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Incidence and predictors of prolonged postoperative ileus after colorectal surgery in the context of an enhanced recovery pathway

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Abstract

Background Prolonged postoperative ileus (PPOI) is common after colorectal surgery but has not been widely studied in the context of enhanced recovery pathways (ERPs) that include interventions aimed to accelerate gastrointestinal recovery. The aim of this study is to estimate the incidence and predictors of PPOI in the context of an ERP for colorectal surgery.

Methods We analyzed data from an institutional colorectal surgery ERP registry. Incidence of PPOI was estimated according to a definition adapted from Vather (intolerance of solid food and absence of flatus or bowel movement for ≥ 4 days) and compared to other definitions in the literature. Potential risk factors for PPOI were identified from previous studies, and their predictive ability was evaluated using Bayesian model averaging (BMA). Results are presented as posterior effect probability (PEP). Evidence of association was categorized as: no evidence (PEP < 50%), weak evidence (50–75%), positive evidence (75–95%), strong evidence (95–99%), and very strong evidence (> 99%).

Results There were 323 patients analyzed (mean age 63.5 years, 51% males, 74% laparoscopic, 33% rectal resection). The incidence of PPOI was 19% according to the primary definition, but varied between 11 and 59% when using other definitions. On BMA analysis, intraoperative blood loss (PEP 99%; very strong evidence), administration of any intravenous opioids in the first 48 h (PEP 94%; strong evidence), postoperative epidural analgesia (PEP 56%; weak evidence), and non-compliance with intra-operative fluid management protocols (3 ml/kg/h for laparoscopic and 5 ml/kg/h for open; PEP 55%, weak evidence) were predictors of PPOI.

Conclusions The incidence of PPOI after colorectal surgery is high even within an established ERP and varied considerably by diagnostic criteria, highlighting the need for a consensus definition. The use of intravenous opioids is a modifiable strong predictor of PPOI within an ERP, while the role of epidural analgesia and intraoperative fluid management should be further evaluated.

Keywords Colorectal · Surgery · Postoperative ileus

Prolonged postoperative ileus (PPOI) is a common source of morbidity after abdominal surgery characterized by delayed return of gastrointestinal (GI) function leading to nausea,

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vomiting, patient discomfort, and the possible need for nasogastric (NG) tube decompression [1]. PPOI is associated with significantly increased in-hospital length of stay (LOS) [2] and is estimated to cost 1.46 billion dollars annually in the USA alone [3].

The reported incidence of PPOI after colorectal surgery varies widely, ranging from 2 to 61%, largely due to variations in the definition applied in different studies [4]. The results from studies aimed to identify predictors of PPOI are also conflicting and inconsistent. This, in part, may be the result of using different model selection strategies (i.e., backward, forward, and stepwise regression models), which identify predictors using a single "best fit" predictive model without accounting for model uncertainty. This potentially leads to different conclusions even when analyzing the same dataset [5]. Recent literature suggests that Bayesian model averaging (BMA) offers a superior approach as it averages prediction estimates from multiple models, accounting for model uncertainty [5–7].

Enhanced recovery care pathways (ERPs) are multimodal, evidence-based pathways that reduce morbidity and hospital LOS [8]. Many interventions included in ERPs are aimed at improving GI function (e.g., gum-chewing, fluid balance, multimodal analgesia, early feeding, no routine use of NG tubes) [8]; however, the incidence and predictors of PPOI have not been widely studied in this context of care. The aim of this study is to evaluate the incidence PPOI in patients undergoing elective colorectal surgery in the context of a well-established perioperative ERP and identify predictors of PPOI using BMA analysis.

Methods

This observational cohort study was designed and reported following the Strengthening the Reporting of Observations studies in Epidemiology Statement [9], and ethics approval was granted from our institutional ethics review board (14-170-SDR).

Data were prospectively collected from patients undergoing elective colorectal surgery in our university-affiliated tertiary teaching hospital between September 2012 and December 2014. Perioperative care followed an established ERP for colorectal surgery that was first implemented in 2006 [10]. The ERP is consistent with recommendations from the ERAS society [8] and includes 23 elements of care (Supplemental Appendix 1). All patients are admitted to the hospital on the day of surgery, and discharge is planned for postoperative day (POD) 3 or earlier.

Data were collected by a dedicated clinical auditor and entered into the Enhanced Recovery After Surgery (ERAS) Interactive Audit system (http://www.erassociety.org, ENCARE, Kist, Sweden). This database includes approximately 140 variables including preoperative patient characteristics, operative data, and postoperative outcomes (complications, visits to the emergency room (ER), rate of readmissions, and re-operations) with a follow-up period of 30 days. For the purpose of this study, postoperative complications were defined a priori according to criteria reported elsewhere [10] and classified according to Clavien–Dindo classification [11]. Severe complications were defined as those with Clavien–Dindo classification III–V [11]. Patients who were scheduled for laparoscopic surgery but were converted to open procedure were analyzed as open surgery (per protocol analysis). Additional information regarding preoperative comorbidities was retrieved from medical records to calculate age-adjusted Charlson comorbidity index [12, 13].

Patients not followed prospectively by the clinical auditor were excluded from the study. As we were only interested in primary PPOI, defined as occurring in the absence of a precipitating complication [1], we also excluded patients with symptoms of PPOI who were subsequently diagnosed with bowel obstruction, anastomotic leak, intra-abdominal abscess or bowel perforation during the primary stay (i.e., secondary postoperative ileus [1]).

We used a modification of the definition proposed by Vather et al. [14] to identify patients with PPOI. This definition, based on a systematic literature review and global survey of experts, diagnoses PPOI if a patient meets at least two of the following five criteria on or after POD 4: (a) nausea or vomiting, (b) inability to tolerate an oral diet over last 24 h, (c) absence of flatus over last 24 h, (d) abdominal distention, (e) radiologic confirmation.

As the database did not include the variables "abdominal distention" and "radiologic confirmation", we adapted Vather's criteria to include only the first three variables related to nausea/vomiting, passage of flatus/bowel movement, and tolerance of oral diet. These adapted criteria are in accordance with the composite end-point "GI-3" (tolerance of solid food and first flatus or bowel movement), which was used as an outcome in several randomized clinical trials [15]. In other words, PPOI was defined as the absence of GI-3 by POD 4. The incidence of PPOI estimated according to this primary definition was compared to other definitions identified in the systematic review by Wolthius et al. [4], including (1) absence of bowel function (GI-3) with a cutoff points varying between 3 and 7 days and (2) the need for NG tube reinsertion. The impact of PPOI on hospital LOS was compared between the different definition criteria.

Variables previously associated with PPOI in the literature were analyzed as potential predictors. These included gender [16–18], surgical approach [16–21], stoma formation [16, 22], estimated blood loss (EBL) [16, 19, 23], operative time [16, 20, 21], age [17, 19, 21, 24], body mass index (BMI) [19, 25], smoking [19], neoadjuvant chemotherapy [19], lack of mechanical bowel preparation [19], age-adjusted Charlson comorbidity index (ACCI) [26], history of previous abdominal surgery [24], American Society of Anesthesiologist (ASA) score > 2 [17, 20], incision size [18], epidural analgesia [27], inflammatory bowel disease (IBD) [17, 19], preoperative radiotherapy [28], rectal resection [4], opioid analgesia [23], and excessive intraoperative intravenous fluid volume [18]. Opioid analgesia was defined as the use any IV opioids in the first 48 h after surgery, including PCA. Excessive IVF was defined as non-compliance with our institutional recommendation regarding intraoperative fluid replacement (maximum of 3 ml/kg/h for laparoscopy and 5 ml/kg/h for open surgery, excluding replacement of EBL) [10, 29].

For univariate analysis, normally distributed continuous data were compared between patients with and without PPOI using independent Student's *t* test and reported as means with standard deviations (SD); non-normally distributed data were compared using Wilcoxon rank-sum and reported as medians with inter-quartile range (IQRs). Categorical data were compared using Fisher's exact test and reported with frequencies and percentages (%). A p value < 0.05 was considered statistically significant.

Multivariate analysis to identify predictors of PPOI was conducted using BMA including all potential predictors described above. To account for model uncertainty, we considered all possible models resulting from including or excluding the predictors of interest. This approach takes into account the relative uncertainty of different models [5–7]. The posterior effect probability (PEP) of each variable was calculated from the averaged estimates from all possible models. Odds ratios (OR) and 95% confidence intervals (CI) were calculated from the averaged coefficients. Missing data were handled using listwise deletion (e.g., no imputation was conducted). In accordance with the previous literature, we interpreted PEP values by categorizing evidence of association as: no evidence (PEP < 50%), weak evidence (50–75%), positive evidence (75–95%), strong evidence (95–99%), and very strong evidence (> 99%) [7, 30]. BMA was conducted using R statistics software (R version 3.4.0; R Foundation for Statistical Computing, Vienna, Austria), while other analyses were performed using Stata 14 (StataCorp, College Station, TX, USA).

Results

Four hundred and forty patients underwent elective bowel resection during the study period. Of those, we excluded 94 that were not followed prospectively by the clinical auditor, and 23 who had potential secondary ileus (1 small bowel obstruction, 3 bowel perforation, 11 anastomotic leak, and 8 intra-abdominal abscess). The remaining 323 patients were included in the final analysis. The mean age of patients was 63.5 (15) years, 51% were males, and the mean BMI was 26 (4.8) (kg/m^2). The most common diagnosis was malignancy (66%), the most common procedure was right hemicolectomy (31%), and the main surgical approach was laparoscopic (74%) with a conversion rate of 9% (Table 1).

Sixty-two patients (19%) developed PPOI according to our primary definition (Table 2). The incidence varied from 11 to 59% when using successive cutoff points for recovery of GI-3 (POD 2–7) and was 18% when PPOI was defined as the need for NG insertion. However, 32% of patients having PPOI using the primary definition did not have NG insertion while 6% of patients having an NG did not meet the primary definition of PPOI. Hospital LOS was significantly higher in patients who developed PPOI in comparison with those with no PPOI, regardless of the definition criteria. Median differences in LOS when using the primary definition was 6 days and ranged from 5 to 7 days for other definitions (Table 2). Diagnosis of PPOI by POD 4 was based on intolerance of oral intake in 72.6% of patients (while still had lower GI function recovery, i.e., passage of flatus or bowel movement), while 22.6% had intolerance of oral intake without evidence of lower GI recovery. Only 4.8% of patients tolerated oral intake but had no evidence of lower GI recovery.

Baseline characteristics of patients diagnosed with PPOI according to the primary definition compared with those without PPOI are shown in Table 3. The development of PPOI was significantly associated with higher ASA scores (> 2), rectal resection, open surgery, new stoma formation, larger incision, higher EBL and longer surgery duration. Patients with PPOI had more intra-operative hemorrhage (i.e., bleeding requiring transfusion of packed red blood cells during surgery or within 24 h after surgery) and received more intra-operative transfusions and total intravenous fluids. There was no difference in compliance with the institutional guidelines for intra-operative IVF administration which was relatively low in both groups.

After surgery, patients with PPOI were more likely to have received intravenous opioids in the first 48 h compared to those without PPOI (Table 4). Nonetheless, there was no difference in the proportion of patients receiving PCA and/or epidural as the main modality of postoperative analgesia. The median time to flatus, bowel movement, tolerance of solid food, time to achieve GI-3 and need for parenteral nutrition, NG insertion, and postoperative transfusion were higher in patients with PPOI. Patients with PPOI had a higher incidence of cardiovascular and infectious complications and higher overall incidence of severe complications within 30 days. However, there were no differences in the rates of ER visits, readmissions and re-operations.

The results of the BMA analysis are presented in Table 5. Seven patients were omitted from this analysis due to missing data on length of incision. From the 20 variables tested in the models, 4 predictors of PPOI were identified:

Table 1 Baseline characteristics

Variable	Overall ($n=323$)
Age, mean (SD)	63.5 (15)
Male, no. (%)	166 (51%)
BMI (kg/m^2), mean (SD)	26 (4.8)
Smoker, no. (%)	34 (11%)
Diabetes, no. (%)	44 (14%)
Hypertension, no. (%)	117 (37%) missing = 5
ASA, no. (%)	
I–II	221 (68%)
III–IV	102 (32%)
ACCI, mean (SD)	4 (2.5)
Primary diagnosis, no. (%)	
Malignancy	212 (66%)
Inflammatory bowel disease	45 (14%)
Crohn's disease	25 (8%)
Ulcerative colitis	20 (6%)
Benign polyp	35 (11%)
Diverticular disease	25 (8%)
Other benign diagnosis	6 (2%)
Procedure, no. (%)	
Small bowel resection	7 (2%)
Ileocecal resection	9 (3%)
Right hemicolectomy	100 (31%)
Left hemicolectomy	21 (6.5%)
Total/subtotal-colectomy	14 (4%)
Anterior resection	55 (17%)
Low anterior resection	65 (20%)
Abdominoperineal resection	20 (6%)
Total proctocolectomy ± IPAA	21 (6.5%)
Other colorectal procedures[a]	11 (3%)
Rectal resection, no. (%)[b]	106 (33%)
New stoma, no. (%)	79 (24.5%)
Surgical approach, no. (%)[c]	
Open	84 (26%)
Laparoscopic	239 (74%)

Data expressed as no. (%), mean (SD), or median [IQR]

SD standard deviation, *IQR* inter-quartile range, *ASA* American Society of Anesthesiologists, *ACCI* age-adjusted Charlson's comorbidity index, *BMI* body mass index, *LAR* low anterior resection, *APR* abdominal perineal resection, *IPAA* ileal pouch–anal anastomosis

[a]Includes reversal of Hartmann's procedure ($n=6$), takedown of end ileostomy + ileorectal anastomosis ($n=3$), enterocutaneous fistula repair ($n=1$), and fashioning of diverting transverse colostomy ($n=1$)

[b]Includes low anterior resection, proctocolectomy, and abdominoperineal resection

[c]Patients who were scheduled for laparoscopic surgery but underwent conversion to open surgery ($n=23$, 9%), were categorized as open approach

intraoperative EBL (PEP 99%, very strong evidence), administration of any IV opioids in the first 48 h (PEP 94%; strong evidence), postoperative epidural analgesia (PEP 56%; weak evidence), and providing more fluids than suggested by the intraoperative fluid management protocol (PEP 55%, weak evidence).

Discussion

In this study, the incidence of PPOI after elective colorectal surgery remained high, despite a high proportion of laparoscopic cases and the use of an established ERP including multiple elements aimed to enhance GI recovery. PPOI was associated with increased postoperative complications and LOS. We identified two strong predictors of PPOI, intraoperative blood loss and use of any IV opioids in the first 48 h postoperatively.

The incidence of PPOI was 19% when using the primary definition, but this varied significantly between 11 and 59% when considering successive times of achieving GI recovery. Need for NG tube insertion yielded a similar incidence as the primary definition, however, it did not always identify the same patients. In 2016, Wolthuis et al. [4] published a systematic review and meta-analysis on the incidence of PPOI after colorectal surgery. The authors reported that both randomized and non-randomized trials have used multiple criteria to define PPOI, resulting in an incidence ranging between 2.3 and 61% depending on the criteria applied. The incidence of PPOI in our cohort lies within this range and is also comparable to ERP cohorts reported by Barbieux et al. [31] and Grass et al. [20], where the incidence of PPOI was 40% and 25%, respectively. The present study is consistent with previous literature demonstrating a strong association between increased LOS and delayed GI recovery after colorectal surgery [32].

Interestingly, most patients with PPOI (73%) were diagnosed based on intolerance of oral intake, despite evidence of recovery of lower GI function (passing flatus/bowel movements). This finding support the notion that PPOI is a delay in GI recovery that can manifest in a spectrum of symptoms with varying severity, and not necessarily a delay in colonic recovery. A new classification and nomenclature for postoperative GI dysfunction was suggested recently that omits delayed colonic function as marker of ileus, but rather relies on a scoring system based on a constellation of symptom severity (i.e., nausea, vomiting, abdominal distension, tolerance of oral intake, and duration of symptoms) [33]. This novel classification system, however, has not been validated clinically.

Estimated intraoperative blood loss (EBL) was the strongest predictor of PPOI in the BMA analysis, and in univariate analysis patients with PPOI also had higher rates of intra- and postoperative transfusion. The association between EBL, perioperative transfusion, and PPOI have been previously described [16, 19, 23]. Increased EBL may be a surrogate

Table 2 Incidence of PPOI (%) according to varying definitions and their effect on LOS

Variable	PPOI	Non-PPOI	*p* value
Primary definition			
PPOI diagnosed if GI-3 not achieved by POD 4	62 (19%)	261 (81%)	< 0.0001
LOS	9 [7, 13]	3 [3, 4]	
Other definitions			
PPOI diagnosed if GI-3 not achieved by POD 2	190 (59%)	133 (41%)	< 0.0001
LOS	5 [3, 8]	3 [3, 4]	
PPOI diagnosed if GI-3 not achieved by POD 3	92 (28%)	231 (72%)	
LOS	8 [5, 11]	3 [3, 4]	< 0.0001
PPOI diagnosed if GI-3 not achieved by POD 5	51 (16%)	272 (84%)	
LOS	10 [8, 14]	4 [3, 5]	< 0.0001
PPOI diagnosed if GI-3 not achieved by POD 6	45 (14%)	278 (86%)	
LOS	10 [8, 14]	4 [3, 5]	< 0.0001
PPOI diagnosed if GI-3 not achieved by POD7	35 (11%)	288 (89%)	
LOS	11 [9, 16]	4 [3, 5]	< 0.0001
PPOI diagnosed if patient required NG insertion	56 (18%)	263 (82%)	
LOS	9.5 [7, 13]	3 [3, 4]	< 0.0001

Data expressed as median [IQR]

GI-3 a composite end-point defined as time to toleration of solid food and first flatus or bowel movement, *NG* nasogastric tube

for case difficulty and increased bowel manipulation, both factors which have also been shown to be associated with PPOI [18].

We also found a strong association between PPOI and receiving IV opioids in the first 48 h. The relationship between opioid use and PPOI has been well described [1, 34–36], and previous studies have shown that opioids are independent predictors of PPOI in patients undergoing colorectal [23] and gastric resections [21]. However, this is an especially important finding in our study, because even within a well-established ERP in which only 25% of patients received PCA as a mode of analgesia, receiving any IV opioids in the first 48 h, regardless of the duration or amount, was still a significant predictor of PPOI. This finding further highlights the importance of opioid-sparing or opioid-free multimodal analgesia regimens [8]. Furthermore, pharmacological agents have been developed to mitigate the effect of opioids on gut motility [37]. Alvimopan is an FDA-approved, μ-opioid receptor antagonist that targets receptors in the GI system without crossing the blood–brain barrier, thereby reducing the effect of endogenous and exogenous opioids on the GI tract, without diminishing their analgesic effects [38]. Multiple randomized trials report a positive effect of alvimopan on GI recovery and LOS in the context of open surgery [37, 39], while the impact after laparoscopic surgery and in the context of multimodal ERPs should be further explored. However, alvimopan is not currently available in Canada.

Evidence suggests that thoracic epidural analgesia containing local anesthetic agents decreases the incidence of PPOI in open surgery [40, 41]. However, two systematic reviews in laparoscopic colorectal surgery found no difference in GI recovery [42] and longer hospital LOS [43] in comparison with PCA. More recently, two randomized clinical trials showed delayed GI function in patients receiving epidural analgesia after laparoscopic surgery [44, 45]. Most patients in our study underwent laparoscopic surgery, and our results suggest a deleterious effect of epidural analgesia, although the evidence was weak. This finding is consistent with the most recent practice guidelines for enhanced recovery after colon and rectal surgery, which recommends against the routine use of epidural analgesia in laparoscopic colectomy [46].

Previous studies have shown an association between total intra-operative IV fluid administration and PPOI [18], but these studies did not all consider confounding factors such as surgery duration, surgical approach and EBL. In our study, instead of only analyzing total intra-operative IV fluid administration, we also analyzed at the association between PPOI and compliance with institutional recommendations for fluid administration which take these factors into account [29]. We found that adherence to the protocol was protective against development of PPOI, highlighting the importance of judicious intra-operative fluid administration [47]. However, overall compliance with the guidelines was low and will require strategies to increase adherence.

This study has several strengths. We excluded patients with bowel perforation, anastomotic leak and intra-abdominal abscess as these patients are more likely to develop a secondary PPOI. The inclusion of these patients is a

Table 3 PPOI versus Non-PPOI: baseline and operative characteristics

Variable	PPOI ($n = 62$)	Non-PPOI ($n = 261$)	p value
Age, mean (SD)	64 (18)	63 (14)	0.78
Male, no. (%)	38 (61%)	128 (49%)	0.09
BMI (kg/m^2), mean (SD)	27 (5)	26 (5)	0.44
ASA, no. (%)			0.02
I–II	34 (55%)	187 (72%)	
III–IV	28 (45%)	74 (28%)	
ACCI, mean (SD)	4.3 (3)	4 (2.4)	0.30
Received neoadjuvant chemotherapy, no. (%)	9 (14.5%)	28 (11%)	0.38
Received neoadjuvant radiotherapy, no. (%)	9 (14.5%)	27 (10%)	0.37
Previous abdominal surgery, no. (%)	30 (48%)	109 (42%)	0.39
Received MBP, no. (%)	43 (69%)	188 (72%)	0.75
Primary diagnosis, no. (%)			0.19
Malignancy	40 (64.5%)	172 (66%)	
Inflammatory bowel disease	14 (23%)	31 (12%)	
Crohn's disease	6 (10%)	19 (7%)	
Ulcerative colitis	8 (13%)	12 (5%)	
Benign polyp	4 (6.5%)	31 (12%)	
Diverticular disease	3 (5%)	22 (8%)	
Other benign diagnosis	1 (2%)	5 (2%)	
Procedure, no. (%)			
Small bowel resection	2 (3%)	5 (2%)	0.62
Ileocecal resection	1 (2%)	8 (3%)	1.00
Right hemicolectomy	12 (19%)	88 (34%)	0.03
Left hemicolectomy	4 (6%)	17 (7%)	1.00
Total/subtotal-colectomy	5 (8%)	9 (3%)	0.16
Anterior resection	5 (8%)	50 (19%)	0.04
Low anterior resection	13 (21%)	52 (20%)	0.86
Abdominoperineal resection	7 (11%)	13 (5%)	0.08
Total proctocolectomy ± IPAA	10 (16%)	11 (4%)	0.002
Other colorectal procedures[a]	3 (5%)	8 (3%)	0.45
Rectal resection, no. (%)[b]	30 (48%)	76 (30%)	0.006
Surgical approach, no. (%)[c]			0.001
Open	27 (44%)	57 (22%)	
Laparoscopic	35 (56%)	204 (78%)	
New stoma, no. (%)	26 (42%)	53 (20%)	0.001
Length of incision (cm)	8 [5, 14] missing = 2	6 [4, 9] missing = 5	0.007
Duration of surgery (min)	226 [168, 305]	174 [133, 230]	0.0002
EBL (ml)	275 [150, 500]	100 [50, 200]	< 0.0001
Intra-operative hemorrhage	6 (10%)	7 (3%)	0.02
Intra-op transfusion, no. (%)	10 (16%)	12 (5%)	0.003
Total intra-op IVF (l)	2 [1.5, 3]	1.7 [1, 2.5]	0.001
Intra-operative fluid compliance, no. (%)[d]	14 (23%)	69 (26%)	0.63

Data expressed as no. (%), mean (SD), or median [IQR]

SD standard deviation, *IQR* inter-quartile range, *ASA* American Society of Anesthesiologists, *ACCI* Age-Adjusted Charlson's comorbidity index, *BMI* body mass index, *MBP* mechanical bowel preparation, *LAR* low anterior resection, *APR* abdominal perineal resection, *IPAA* ileal pouch–anal anastomosis, *EBL* estimated blood loss, *TIVA* total intravenous anesthesia

[a]Includes reversal of Hartmann's procedure ($n = 6$), takedown of end ileostomy + ileorectal anastomosis ($n = 3$), enterocutaneous fistula repair ($n = 1$), and fashioning of diverting transverse colostomy ($n = 1$)

[b]Includes low anterior resection, proctocolectomy, and abdominoperineal resection

[c]Patients who were scheduled for laparoscopic surgery but underwent conversion to open surgery ($n = 23$, 9%), were categorized as open approach

[d]Intraoperative maintenance fluids excluding replacement of blood loss: for laparoscopy 3 ml/kg/h; for open 5 ml/kg/h

Table 4 PPOI versus Non-PPOI: postoperative management and outcomes within 30 days

Variable	PPOI ($n=62$)	Non-PPOI ($n=261$)	p value
Mode of analgesia, no. (%)			
Epidural	48 (77%)	185 (71%)	0.35
PCA	13 (22%) PCA missing = 3	69 (28%) PCA missing = 12	0.42
Received IV opioids in the first 48 h, no. (%)[a]	29 (47%)	86 (33%)	0.05
Time to first flatus (days)	2 [1,3]	1 [1, 1]	< 0.0001
Time to first bowel movement (days)	2 [2, 4]	2 [1, 2]	< 0.0001
Time to first tolerance of solids (days)	7 [5, 9]	1 [1, 2]	< 0.0001
Time to GI-3 (days)	7 [5, 9]	1 [1, 2]	< 0.0001
Received parenteral nutrition, no. (%)	13 (21%)	8 (3%)	< 0.0001
NGT inserted, no. (%)	41 (68%) Missing = 2	15 (6%) Missing = 1	< 0.0001
Severe complications, no. (%)	4 (6%)	3 (1%)	0.03
Postoperative transfusion, no. (%)	11 (18%)	13 (5%)	0.002
Cardiovascular complications, no. (%)[b]	7 (11%)	5 (2%)	0.003
Respiratory complications, no. (%)[c]	4 (6%)	7 (3%)	0.23
Infectious complications, no. (%)[d]	14 (23%)	12 (5%)	< 0.0001
Emergency department visits, no. (%)	12 (19%)	51 (20%)	1.0
Hospital readmission, no. (%)	8 (13%)	33 (13%)	0.96
Re-operation, no. (%)[e]	2 (3%)	7 (3%)	0.69

Data expressed as no. (%), mean (SD), or median [IQR]

NGT nasogastric tube, *POD* postoperative day, *IVF* Intravenous fluids, *GI-3* a composite end-point defined as time to toleration of solid food and first flatus or bowel movement

[a]Includes any patient who received any intravenous (IV) opioids in the first 48 h after surgery, including those who received PCA.

[b]Cardiovascular complications included heart failure, acute myocardial infarction, cardiac arrhythmias, deep venous thrombosis, and pulmonary embolism

[c]Respiratory complications included pneumonia, lobar atelectasis, pleural effusion, respiratory failure, pulmonary edema

[d]Infectious complications included urinary tract infection, wound infection, sepsis, and other infections

[e]In the PPOI group, one patient underwent surgery for hemorrhage during primary stay, and one patient underwent surgery for small bowel obstruction after discharge. In the Non-PPOI group, three patients underwent surgery for anastomotic leak after discharge, two patients for small bowel obstruction, and one patient for each stoma recreation and wound dehiscence

potential source of bias in previous studies identifying predictors of PPOI [16–20, 23, 25, 31]. The data were collected prospectively by an independent auditor specifically trained to assess patient recovery within ERPs using established definitions, which should mitigate the risk of bias arising from misclassification and measurement error. Another strength is the use of BMA to account for model uncertainty while identifying predictors of PPOI [5–7]. Our study also has some limitations. This is a retrospective analysis, and it is therefore impossible to control for all potential confounders. We did not include 21% of patients having elective bowel resection during the study time period as they were not entered into the database. However, a previous analysis of the database found no evidence of systematic selection bias arising from missing data [10]. We used an established definition of PPOI but had to adapt this as two of the criteria (distention and radiologic confirmation) were not available in the ERAS Audit System database, therefore, the true incidence of PPOI might have been underestimated. However, abdominal distention is a very subjective marker which may be present in a high proportion of patients, regardless of whether they have clinically relevant PPOI [48].

Also, Vather et al. use passage of flatus as a potential criteria to identify PPOI while a previous study, based on scintigraphic evaluation of colonic motility and gastric emptying, suggests this may not be an accurate marker of lower GI recovery [49]. We used NGT insertion as an alternative definition to estimate the incidence of PPOI, without accounting for other possible indications of NGT insertion (e.g., endotracheal intubation). Finally, the sample size of 323 patients included 62 patients in the PPOI group, which is a relatively small number. A study with a larger number of patients may derive different results.

Table 5 BMA analysis of all potential predictors of ileus

Covariate	Multivariate BMA analysis		
	PEP	OR	95% CI
BMI	0.5	1.0	1.0–1.0
Chemotherapy	0.5	1.0	0.93–1.1
Previous surgery	0.5	1.0	0.95–1.1
Smoker	0.5	1.0	0.93–1.1
Mechanical bowel preparation	0.6	1.0	0.94–1.1
Radiotherapy	0.6	1.0	0.93–1.1
Length of incision (in cm)	1.3	1.0	0.99–1.0
Gender	1.4	1.0	0.90–1.1
Age	1.9	1.0	0.99–1.0
ACCI	2.8	1.0	0.96–1.1
Rectal resection[a]	5.2	1.0	0.77–1.4
Laparoscopic surgery (as treated)	9.6	0.94	0.60–1.5
New stoma formation	16.3	1.1	0.62–2.1
Surgery duration (h)	26.1	1.1	0.83–1.4
IBD[b]	26.9	1.3	0.50–3.3
ASA ≥ 3	46.5	1.4	0.59–3.6
Post-op epidural	56.3	2.1	0.49–8.6
Intra-op fluid compliance[c]	54.8	0.6	0.17–1.9
IV opioids within 48 h[d]	94.4	3.9	1.11–13
EBL (units of 50 ml)	99.3	1.1	1.03–1.2

Data expressed in OR and 95% CI. The OR in the BMA analysis is calculated from the mean of the beta coefficients (weighted averages via BMA). The likelihood probability that the PEP of the mean is nonzero [P ($B \neq 0$)] is reported in percentages (%)

PEP posterior effect probability, *BMI* body mass index, *ACCI* age-adjusted Charlson comorbidity index, *ASA* American Society of Anesthesiologists score

[a]Includes any patient receiving surgery that include rectal resection; low anterior resection, proctocolectomy, and abdominoperineal resection

[b]Patients with IBD as the primary diagnosis and indication for surgery

[c]Intraoperative maintenance fluids excluding replacement of blood loss: for laparoscopy 3 ml/kg/h; for open 5 ml/kg/h

[d]Includes any patient who received intravenous (IV) opioids in the first 48 h after surgery, including those who received PCA.

Conclusion

The incidence of PPOI after colorectal surgery is still significant, even with a high proportion of laparoscopic surgery and an established ERP. Our results are consistent with previous literature suggesting an association of PPOI with other postoperative complications and increased LOS. Intraoperative EBL, IV opioids in the first 48 h and use of epidural analgesia were associated with higher rates of PPOI, while judicious fluid administration was protective. As the use of intravenous opioids is a modifiable strong predictor of PPOI, efforts should be directed toward reducing the utilization of opioids in postoperative analgesia and investigating u-receptor antagonists in the context of minimally invasive surgery and enhanced recovery pathways.

Compliance with ethical standards

Disclosures Drs. Alhashemi, Fiore, Safa, Al Mahroos, Mata, Pecorelli, Baldini, Dendukuri, Stein, Liberman, Charlebios, Carli, and Feldman have no conflict of interest or financial ties to disclose.

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