery significantly.

Postoperative ileus (POI) is an expected, temporary decline in gastrointestinal motility that typically lasts 48 to 72 h in patients with colorectal cancer [4]. In contrast, prolonged postoperative ileus (PPOI) refers to a failure of gastrointestinal function to recover beyond this timeframe [5]. PPOI is a common postoperative complication that can hinder recovery and disrupt the success of ERAS protocols. It is characterized by various symptoms, including abdominal distension, nausea, and vomiting [6]. Studies indicate that the incidence of PPOI after colorectal surgery ranges from 3% to 32% [7]. Early identification of the risk factors associated with PPOI and timely implementation of appropriate treatment strategies are crucial for the successful execution of ERAS protocols and to promote patient recovery.

While some research has explored the risk factors for PPOI after colorectal surgery, the perioperative management

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Published online: 23 May 2025

strategies for colonic and rectal surgeries differ in several aspects. For example, preoperative radiotherapy and the creation of a stoma for rectal cancer may impact postoperative gastrointestinal recovery. Despite this, there are very few studies specifically focused on the risk factors for PPOI following rectal surgery. Therefore, we conducted this single-center, retrospective study with a propensity score matching (PSM) method to analyze the clinical characteristics and risk factors associated with PPOI after laparoscopic TME for rectal cancer.

Methods

Patients

We conducted a single-center retrospectives trial and analyzed the clinical data of patients with rectal cancer who were admitted to the Department of General Surgery at Peking Union Medical College Hospital from March 2019 to August 2023. The inclusion criteria include: (1) patients aged ≥ 18 years old, regardless of gender; (2) patients with a pathological diagnosis of rectal adenocarcinoma; and (3) patients who underwent laparoscopic radical surgery. The exclusion criteria include: (1) patients with acute obstruction or perforation requiring emergency surgery; (2) patients with other synchronous malignancies or serious illnesses; (3) patients who received open surgery or were converted to open surgery; and (4) patients with incomplete case data. A total of 1090 patients met the inclusion and exclusion criteria and were enrolled in this study. The flowchart of this study is shown in Fig. 1.

Perioperative management

All patients underwent laparoscopic radical surgery performed by specialized colorectal surgeons. For patients diagnosed with locally advanced rectal cancer, neoadjuvant

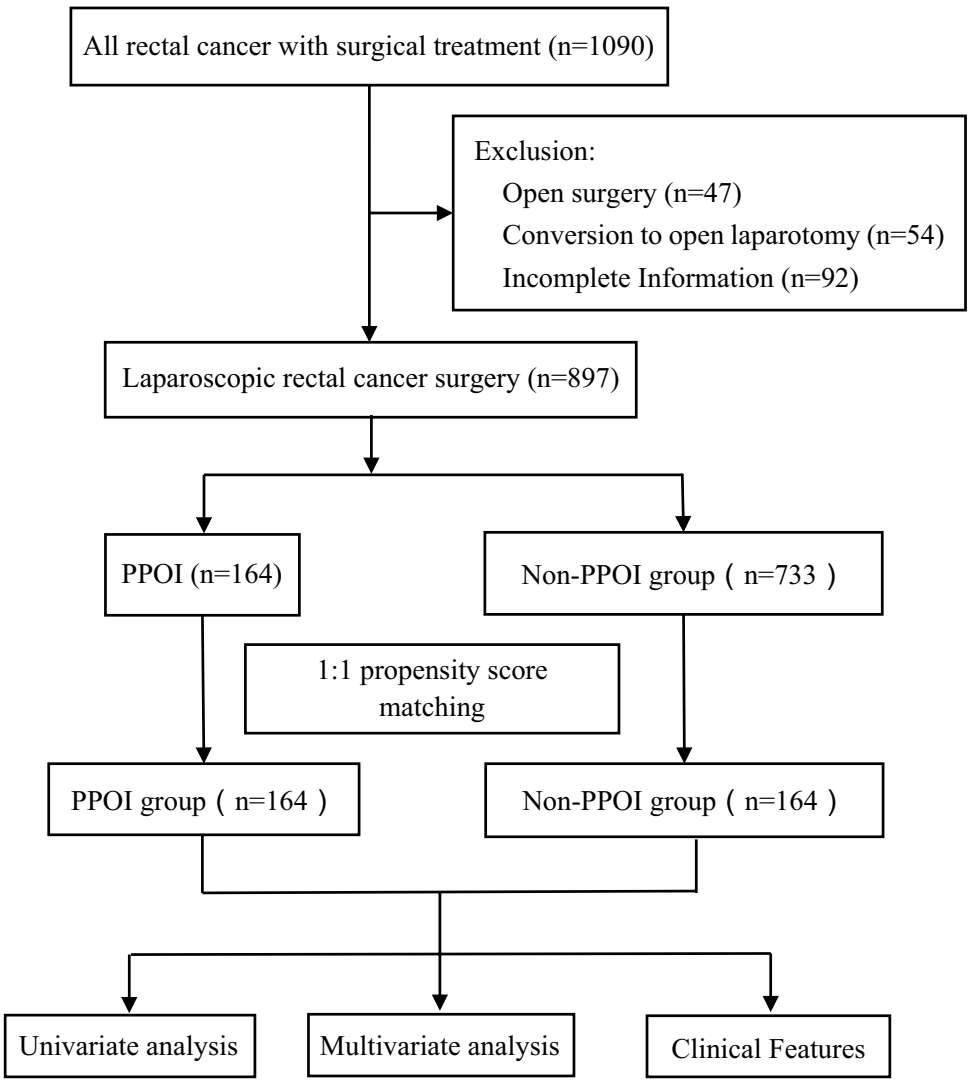

Fig. 1 Flow chart of the study design

therapy was administered. Prior to surgery, standard bowel preparation and prophylactic antibiotics were given. Bowel preparation primarily involved the use of polyethylene glycol electrolyte powder, combined with fasting and fluid replacement. Fluid replacement strategies included enteral nutrition, parenteral nutrition, or glucose alone, with no preference. After the operation, patients were managed similarly, including early mobilization and a clear liquid diet starting on postoperative day 1 (POD 1). Multimodal analgesia and necessary antiemetic treatments were also utilized on the basis of the patient's condition.

For the patients who developed PPOI, treatment primarily consisted of conservative measures. Initially, probiotics (such as *Bacillus licheniformis* and *Bifidobacterium*) were administered, along with water fasting. Depending on the severity of the condition, oral vancomycin was provided. If abdominal distension persisted for 2 days or if new vomiting symptoms developed, decompression options, such as the placement of a transnasal ileus tube or a nasogastric tube, would be considered [8].

Assessment parameters and definition

PPOI was defined according to the recommendations of Vather et al. [9]. It was diagnosed if two or more of the following five criteria were met on or after POD 4: (1) Nausea or vomiting; (2) Inability to tolerate a solid oral diet for the past 24 h; (3) absence of flatus for the last 24 h; (4) abdominal distension; and (5) radiologic confirmation. The typical clinical manifestation is shown in Fig. 2.

Demographic information, including age, gender, body mass index (BMI), and American Society of Anesthesiologists Physical Status (ASA-PS) was recorded [10]. Preoperative clinical indicators, such as the bowel preparation method, whether a preoperative colonoscopy was performed, and the fluid replacement strategy on the day before surgery, were documented. Tumor assessments included the distance of the tumor from the anal verge and the clinical TNM stage. Operative parameters recorded included total operative time, blood loss, and type of ostomy. Postoperative parameters comprised the use of antibiotics after surgery (specifically those administered before the onset of PPOI), along with the clinical features, duration, and treatment plan for PPOI.

Statistical analysis

To address possible bias in selecting patients, we used a PSM method in a 1:1 ratio to match patients with and without PPOI. Three basic patient characteristics (age, BMI, and ASA score) were taken into account. Categorical variables were presented as frequencies (percentages), which were compared with Chi-squared or with Fisher's exact test. Continuous parameters were analyzed using the Student's *t*-test or Mann–Whitney *U* test on the basis of the distribution. Normally distributed quantitative data were presented as mean ± standard deviation (SD), and non-normally distributed quantitative data were presented as median (interquartile range). A two-tailed *p*-value less than 0.05 was considered statistically significant. Variables with a *p*-value less than 0.05 in univariate analysis were included in logistic regression analysis to calculate the odds ratio (OR) and 95% confidence interval. All statistical analyses were conducted using SPSS version 26.0 software (IBM Corporation, Chicago, IL) and R version 4.3.0.

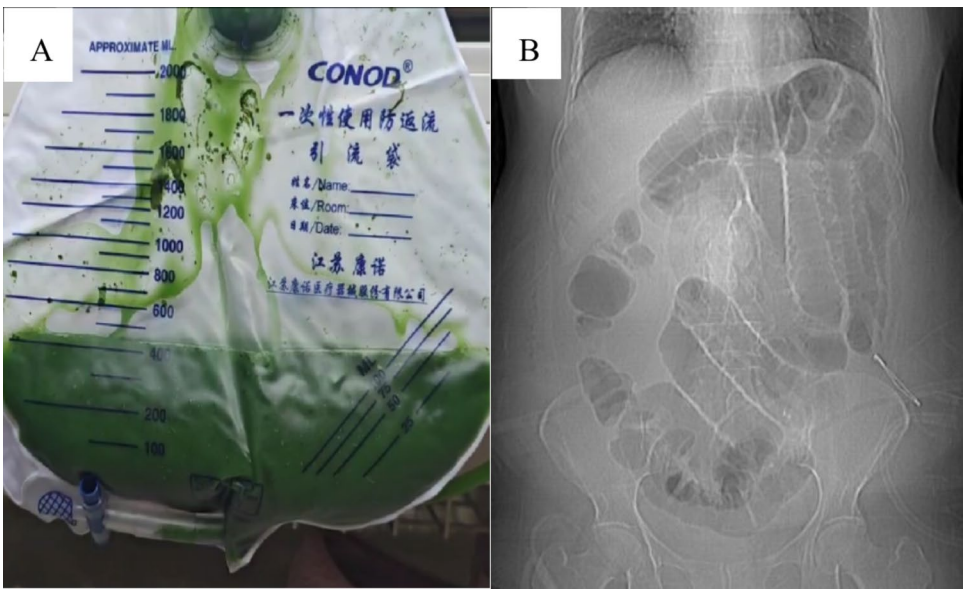

Fig. 2 Typical clinical manifestations of PPOI. **A** Green gastric contents drained from a nasogastric tube; **B** abdominal X-ray examinations showed significant enlarged intestines

Results

From March 2019 to September 2023, we identified 1090 patients diagnosed with rectal cancer who underwent TME surgery at Peking Union Medical College Hospital (PUMCH) from the colorectal cancer database. We excluded 47 patients who underwent open surgery, 54 who had conversion to open surgery, and 92 with incomplete information, resulting in a final study population of 897 patients who underwent laparoscopic TME surgery. Among these, 164 patients (18.3%) developed PPOI. On the basis of the occurrence of PPOI, we divided the patients into two groups: the PPOI group and the non-PPOI group. Owing to the high heterogeneity, we conducted a 1:1 PSM, and 164 patients in each group were selected for further analysis.

Baseline clinical characteristics

After PSM, Demographic and clinical features of the two groups after PSM are presented in Table 1. In the PPOI group, there were 126 male patients (76.8%), while the non-PPOI group had 117 male patients (71.3%) ($p=0.257$). A total of 72 patients (43.9%) in the PPOI group and 82 patients (50.0%) in the non-PPOI group received neoadjuvant chemoradiotherapy prior to surgery ($p=0.269$). There were also no significant differences between the two groups regarding age, body mass index (BMI), ASA Physical Status (ASA-PS), gender, comorbid conditions (such as hypertension, diabetes mellitus, and coronary heart disease), history of abdominal surgery, distance from the lower border of the tumor to the anal verge, and clinical stage.

Univariate and multivariate analysis

Compared with the non-PPOI group, more patients in the PPOI group experienced bowel obstruction before surgery ($p=0.006$). All patients underwent mechanical bowel preparation with oral laxatives before surgery, with no statistical difference in the quantity of oral laxatives used between the two groups ($p=0.532$). However, differences were observed in the preoperative fluid replacement strategy and the use of prophylactic anaerobic antibiotics between the groups ($p<0.001$). The types of stomas also differed significantly, with more patients in the PPOI group receiving ileostomy ($p<0.001$). The antibiotic use after surgery was similar, with 13 patients (7.9%) in the non-PPOI group and 14 patients (8.5%) in the PPOI group receiving antibiotics ($p=0.841$) (Table 2).

In the previous univariate analysis, factors such as preoperative bowel obstruction, preoperative prophylactic anaerobic antibiotic therapy, preoperative fluid replacement strategy, and stoma type were identified as significant differences. These factors were then included in a logistic regression analysis. The results, detailed in Table 3, indicated that the use of glucose alone before surgery, preoperative bowel obstruction (odds ratio [OR] = 2.08; 95% confidence interval [CI] 1.08–4.04; $p=0.029$), and the presence of an ileostomy (OR = 3.57; 95% CI 1.52–8.39; $p=0.003$) were identified as independent risk factors for developing PPOI. Conversely,

Table 1 Demographic and clinical features after PSM

	PPOI ($n=164$)	Non-PPOI ($n=164$)	p
Age, > 65 years, *n* (%)	69 (42.1)	69 (42.1)	1.000
BMI, > 23.9 kg/m^2, *n* (%)	93 (56.7)	93 (56.7)	1.000
ASA, I–II, *n* (%)	144 (87.8)	144 (87.8)	1.000
Male, *n* (%)	126 (76.8)	117 (71.3)	0.257
Hypertension, *n* (%)	50 (30.5)	49 (29.9)	0.904
DM, *n* (%)	31 (18.9)	26 (15.9)	0.466
CHD, *n* (%)	12 (7.3)	19 (11.6)	0.186
History of abdominal surgery, *n* (%)	25 (15.2)	21 (12.8)	0.525
Distance from lower border of tumor to anal verge, *n* (%)			
< 5 cm	37 (22.6)	44 (26.8)	0.704
5–10 cm	63 (38.4)	64 (39.0)	
> 10 cm	64 (39.0)	56 (34.2)	
Clinical T stage, *n* (%)			
1–2	30 (18.3)	40 (24.4)	0.178
3–4	134 (81.7)	124 (75.6)	
Clinical *N* stage, *N*+, *n* (%)	108 (65.9)	116 (70.7)	0.342
Neoadjuvant therapy, *n* (%)	72 (43.9)	82 (50.0)	0.269

BMI body mass index, *ASA* American Society of Anesthesiologists Physical Status, *DM* diabetes mellitus, *CHD* coronary heart disease

Table 2 Univariate analysis of the PPOI group and non-PPOI group after PSM

Variables	PPOI ($n=164$)	Non-PPOI ($n=164$)	p
Operation time, min, M (IQR)	117.50 (100.00, 140.00)	120.00 (100.00, 143.00)	0.402
Stage I opening of prophylactic ileostomy, *n* (%)	63 (52.94)	69 (64.49)	0.079
Preoperative bowel obstruction, yes, *n* (%)	38 (23.2)	19 (11.6)	0.006*
Number of laxatives, *n* (%)			
1–2 packet	123 (75)	118 (72)	0.532
3–4 packet	41 (25)	46 (28)	
Antibiotic use after surgery, *n* (%)	14 (8.5)	13 (7.9)	0.841
Preoperative nutrition support, *n* (%)			
Single glucose 5%	84 (51.2)	44 (26.8)	< 0.001*
Enteral nutrition	45 (27.4)	51 (31.1)	
Parenteral nutrition	35 (21.3)	69 (42.1)	
Prophylactic anaerobic antibiotic therapy, *n* (%)	94 (57.3)	60 (36.6)	< 0.001*
Type of stroma, *n* (%)			
None	44 (26.8)	55 (33.5)	< 0.001*
Ileostomy	101 (61.6)	57 (34.8)	
Colostomy	19 (11.6)	52 (31.7)	

M median, *IQR* interquartile range

*Significant statistical difference

Table 3 Multivariate logistic regression analysis

Variables	β	Wald's	OR (95% CI)	p
Preoperative bowel obstruction, yes/no	0.73	2.18	2.08 (1.08–4.04)	0.029
Preoperative fluid replacement				
Glucose 5%	ref	ref	ref	ref
Enteral nutrition	–1.26	0.38	0.28 (0.13–0.60)	< .001
Parenteral nutrition	–1.17	0.41	0.31 (0.14–0.70)	0.005
Type of stroma				
None	ref	ref	ref	ref
Colostomy	–1.59	–4.44	0.20 (0.10–0.41)	< .001
Ileostomy	1.27	2.92	3.57 (1.52–8.39)	0.003
Prophylactic anaerobic antibiotic therapy, yes/no	–0.19	0.33	0.82 (0.43–1.57)	0.556

preoperative nutritional supplementation (enteral nutrition: OR = 0.28, 95% CI 0.10–0.41, $p < 0.001$; parenteral nutrition: OR = 0.31, 95% CI 0.14–0.70, $p = 0.005$), along with a colostomy (OR = 0.20; 95% CI 0.10–0.41; $p < 0.001$), were regarded as protective factors.

Analysis of clinical features of PPOI

Among the 164 patients who experienced PPOI, symptoms typically manifested around POD 4–5. In total, 48 patients (29.3%) exhibited a white blood cell count exceeding 5/HPF in their stool routine tests. The positivity rate for *Clostridium difficile* in their stool was 17.7%. The

Table 4 Clinical characteristics of patients with PPOI

Clinical features	Statistics, *n* (%)
Clavien–Dindo grades	
Grade I–II	135 (82.3)
Grade IIIa	27 (16.5)
Grade IIIb	1 (0.6)
Grade IV	1 (0.6)
Onset time of PPOI	
POD 4–5	143 (87.2)
> POD 5	21 (12.8)
The results of stool test (WBC/HPF)	
0	17 (10.4)
1–10	50 (30.5)
11–20	18 (11.0)
> 20	40 (24.4)
Not available	39 (23.8)
Detection of Clostridium difficile *toxins*	
Positive	29 (17.7)
Negative	63 (38.4)
Not available	72 (43.9)

WBC white blood cell, *POD* postoperative day

Clavien–Dindo grade for PPOI of the cases was primarily I–II (Table 4). As for the treatment of PPOI, 134 patients (81.7%) received oral probiotics, and 140 patients (85.4%) were prescribed oral vancomycin. As patients experienced symptom relief, the use of probiotics and vancomycin was gradually discontinued (Table 5). In addition, 48 patients

Table 5 Treatment strategies of PPOI

	Statistics, *n*(%)
Treatment strategy	
Probiotics	132 (80.5)
Oral vancomycin	140 (85.4)
Nasogastric tube	48 (29.3)
Transnasal ileus tube	27 (16.5)
Duration of oral vancomycin therapy	
1–2 d	10 (7.14)
3–5 d	72 (51.4)
6–8 d	31 (22.1)
> 8 d	27 (19.3)
Time of nasogastric tube placement	
1–2 days after diagnosis	33 (68.8)
3 days after diagnosis	8 (16.7)
More than 3 days after the diagnosis	7 (14.6)
Duration from nasogastric tube placement to symptom improvement	
1–3 d	13 (27.1)
4–6 d	14 (29.2)
> 6 d	5 (10.4)
Treatment failure	16 (33.3)
Time of transnasal ileus tube placement	
1–2 days after diagnosis	7 (25.9)
3–4 days after diagnosis	15 (55.6)
More than 4 days after the diagnosis	5 (18.5)
Duration of transnasal ileus tube drainage	
1–3 d	8 (29.6)
4–5 d	14 (51.9)
> 5 d	5 (18.5)

(29.3%) required nasogastric tube placement due to severe abdominal distension or failure to relieve symptoms with drug treatment. Moreover, 27 patients (16.5%) presented with severe symptoms of small bowel obstruction or ineffective decompression from the gastric tube, leading to the insertion of transnasal ileus tubes. For patients requiring gastrointestinal decompression, tubes were removed when the drainage volume remained below 20 mL for 2 consecutive days. Most nasogastric tubes were removed after 3 days, and transnasal ileus tubes were removed after 4 days. The majority of patients experienced symptom relief after the aforementioned treatments. Only one patient required admission to the intensive care unit (ICU) due to infectious shock.

Discussion

PPOI is associated with poorer patient outcomes and prolonged hospitalization. The definition of PPOI varies among studies but generally includes: (a) the reinsertion of a nasogastric tube, and (b) the absence of bowel function on POD 3, POD 5, or POD 7. In our study, we adopted the definition recommended by Vather et al., which incorporates signs, symptoms, and imaging findings. Our retrospective study found that the incidence of PPOI after laparoscopic total mesorectal excision (TME) is 18.3%, which is consistent with previously reported results.

With the implementation of ERAS protocols in gastrointestinal surgery, there have been more options for nutritional supplementation the day before surgery. Our study results showed that comprehensive nutritional replacement before surgery is more beneficial than using single glucose for reducing the incidence of PPOI. Enteral nutrition is a more physiological approach, promoting the activity of gastrointestinal mucosal cells through luminal sensing mechanisms [11, 12]. In contrast, relying solely on glucose may compromise the mucosal barrier, leading to bacterial and endotoxin translocation and subsequent intestinal inflammatory responses [13]. In addition, preoperative comprehensive nutrition helps improve patients' nutritional status and enhances their tolerance to surgical trauma.

However, the exact pathogenesis of PPOI remains unclear. The balance of gut microbiota is critical for maintaining overall health. Bowel resection and preparation before surgery also significantly affect gut microbiota, often reducing its composition, particularly the abundance of *Lactobacillaceae* [14]. Intestinal flora dysbiosis (IFD), which refers to the disruption of microbial communities in the gut—encompassing changes in type, quantity, and proportions of microbiota—may be an important factor contributing to PPOI. *Clostridium difficile* (*C. difficile*) infection (CDI) is a potential manifestation of IFD [15]. The cytotoxic effects of toxins A and B on the colonic epithelium cause diarrhea, colonic inflammation, and the characteristic pseudomembranous colitis [16]. However, in this study, only about 17.7% of patients tested positive for *C. difficile* toxin. This low detection rate may result from the limited accuracy of *C. difficile* toxin testing [17]. In addition, our univariate analysis indicated that prophylactic anaerobic antibiotic therapy was more common in the PPOI group. While this finding was not confirmed in multivariate logistic regression analysis, it warrants further attention. The use of anti-anaerobic antibiotics may inhibit commensal bowel flora, disrupt gut microbiota, and allow pathogens such as *C. difficile* to thrive [18, 19]. Although we did not assess the intestinal flora of the enrolled patients, the relationship between IFD and PPOI requires further investigation, which our team is actively pursuing.

In our study, both univariate and multivariate analyses revealed that ileostomy is an independent risk factor for PPOI. The choice of stoma type is a significant consideration for the temporary decompression of colorectal anastomosis. The relationship between postoperative ileus and stoma type remains uncertain. For instance, a meta-analysis by Zheng Ge et al. found no significant difference between ileostomy

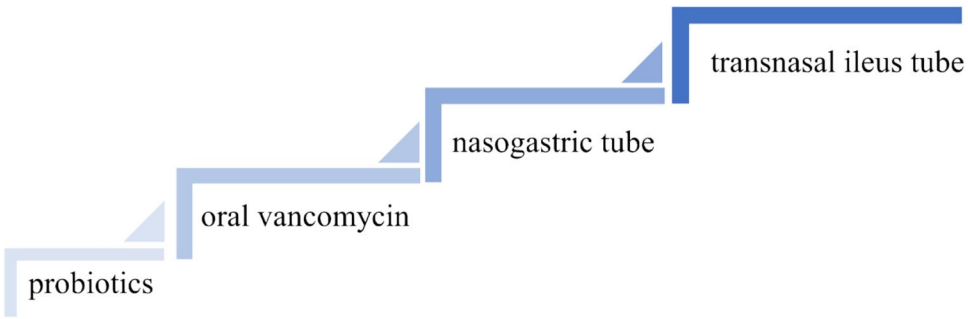

Fig. 3 Innovative multi-step treatment strategy for PPOI

and colostomy groups, while Rui Du et al. reported that patients with colostomy had a lower rate of ileus. Therefore, caution is necessary when interpreting these findings [20, 21]. The ileum has a higher concentration of *Lactobacillus* compared with the colon, and directing small bowel contents through an ileostomy may reduce these beneficial bacteria [22, 23]. This increased rate of IFD may explain the higher incidence of PPOI in patients with ileostomy. Hence, surgeons should carefully select the appropriate stoma type on the basis of individual patient circumstances. For patients with ileostomy, vigilance regarding potential PPOI is crucial to facilitate early intervention.

In this study, we analyze the treatment and recovery of PPOI. Our center's strategy for managing PPOI can be summarized as a multi-stage protocol (Fig. 3). First, for patients suspected of having PPOI, we will begin early and broad oral administration of probiotics. Probiotic therapy not only helps regulate gut microbiota but also mitigates chemotherapy-induced intestinal damage by restoring the overall structure of intestinal villi [24]. Secondly, in cases with elevated fecal white blood cells (WBCs) or a positive test for *Clostridioides difficile* toxin, IFD or intestinal infection—particularly CDI—may contribute to the development of PPOI. Oral vancomycin, recommended as the first-line treatment for mild CDI and characterized by minimal systemic absorption, was therefore selected as a safe therapeutic option and demonstrated favorable effectiveness in our clinical practice. For patients experiencing symptoms such as severe abdominal distension or confirmed paralytic ileus on imaging, the insertion of a nasogastric tube will be deemed necessary. Finally, for patients whose symptoms remain unresolved, the placement of a transnasal ileus tube will be chosen.

Gastrointestinal decompression is a critical treatment for PPOI, and some researchers suggest that the reinsertion of a nasogastric tube should be considered a definitive criterion for PPOI diagnosis [7]. However, gastrointestinal decompression tubes are thought to be associated with a higher risk of fever, pneumonia, and even a delayed return of gastrointestinal function [25]. Through our treatment of patients with PPOI, we have observed that a significant number could benefit from proper drugs, including the use of oral probiotics and vancomycin, thus mitigating the need for gastrointestinal decompression. It is also important to note that single drug application might delay the timely insertion of a gastrointestinal decompression tube for patients who do not respond to oral probiotics and vancomycin. Identifying these patients and providing targeted treatment is crucial.

This study has several limitations. Firstly, as a retrospective case–control study, it may be prone to selection bias despite employing PSM. Secondly, the multi-stage diagnostic and therapeutic regimen was developed on the basis of empirical observations at our center and requires validation through prospective studies. In addition, the effectiveness of probiotic treatment in reducing the incidence of PPOI in high-risk patients, as well as the relationship between PPOI and IFD, has yet to be verified, necessitating further prospective research.

Conclusions

In summary, special attention must be given to patients following TME to prevent the occurrence of PPOI. Providing nutritional support, particularly enteral nutrition, the day before surgery, and carefully selecting the type of ostomy on the basis of the patient's condition during surgery are both beneficial strategies. Regarding the treatment of PPOI, our team's multi-stage treatment protocol may be effective and can help avoid unnecessary gastrointestinal decompression tube placement.

Author contributions X.Z. and C.W. contributed equally to this study, they drafted the manuscript and conducted the data analysis. J.L., L.X., B.W., Y.X., and Guo.L. enrolled and managed patients. X.Z., C.W., Gan.L., X.Q., and W.C. collected clinical data, made the table and drew the figures. Y.X. and Guo.L. conceptualized the research and revised the manuscript. All the authors have read and approved the final manuscript.

Funding This work was supported by grants from The National High Level Hospital Clinical Research Funding (Grant number: 2022-PUMCH-C-005).

Data availability The data that support the findings of this study are available on request from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical and informed consent This retrospective study was approved by the Ethics Committee of Peking Union Medical College Hospital (Approval ID: I24PJ0719). The requirement for informed consent was waived by the ethics committee due to the retrospective nature of this study.

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