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Targets for Intervention? Preoperative Predictors of Postoperative Ileus after Colorectal Surgery in an Enhanced Recovery Protocol

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Abstract

Background: Postoperative ileus occurs in up to 30% of colorectal surgery patients and is associated with increased length of stay, costs, and morbidity. While Enhanced Recovery Protocols seek to accelerate postoperative recovery, data on modifiable *preoperative* factors associated with postoperative ileus in this setting are limited. We aimed to identify preoperative predictors of postoperative ileus following colorectal surgery in Enhanced Recovery Protocols, to determine new intervention targets.

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Methods: We performed a retrospective single-center cohort study of patients ≥18 years-old who underwent colorectal surgery via Enhanced Recovery Protocols (7/2015-7/2017). Postoperative ileus was defined as nasogastric tube insertion postoperatively or nil-per-os by postoperative day 4. Preoperative risk factors, including comorbidities and medication use, were identified using multivariable stepwise logistic regression.

Results: Of 530 patients, 14.9% developed postoperative ileus. On univariate analysis of perioperative and postoperative factors, postoperative ileus patients had increased psychiatric illness, antidepressant and antipsychotic use, American Society of Anesthesiologists classification, ileostomy creation, postoperative opioid use, complications, surgery duration, and length of stay ($p<0.05$). Multivariable logistic regression model for *preoperative* factors identified psychiatric illness, preoperative antipsychotic use, and American Society of Anesthesiologists classification ≥3 as significant predictors of postoperative ileus ($p<0.05$).

Discussion: Postoperative ileus remains a common complication following colorectal surgery under Enhanced Recovery Protocols. Patients with pre-existing psychiatric comorbidities and preoperative antipsychotic use may be a previously overlooked cohort at increased risk for postoperative ileus. Additional research and preoperative interventions within Enhanced Recovery Protocols to reduce postoperative ileus for this higher-risk population are needed.

Keywords

postoperative ileus; enhanced recovery protocol; colorectal surgery

Introduction

Postoperative ileus (POI) occurs in up to 30% of colorectal surgery patients and is associated with increased morbidity, length of stay, and costs.[1-4] POI, or transient cessation of coordinated bowel motility following surgery, is associated with increased burden on both the patient and healthcare system.[4-10] Risk factors for POI following abdominal surgeries via standard care pathways include colorectal surgery, open surgery, prolonged operative time, male gender, smoking, American Society of Anesthesiologists (ASA) classification ≥3, intraoperative and postoperative opioid use, inflammatory bowel disease (IBD), and new stoma creation.[8,11-15]

Enhanced Recovery Protocols (ERP) aim to optimize organ function following surgical stress in order to maintain homeostasis and accelerate postoperative recovery.[10] Since colorectal surgery itself has been identified as an independent risk factor for POI, there has been recent interest in examining factors associated with POI following colorectal surgery under ERP. However, in prior studies, factors associated with POI after colorectal surgery via ERP are mostly intra/postoperative and difficult to modify preoperatively, such as intraoperative blood loss, postoperative opioid use, and postoperative complications such as urinary retention.[13,14,16,17] Given the nature and timing of currently known risk factors, designing preoperative interventions to mitigate POI in these patients remains a challenge. Efforts have been made to reduce opioid use perioperatively and postoperatively via ERPs, but more durable targeted *preoperative* interventions are limited.[10,18] Furthermore, targeting new interventions to the appropriate at-risk patients requires preoperative identification of this cohort. Few modifiable preoperative factors have been examined. Thus, we aimed to identify *preoperative* risk factors of early POI for patients undergoing colorectal surgery in the era of ERP.

Materials and Methods

A retrospective cohort study was performed for all patients undergoing colorectal surgery via ERP at a single academic tertiary referral institution from July 2015 to July 2017 after approval by the Institutional Review Board. Inclusion criteria included age ≥18 years and patients who underwent non-emergent colorectal surgery by colorectal surgeons via ERP. All non-emergent colorectal surgeries were enrolled in the same ERP; emergent surgeries were *not* enrolled. Exclusion criteria included lack of ERP enrollment and length of stay ≤48 hours. Patients with length of stay ≤48 hours were excluded, as data on post-discharge medication use were unavailable and our aim was to examine risk factors for POI despite ERP enrollment to identify targets for improvement in the current ERP program.

Patient demographics, medical history, preoperative outpatient medications, surgery indication and type, postoperative opioid use, length of stay, and postoperative complications were collected from the electronic medical record. Preoperative psychiatric illness included diagnoses like anxiety, depression, bipolar disorder, psychotic disorder, and schizophrenia. Postoperative complications included urinary tract infection, bacteremia, deep and superficial surgical site infection, pneumonia, postoperative bleeding, anastomotic leak, and postoperative ileus. Postoperative opioid consumption was calculated as oral morphine equivalents (OME) based on published guidelines.[19] According to definitions described in literature, clinical POI was defined as nasogastric tube insertion postoperatively or nil per os (NPO) by postoperative day (POD) 4.[3,6,12-14,17] Patients who developed early ileus, were unable to tolerate early oral intake, and were NPO on POD4 were included in the POI group. Patients who tolerated oral diet through POD4 but subsequently developed late ileus were excluded, as other postoperative complications may contribute to later development of ileus.

Surgical indications were extracted from the electronic medical record and coded into these categories: attention to non-IBD ileostomy/colostomy, malignant gastrointestinal neoplasm, IBD-related complications, benign gastrointestinal neoplasm, intra-abdominal infection or diverticulitis, and other. Surgery types were coded based on operative reports: small bowel resection, segmental colon resection, total abdominal colectomy, abdominopelvic surgery without perineal incision, pelvic surgery with perineal incision, and other.

Components of the ERP program at our institution were outlined in Table 1. Preoperative phase focused on nutrition education, encouragement of protein and carbohydrate-rich foods, and daily exercise until day of surgery. Multimodal pain management to reduce opioid use was emphasized throughout the ERP. Patient controlled analgesia (PCA) of intravenous opioids was reserved for poor pain control despite standard ERP regimen. Intraoperative goal-directed fluid therapy included guidelines of 2 milliliter (mL)/kilogram of actual body weight per hour for laparoscopic cases, and 4mL/kilogram/hour for laparotomies. Crystalloid or colloid boluses of 250mL-500mL were given as necessary for mean arterial pressure <60mmHg or <20% of baseline. Postoperative intravenous fluids were maintained at 40mL/hour until POD1 or until diet is advanced, then discontinued. Additional fluids could be given based on the physician's clinical judgement for conditions such as dehydration and acute kidney injury.

ERP compliance was tracked for six domains: 1) pre/intraoperative multimodal analgesia (compliant: ≥2 medications, including intrathecal/intravenous/enteral nonopioid analgesics); 2) postoperative nausea/vomiting prophylaxis (compliant: ≥2 medications, including ondansetron, scopolamine, perphenazine, aprepitant); 3) postoperative multimodal analgesia (compliant: ≥2 medications, including intravenous/enteral ibuprofen, ketorolac, lidocaine, acetaminophen); 4) oral food intake more than clear liquids before POD2; 5) mobilization out of bed by POD1; 6) urinary catheter removal by POD1. Compliance for each domain was binary, as defined above. For each patient, overall ERP compliance across domains was defined as number of compliant domains divided by total number of domains.

Patient characteristics, preoperative medications, medical comorbidities, intraoperative factors, and postoperative analgesics, complications, and outcomes were compared between the non-POI and POI groups by t-test for continuous measures, or by Chi-square or Fisher's exact test for categorical measures. Continuous measures were presented as mean ± standard deviation. Frequencies and percentages of categorical variables were listed.

We assessed preoperatively-known factors (medical comorbidities, social factors, outpatient medications, laboratory values, surgery type) as predictors of POI with stepwise logistic regression. Iteratively, we evaluated multiple combinations of preoperative factors with alpha ≤0.20 at the univariate level such that the number of explanatory variables did not exceed 8 in our exploratory models. Non-normally distributed continuous variables were logarithmically-transformed. We eliminated variables with alpha >0.10 in the multivariable model if the parameter estimates of the remaining variables changed by ≤20% after eliminating the variable. After several iterations, a core set of explanatory variables remained. Each variable that had been eliminated was added back into the model, confirming that the core set of explanatory variables still remained significant at alpha <0.05 and their parameter estimates remained stable. Variables retained in the final model were consistently significant predictors of POI and demonstrated highest stability in various combinations of covariates. We used Stukel's test to evaluate the final model's goodness-of-fit. BMI was treated as a categorical variable (low: BMI <18.5; normal/overweight: BMI 18.5-30; obese: BMI >30), with BMI 18.5-30 as the reference group. Statistical analyses were performed in SAS v9.4 (copyright 2016 SAS Institute Inc., Cary, NC, USA) and STATA 15.1 (copyright 2017 StataCorp LLC, College Station, TX, USA).

Results

Patient demographics and POI versus non-POI group differences

All 588 patients (333 female, 255 male) who underwent non-emergent colorectal surgery were enrolled in the same ERP. Among them, 58 patients with length of stay ≤48 hours were excluded. The remaining 530 patients (306 female, 224 male) were included, of which 79 (14.9%) developed POI. In the POI group, 25 (31.6%) remained NPO by POD4, 30 (38.0%)

required nasogastric tube insertion, and 24 (30.4%) required both. Patient demographics including age, gender, race, and BMI were not significantly different between those with and without POI ($p>0.30$). Compared to those without POI, those who developed POI had higher incidences of psychiatric illness, preoperative psychiatric (antidepressant and antipsychotic) and anticonvulsant medication use, ASA class ≥3, and lower preoperative albumin level ($p<0.05$, Table 2). The number of patients who had psychiatric diagnoses with psychiatric medication use (non-POI: 103, POI: 31) and the number of patients who were using psychiatric medications without psychiatric diagnoses (non-POI: 61, POI: 9) were not significantly different between non-POI and POI groups ($p>0.05$). Among patients who were using psychiatric medications, 37% did not have a documented psychiatric diagnosis. Among patients who had pre-existing outpatient opioid medication use, 50% also had history of psychiatric illnesses. Surgery indication and type were not significantly different between groups ($p>0.15$, Table 3).

Intraoperative and postoperative factors were compared between groups. Compared to the non-POI group, longer duration of surgery, more frequent ileostomy creation, and higher intraoperative vasopressor and transfusion requirements were seen in the POI group ($p<0.01$). PCA and total opioid use during the first 48 hours postoperatively (as measured by OME) were also higher in the POI group compared to the non-POI group ($p<0.05$, Table 4). Total opioid use during the first 48 hours postoperatively was higher for patients with psychiatric illness (mean total OME: 284.6), compared to those without psychiatric illness (mean total OME: 143.2, $p<0.001$). 22.5% of patients with history of psychiatric disorders required postoperative PCA, while only 13.4% of patients without psychiatric disorders needed postoperative PCA ($p<0.01$).

Among the 530 patients, overall average ERP compliance across all six domains was 91% (non-POI: 92%, POI: 84%, $p<0.01$). In both non-POI and POI groups, compliance was ≥82% for four of the six ERP domains (Table 5). The two domains with lowest compliance in the POI group were oral food intake before POD2 (76%) and urinary catheter removal by POD1 (53%). Patients with history of psychiatric illness or antipsychotic use had high overall ERP compliance (89%), which was not significantly different from that of patients without psychiatric illness or antipsychotic use (91%, $p=0.08$). Postoperative outcomes were also different between the POI and non-POI groups. Overall complication rate (excluding POI), ICU admission rate, and hospital length of stay were significantly higher in the POI group compared to the non-POI group ($p<0.0001$, Table 6). Complication rates for anastomotic leak, surgical site infections, bacteremia, urinary tract infection, and pneumonia were also higher in the POI group compared to the non-POI group ($p<0.05$).

Multivariable analysis: Preoperative factors associated with POI

Stepwise logistic regression modeling was performed to determine preoperative risk factors for POI. Psychiatric diagnosis and psychiatric medication use were included in the multivariable analysis as two separate variables, because psychiatric medication use did not fully represent those with psychiatric diagnoses. Stukel’s test for goodness-of-fit of the regression model produced a Wald chi-square of 0.19 (df=2, $p=0.91$), indicating adequate fit of the final model for prediction. Pre-existing psychiatric illness, antipsychotic use, and

ASA class ≥3 remained significant preoperative predictors of POI after considering other preoperative covariates ($p<0.05$, Table 7). Notably, the odds of developing POI were over four times higher in those who used antipsychotics preoperatively than those who did not (OR=4.31, 95% CI: 1.42-13.08, p=0.01). The odds of developing POI were nearly two times higher in those with pre-existing psychiatric illness than those who did not (OR=1.97, 95% CI: 1.19-3.27, p=0.01). The odds of developing POI were lower in those with BMI >30 as compared to those in the reference BMI range 18.5-30 (OR=0.46, 95% CI: 0.24-0.87, p=0.02).

Discussion

POI is a common postoperative complication, associated with higher morbidity and costs, particularly in patients undergoing colorectal surgery.[1-3,8] There has been rising interest in examining POI following colorectal surgery via ERP since many ERP interventions aim to reduce POI. Previously described factors associated with POI are often determined too late in the intra/postoperative stages and unable to be modified preoperatively.[8,11-14,16] Few studies examined a wide range of preoperative factors and none in such a comprehensive manner as in this study, with most reports done outside of the United States.[13,14,16,17] Based on an institutional ERP in the United States, with focus on preoperative factors, our large cohort study demonstrated that psychiatric illness, antipsychotic medication use, and ASA class ≥3 were significantly associated with early POI following colorectal surgery via an ERP. The granularity of our preoperative demographics, medical comorbidities, and outpatient medication history are unique from prior literature. We identified novel risk factors of pre-existing psychiatric illness and antipsychotic medication use, which were the strongest risk factors for POI on multivariable analysis. Higher-risk patients identified preoperatively may benefit from new interventions within current ERPs.

The risks of psychiatric disorders and medications in the preoperative period are often overlooked for other POI risk factors. Paralytic ileus has been described in psychiatric patients, especially with use of antipsychotics like clozapine and quetiapine, or tricyclic antidepressants because of their increased affinity for muscarinic receptors in the gastrointestinal tract.[20-24] Patients on preoperative antidepressant or antianxiety medications are at higher risk for complications and have longer postoperative hospital stays.[25] Additionally, patients with psychiatric illnesses may have different psychological responses during the peri/postoperative periods. For example, they may experience more intense psychological response to acute stress or pain, and have lower motivation to be physically active when cognitively overloaded by the psychological and physiological postsurgical stress, which could increase their risk of postoperative ileus development. ERPs could be modified to target this at-risk population by including mind-body psychological interventions, which has shown promise in cardiac and pancreatic surgery patients.[26,27] For example, preoperative counseling on expectations for recovery during and after hospitalization, and education on cognitive behavioral strategies in response to anxiety and pain could help patients with pre-existing psychiatric illnesses better manage the acute stress and changes they could experience during the peri/postoperative periods As surgery can be a stressful experience, these interventions could motivate patients to take control of modifiable factors during the preparation for and recovery from surgery.

Other targeted ERP interventions for patients with psychiatric comorbidities could include preoperative psychiatric medication reconciliation and postoperative follow-up to optimize outpatient medication use and minimize polypharmacy or compounded pharmacological side effects. However, one should be mindful of temporary discontinuation of psychiatric medications. Discontinuation of antidepressants could cause withdrawal syndromes, psychological distress, and provoke mania.[28,29,30] Abrupt discontinuation of antipsychotics could also trigger rebound psychosis and withdrawal syndromes, including nausea, vomiting, dyskinesia, and anxiety.[31,32] A combination of behavioral and pharmacological counseling may be helpful. Surgical patients with psychiatric comorbidities may be a higher-risk population with opportunity for additional research and preoperative interventions to reduce POI and related morbidity.

ASA class ≥3 was a risk factor for POI in our cohort, which is consistent with prior studies.[16] Higher ASA class has been associated with other adverse outcomes such as increased postoperative complications, length of stay, operative time, transfusion requirement, and mortality.[33] As many postoperative complications (e.g. anastomotic leak, surgical site infection, urinary tract infection, pneumonia) develop several days after surgery, we suspect that a late (rather than early) development of POI would more likely be a manifestation of other postoperative complications. Thus, our focus was examining development of *early* POI, and defined POI as such, to reduce confounding of postoperative complications as a contributing factor to later POI development. Furthermore, ASA class has not historically been considered modifiable. However, ASA class depends on social and medical factors.[34] Thus, by changing behaviors involving smoking/alcohol and achieving better control of medical comorbidities such as hypertension, chronic obstructive pulmonary disease, poor nutrition, anemia, and hyperglycemia, ASA class may be modifiable preoperatively following prehabilitation.

The incidence of POI in our cohort was 14.9%, which was consistent with POI rates reported in the literature, including a recent multicenter prospective registry data analysis, which reported 15.4% POI.[13,14,16,17] Also consistent with prior studies, hypoalbuminemia was associated with POI on univariable analysis in our study, though this did not maintain significance on multivariable analysis.[6,8,12] Hypoalbuminemia could indicate poor nutritional status or be a marker of frailty.[35,36] The benefits of lower mortality and complications related to increased muscle mass and adequate nutrition, particularly enteral and protein nutrition, have been well-established in postsurgical and ICU patients in catabolic states.[37,38] Higher rather than lower BMI was more strongly associated with lower odds of POI in our study. Having a higher BMI may appear more protective for POI than being underweight, but one should be cautious on interpretation of these results as BMI does not take into account muscle mass versus body fat, functional status, or other medical comorbidities. Overall, preoperative interventions to improve nutrition and physical function in ERPs are likely beneficial to reducing postoperative morbidity, but it is unclear if they would reduce POI incidence, warranting further prospective studies.

Our secondary results for other intraoperative factors were also consistent with literature.[8,12,16] Duration of surgery and ileostomy creation rates were higher in those with POI, versus those without POI. Intraoperative transfusion and vasopressor requirements were also significantly higher in the POI group, compared to the non-POI group. These could indicate more extensive surgery or disease severity, which have been previously associated with POI.[10,34,38] While we aimed to identify preoperative risk factors of POI in order to preoperatively identify patients for targeted POI prevention measures, we must not overlook that intraoperative and postoperative factors may also contribute to POI development, as suggested by prior and current studies.[11-17] Additionally, there were factors that could both contribute to, but also be the result of POI, such as postoperative opioid consumption and ERP compliance.

As expected, postoperative PCA and total OME use in the first 48 hours, overall complication rate (not including POI), ICU admission, and length of stay were higher in those with POI, compared to the non-POI group. This is consistent with previous studies on other surgical cohorts.[6,8,11-13,16,39] Opioid use has various associated morbidities, including but not limited to decreased bowel motility, respiratory depression, and dependence.[15,40-42] It is not known if increased OME use was secondary to POI or to the pain associated with POI itself. Most ERPs across institutions include multimodal peri/postoperative pain management. Institution-specific ERPs may be modified to incorporate additional components to reduce opioid use with adjuncts such as lidocaine, ketamine, and regional nerve blocks.[10,18]

Interestingly, pre-existing opioid use was not a significant preoperative predictor of POI on multivariable analysis. A recent retrospective review reported that preoperative prescription opioid and sedative use was associated with increased composite 30-day adverse outcomes and length of stay following colorectal surgery.[43] However, the adverse outcomes examined did not specifically include POI and these patients may not have been enrolled in ERPs. For gastrointestinal surgery, the association between intra/postoperative opioid use and POI has been studied.[9,10,18,44] However, research on *preoperative* opioid use and POI following colorectal surgery, particularly in the setting of ERP, is limited and warrants further investigation.

Increased ERP compliance has been associated with shorter hospital stays and fewer complications, including POI.[17,45] Similar to opioid use, it is difficult to determine if compliance deviation contributed to or was the result of POI. As expected, overall compliance was higher in the non-POI group compared to the POI group. The two domains with lowest compliance were food intake before POD2 and urinary catheter removal by POD1. Compared to those without POI, compliance for food intake before POD2 was significantly lower for the POI group, likely due to ileus development and associated symptoms. Low compliance for urinary catheter removal by POD1 in the POI group could be related to surgical complexity, as surgeons often maintain urinary catheters for longer and deviate from ERP if there was intraoperative bladder injury or reconstruction, or if catheters were needed for volume status assessment in the setting of POI. Nevertheless, overall ERP compliance across domains for our cohort remains high (91%), even for patients with psychiatric illnesses or antipsychotic medication use (89%).

It is also important to consider the limitations of our study. Since this was a single tertiary institution study, it has limitations on generalizability. Multicenter or multinational studies may address this, but such studies also have inherent limitations, because ERP criteria and implementation vary across hospitals and countries. Although data were from a single institution, our cohort was large, including over 500 patients, with a range of procedures and indications. Additionally, since this was a retrospective cohort study, we cannot draw conclusions on causation. However, the risk factors identified in our study could help direct new ERP programming, to prepare for future prospective studies on efficacy of new ERP interventions that preoperatively target those at increased risk of POI.

Institution-specific ERPs may be modified to incorporate new components to reduce POI such as gum-chewing, caffeine intake, peripheral opioid receptor antagonists such as alvimopan, analgesia adjunctive medication use such as ketamine and lidocaine, and increased use of neuraxial blocks for analgesia. Preoperative psychiatric counseling and relaxation techniques targeted for surgery could help optimize medication use, expectations, and behavioral strategies for patients when faced with the psychological and physiological stress associated with surgery. Our research highlighted the burden of POI in the current era of ERP and identified subgroups at risk for POI even in this setting. Psychiatric illness, antipsychotic medication use, ASA score, and BMI can be identified preoperatively. Thus, these at-risk patients could benefit from new preoperative interventions in existing ERPs.

Conclusion

POI, which is associated with increased morbidity, length of stay, opioid use, and costs, remains a common complication following colorectal surgery via ERP. However, few *preoperative* factors have been identified to guide new modifications to existing ERPs. History of psychiatric illness, antipsychotic medication use, and ASA class ≥3, were significant preoperative predictors of POI following colorectal surgery in an ERP. Patients with psychiatric comorbidities and psychiatric medication use may be previously overlooked, higher-risk populations with opportunity for further research and new ERP interventions to reduce POI and related morbidity.

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Table 1:

Institutional Enhanced Recovery Protocol

Protocol Phase	Protocol Metric	Protocol Component
Preoperative	**Preoperative Clinic**	ERP[a] patient education
		Protein/carbohydrate rich diet the week prior to surgery
		Exercise 30 minutes per day
		Clear liquids until 3 hours prior to surgery
	Analgesia	Acetaminophen
		Gabapentin
	PONV[b] Prophylaxis	Perphenazine or aprepitant
		Scopolamine by discretion
	Miscellaneous	VTE[c] Prophylaxis
		Antibiotic Prophylaxis
Intraoperative	**Regional/Neuraxial Analgesia**	Intrathecal morphine
	Anesthesia	General anesthesia
	Analgesia Adjunct	Ketamine infusion
		Lidocaine infusion
	PONV[b] Prophylaxis	Dexamethasone
		Ondansetron
	Fluid management	Goal directed intravenous fluid protocol
Postoperative	**Analgesia**	Acetaminophen
		NSAIDs[d]
		Lidocaine infusion for 24 hours
		Opioids only as needed
	Activity	Out of bed to chair for all meals Ambulation in halls POD[e] 0-1
	Diet	Clear liquids POD[e] 0; Advance diet POD[e] 1 or earlier
	Foley Management	Remove within 24 hours
	Fluid Management	Lactated ringers at 40mL/hour until POD[e] 1 or when diet is advanced. Additional fluids given as needed by discretion.

[a]ERP=enhanced recovery protocol

[b]PONV=postoperative nausea and vomiting

[c]VTE=venous thromboembolism

[d]NSAIDs=nonsteroidal anti-inflammatory drugs

[e]POD=postoperative day

Table 2.

Patient demographics and preoperative characteristics

	Non-POI[a] N=451	POI[a] N=79	p-value
Demographics			
Age (years)	51.8 ± 18.5	53.5 ± 15.6	0.44
Female	250 (55.4%)	47 (59.5%)	0.50
Race	Black: 31/431 (7.2%) Asian: 4/431 (0.9%) White: 396/431 (91.9%)	Black: 2/77 (2.6%) Asian: 1/77 (1.3%) White: 74/77 (96.1%)	0.31
Medical Comorbidities			
BMI[b]	27.3 ± 6.6	26.0 ± 5.5	0.07
ASA class[c] ≥ 3	252 (55.9%)	55 (69.6%)	**0.02**
Psychiatric disease	146 (32.4%)	41 (51.9%)	**0.001**
Coronary artery disease	42 (9.3%)	11 (13.9%)	0.21
Myocardial infarction	1 (0.2%)	0 (0%)	1.00
Congestive heart failure	26 (5.8%)	4 (5.1%)	1.00
Atrial fibrillation	20 (4.4%)	2 (2.5%)	0.76
Stroke/TIA[d]	19 (4.2%)	3 (3.8%)	1.00
Peripheral vascular disease	8 (1.8%)	1 (1.3%)	1.00
Hyperlipidemia	62 (13.8%)	8 (10.1%)	0.38
Hypertension	156 (34.6%)	23 (29.1%)	0.34
COPD[e]	36 (8.0%)	11 (13.9%)	0.09
Obstructive sleep apnea	52 (11.5%)	9 (11.4%)	0.97
Pneumonia	12 (2.7%)	4 (5.1%)	0.28
Acute/chronic kidney disease	22 (4.9%)	8 (10.1%)	0.11
Diabetes	49 (10.9%)	8 (10.1%)	0.85
Inflammatory bowel disease	188 (41.7%)	29 (36.7%)	0.41
Malignancy	115 (25.5%)	20 (25.3%)	0.97
Preoperative chemo	44 (9.8%)	9 (11.4%)	0.65
Preoperative radiation	35 (7.8%)	6 (7.6%)	0.96
Social Factors			
Smoking (current)	75 (16.6%)	16 (20.3%)	0.43
Alcohol use (current)	212 (47.0%)	29 (36.7%)	0.09
Illicit drug use (current)	27 (6.0%)	4 (5.1%)	1.00
Preoperative outpatient medications			
Any psychiatric medication	164 (36.4%)	40 (50.6%)	**0.02**
Antidepressant	105 (23.3%)	30 (38.0%)	**0.006**
Antipsychotics	8 (1.8%)	7 (8.9%)	**0.001**
Benzodiazepine	100 (22.2%)	25 (31.7%)	0.07

	Non-POI[a] N=451	**POI[a] N=79**	**p-value**
Anticonvulsants	13 (2.9%)	7 (8.9%)	**0.02**
Opioid	93 (20.6%)	21 (26.6%)	0.23
Opioid, scheduled	21 (4.7%)	5 (6.3%)	0.57
Opioid, as needed	82 (18.2%)	18 (22.8%)	0.33
Any non-opioid analgesic	123 (27.3%)	22 (27.9%)	0.92
NSAIDs[f]	78 (17.3%)	15 (19.0%)	0.72
Gabapentin/pregabalin	25 (5.5%)	7 (8.9%)	0.30
Muscle relaxants	17 (3.8%)	1 (1.3%)	0.50
Migraine medication	12 (2.7%)	1 (1.3%)	0.70
Diuretics	48 (10.6%)	6 (7.6%)	0.41
ARB[g]/ACEI[h]	80 (17.8%)	14 (17.7%)	0.99
Other anti-HTN[i] meds	92 (20.4%)	15 (19.2%)	0.81
Diabetes medication (oral)	33 (7.3%)	3 (3.8%)	0.25
Insulin	19 (4.2%)	3 (3.8%)	1.00
Steroids (systemic)	71 (15.7%)	10 (12.7%)	0.48
Preoperative laboratory values			
Creatinine[j]	0.9 ± 0.6 (n=436, 97%)	0.9 ± 0.4 (n=78, 99%)	0.87
Albumin[k]	3.7 ± 0.7 (n=308, 68%)	3.5 ± 0.7 (n=63, 80%)	**0.04**

[a]POI=postoperative ileus

[b]BMI=body mass index

[c]ASA class=American Society of Anesthesiologists classification

[d]TIA=transient ischemic attack

[e]COPD=chronic obstructive pulmonary disease

[f]NSAIDs=non-steroidal anti-inflammatory drugs

[g]ARB=angiotensin-receptor blocker

[h]ACEI=angiotensin converting enzyme inhibitor

[i]HTN=hypertension

[j]Creatinine data available for 436 (97%) patients without POI and 78 (99%) patients with POI.

[k]Albumin data available for 308 (68%) patients without POI and 63 (80%) patients with POI.

Results presented as mean ± standard deviation or frequency (percentage).

Table 3:

Indication for surgery and type of surgery performed

	Non-POI[a] N=451		POI[a] N=79		p-value
Indication for surgery	Attention to non-IBD[b] stoma:	50 (11.1%)	Attention to non-IBD[b] stoma:	7 (11.4%)	0.18
	Malignant GI[c] neoplasm:	96 (21.3%)	Malignant GI[c] neoplasm:	15 (19.0%)	
	IBD[b]-related complications:	191 (42.4%)	IBD[b]-related complications:	30 (38.0%)	
	Benign GI[c] neoplasm:	27 (6.0%)	Benign GI[c] neoplasm:	1 (1.3%)	
	Intra-abdominal infection:	54 (12.0%)	Intra-abdominal infection:	16 (20.3%)	
	Other:	33 (7.3 %)	Other:	8 (10.1%)	
Type of surgery	Small bowel resection:	50 (11.1%)	Small bowel resection:	9 (11.4%)	0.92
	Segmental colon resection:	221 (49.0%)	Segmental colon resection:	36 (45.6%)	
	Total abdominal colectomy:	54 (12.0%)	Total abdominal colectomy:	10 (12.7%)	
	Pelvic without perineal incision:	42 (9.3%)	Pelvic without perineal incision:	10 (12.7%)	
	Pelvic with perineal incision:	41 (9.1%)	Pelvic with perineal incision:	8 (10.1%)	
	Other:	43 (9.5%)	Other:	6 (7.6%)	

[a]POI=postoperative ileus

[b]IBD=inflammatory bowel disease

[c]GI=gastrointestinal

Results presented as frequency (percentage).

Table 4:

Intraoperative factors and postoperative opioid use

	Non-POI[a] N=451	**POI[a] N=79**	**p-value**
Intraoperative factors			
Duration of Surgery (minutes)	198.6 ± 97.0	243.0 ± 114.3	<**0.001**
Open procedure	149 (33.0%)	34 (43.0%)	0.08
Anastomosis	312/445 (70.1%)	56/79 (70.9%)	0.89
Ileostomy	96 (21.3%)	32 (41.0%)	**0.0002**
Intraoperative Transfusion	6 (1.3%)	6 (7.6%)	**0.004**
Intraoperative Vasopressors	314 (69.6%)	68 (86.1%)	**0.003**
Intraoperative total intravenous fluid (mL/kg/hour)[b]	8.6 ± 4.5	8.5 ± 5.8	0.90
Postoperative opioid use			
PCA[c]	58 (12.9%)	30 (38.0%)	< **0.0001**
PCA[c] OME[d] POD[e] 0-2	46.5 ± 180.8	147.5 ± 311.7	**0.006**
Total OME[d] POD[e] 0-2	175.7 ± 226.5	292.3 ± 463.5	**0.03**

[a]POI=postoperative ileus

[b]mL/kg/hour=milliliter per kilogram actual body weight per hour

[c]PCA=patient-controlled analgesia

[d]OME=oral morphine equivalents

[e]POD=postoperative day

Results presented as mean ± standard deviation or frequency (percentage).

Table 5:

Compliance with Enhanced Recovery Protocol by domain

Enhanced Recovery Protocol Domain	**Non-POI[a] N=451**	**POI[a] N=79**	**p-value**
Pre/Intraoperative Multimodal Analgesia ≥2 medications	451 (100%)	78 (99%)	0.15
PONV[b] prophylaxis ≥2 medications	437 (97%)	72 (91%)	**0.03**
Postoperative Multimodal Analgesia ≥2 medications	371 (82%)	66 (84%)	0.87
Diet more than clear liquids before POD[c] 2	421 (93%)	60 (76%)	<**0.01**
Mobilization by POD[c]1	451 (100%)	79 (100%)	1.00
Urinary catheter removal by POD[c]1	356 (79%)	42 (53%)	<**0.01**

[a]POI=postoperative ileus

[b]PONV=postoperative nausea/vomiting

[c]POD=postoperative day

Results presented as frequency (percentage).

Table 6:

Postoperative outcomes

Postoperative outcomes	Non-POI[a] N=451	POI[a] N=79	p-value
Complication Rate (excluding POI[a])	34 (7.5%)	25 (32.1%)	< **0.0001**
ICU[b] admission	22 (4.9%)	17 (21.8%)	< **0.0001**
Hospital length of stay (days)	5.7 ± 4.3	11.3 ± 5.7	< **0.0001**
Readmission	74 (16.4%)	18 (23.1%)	0.15
30-day mortality	1 (0.2%)	0 (0%)	1.00

[a]POI=postoperative ileus

[b]ICU=intensive care unit

Results presented as frequency (percentage) or mean ± standard deviation.

Table 7:

Multivariable logistic regression model of Preoperative Predictors of Postoperative Ileus

Preoperative factors	Odds Ratio	95% Confidence Interval	p-value
History of psychiatric illness	1.97	[1.19 – 3.27]	**0.01**
Antipsychotic use	4.31	[1.42 – 13.08]	**0.01**
ASA class[a] ≥3	1.74	[1.03 – 2.96]	**0.04**
BMI[b] low (<18.5)	0.79	[0.29 – 2.18]	0.65
BMI[b] obese (>30)	0.46	[0.24 – 0.87]	**0.02**

[a]ASA class=American Society of Anesthesiologists classification

[b]BMI=body mass index