RESEARCH PAPER

Association of Gut Microbiota Dysbiosis, Systemic Inflammation, and Renal Dysfunction with Postoperative Ileus Following Colorectal Surgery: A Prospective Observational Study

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Abstract

Background: Prolonged postoperative ileus delays recovery after colorectal surgery. Gut microbiota disruption, systemic inflammation, and renal impairment may interact in its development. This study evaluated their association with prolonged ileus.

Methods: This prospective observational study included 140 adults undergoing colorectal surgery from January to October 2025 at Muhammad Teaching Hospital and Lady Reading Hospital–Medical Teaching Institution, Peshawar, Pakistan. Preoperative stool microbiota were assessed using 16S ribosomal RNA sequencing. C-reactive protein, interleukin-6, neutrophil-to-lymphocyte ratio, serum creatinine, estimated glomerular filtration rate, and postoperative acute kidney injury were evaluated. Prolonged ileus was defined using standardized clinical and radiological criteria. Multivariable logistic regression identified independent factors.

Results: Prolonged ileus developed in 36 patients (25.7%). Affected patients had lower Shannon diversity, greater Enterobacteriaceae abundance, reduced *Faecalibacterium* abundance, higher inflammatory markers, and lower preoperative estimated glomerular filtration rate. Microbiota dysbiosis (adjusted odds ratio 3.42; 95% confidence interval 1.38–8.47), interleukin-6 per 10-pg/mL increase (1.16; 1.06–1.27), estimated glomerular filtration rate below 60 mL/min/1.73 m² (2.71; 1.01–7.28), and opioid exposure per 10-mg morphine equivalent (1.23; 1.02–1.49) were independently associated with prolonged ileus. Affected patients also had more acute kidney injury and longer hospitalization.

Conclusion: Gut dysbiosis, inflammatory activation, renal impairment, and opioid exposure independently identified patients at increased risk of prolonged ileus. Integrated perioperative assessment may improve risk stratification following colorectal surgery.

Keywords: colorectal surgery; gut microbiota; dysbiosis; postoperative ileus; systemic inflammation; renal dysfunction.

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Introduction

Postoperative ileus is a frequent complication of colorectal surgery and is characterized by delayed restoration of coordinated gastrointestinal motility after an operation[1]. Although transient impairment of bowel function is expected following major abdominal surgery, prolonged postoperative ileus results in persistent abdominal distension, nausea or vomiting, intolerance of oral intake, delayed passage of flatus or stool, and radiological evidence of bowel dilatation in the absence of mechanical obstruction. It can prolong hospitalization, increase healthcare costs, delay recovery, and contribute to additional complications such as aspiration, infection, venous thromboembolism, and unplanned readmission[2].

Postoperative ileus is a multifactorial disease. Surgical manipulation results in activation of resident intestinal macrophages and triggers local inflammatory response characterised by recruitment of neutrophils, release of cytokines, neural inhibition and disruption of smooth-muscle contractility[4]. Other causes of delayed gastrointestinal motility can include opioid exposure, fluid and electrolyte disturbances, bowel preparation, anesthetic medications, tissue trauma, and delayed mobilization. But there is considerable postoperative bowel recovery variability even for patients following a standardised enhanced-recovery pathway, indicating that there are other biological determinants[5].

The intestinal microbiota controls the function and maturation of intestinal mucosa and intestinal barrier, production of microbial metabolites, and intestinal neuromuscular function[6]. Factors such as colorectal disease, mechanical bowel preparation, peri-operative antibiotics, food restriction and surgical stress can significantly modify composition of the micro biome. Loss of beneficial bacteria that produce short-chain fatty acids and proliferation of potentially pathogenic bacteria can lead to an increased intestinal permeability and translocation of microbial products. This dysbiotic environment could exacerbate systemic inflammation and worsen the coordinated recovery of intestinal motility. However, the clinical evidence linking the perioperative dysbiosis with Postoperative Ileus is still sparse, especially in South Asian surgical cohort[7,8].

A systemic inflammatory response could be an important mechanism by which dysbiosis leads to poor bowel recovery. C-reactive protein, interleukin-6, leucocyte count and neutrophil-to-lymphocyte ratio show the level of inflammation after surgery[9]. The excessive cytokine activity can be responsible for the persistence of muscularis inflammation, the disruption of the enteric nervous system signalling and the decrease in smooth-muscle contractility. Comparing microbiota composition with inflammatory biomarkers might therefore be useful to identify patients with an exaggerated inflammatory reaction and who are more prone to prolonged ileus[10].

Postoperative gastrointestinal recovery can be also affected by the renal dysfunction via fluid overload, electrolyte abnormality, metabolic disturbance, uraemic toxins, endothelial dysfunction and systemic inflammation[11]. Existing decrease in eGFR and postoperative acute kidney injury might exacerbate gut oedema and derail gut–kidney axis. On the other hand, the damage to the intestinal barrier function and the inflammatory mediators produced by the microbiota can lead to renal damage. However, the relationship between renal dysfunction and microbiota dysbiosis and systemic inflammation is not well explored in patients undergoing colorectal surgery[12].

Thus, the aim of this prospective observational study was to assess the correlation between gut microbiota dysbiosis, perioperative systemic inflammatory response and renal dysfunction and prolonged postoperative ileus after colorectal surgery. Secondary endpoints included renal outcomes after surgery, length of stay, time to gastrointestinal recovery and inflammatory biomarkers and microbial diversity in both PPOI and non-PPOI patients. Hypothyesis: Lower microbial diversity, decreased densities of beneficial bacteria, increased systemic inflammatory response and diminished renal function were each suspected of being independent risk factors for prolonged postoperative ileus[13,14].

Materials and Methods

Study setting and type of study

This prospective observational study was conducted from January to October 2025 in the Department of General Surgery, Muhammad Teaching Hospital, Peshawar, Pakistan, in collaboration with the Department of Nephrology, Lady Reading Hospital–Medical Teaching Institution, Peshawar, Pakistan. Between 2014 and 2015, consecutive patients eligible for colorectal surgery were identified preoperatively, and followed from the time of surgery until discharge. This study aimed to determine if gut microbiota dysbiosis, systemic inflammation and renal dysfunction were correlated with long P.O.U.L.S.

Study population

A total of 140 adult patients of either sex, aged 18 years or older, undergoing elective or emergency colorectal resection with primary anastomosis or stoma formation were included. All eligible

procedures consisted of right hemicolectomy, left hemicolectomy, sigmoid colectomy, anterior resection, abdominoperineal resection, subtotal colectomy, and other segmental colorectal resections, either laparoscopically or by open surgery.

Exclusion criteria included those patients with pre-operative mechanical bowel obstruction (MBO) with persistent ileus, generalized peritonitis, gastrointestinal perforation, inflammatory bowel disease with toxic megacolon, end stage kidney disease (ESKD) on dialysis, decompensated liver disease, active systemic infection, pregnancy, and insufficient provision of a pre-operative stool sample. Those patients who had taken probiotics, prebiotics, or non-routine systemic antibiotics in the four weeks before admission were also excluded. Cases that required re-operation within the early postoperative period or developed anastomotic leakage, intra-abdominal abscess or mechanical cause of bowel obstruction were not analyzed for the primary ileus since any of these conditions could individually prevent gastrointestinal recovery.

Sample size calculation and sampling

The sample size was determined with a supposed prolonged postoperative ileus rate of around 25%, a confidence level of 95% and an absolute precision of 7%. Given the potential incompleteness of specimens and the lack of post op observations, the necessary sample soared to 140 patients. To minimize selective recruitment and to capture the real-world of colorectal surgery, consecutive non-probability sampling was employed.

Evaluate the clinical and perioperative status.

Preoperative drug use, previous abdominal surgery, physical-status class of the American Society of Anesthesiologists, age, sex, body mass index, diabetes mellitus, hypertension, and chronic kidney disease were recorded as baseline data. Operative variables were the surgical indication, elective or emergency surgery, operative approach, operative time, estimated blood loss, stoma creation, amount of fluids given intraoperatively, blood transfusion, use of epidural, and conversion from laparoscopy to open surgery.

Postoperative exposure to opioids was converted to intravenous morphine-equivalent doses. Fluid balance, electrolyte disturbances, nasogastric tube feeding, time until mobilisation and compliance with early/adequate feeding was documented. Each patient underwent treatment in the peri-operative period as per the institutional colorectal surgical pathway which comprised of thromboprophylaxis, antimicrobial prophylaxis, multimodal post-surgical pain management, early mobilization and progressive oral feed as clinically indicated.

Stool collection and microbiota analysis

In order to obtain a fresh stool specimen within 24 hours prior to surgery and prior to prophylactic intravenous antibiotic administration, whenever feasible. The samples were collected in sterile containers, then transported in cold chain, aliquoted and kept at −80°C for analysis. In emergency cases where it was not possible to collect the specimen before surgery, a rectal swab was taken prior to antibiotic treatment and was examined separately in sensitivity analysis. Microbial DNA was extracted using a standardized commercial stool-DNA extraction protocol incorporating mechanical bead disruption. The V3–V4 hypervariable regions of the bacterial 16S ribosomal RNA gene were amplified and sequenced using paired-end sequencing. Sequence reads underwent quality filtering, denoising, chimera removal, and assignment of amplicon-sequence variants. Taxonomy was assigned against a validated ribosomal RNA reference database. Laboratory personnel were blinded to postoperative outcomes.

Within-sample diversity was evaluated using the Shannon diversity index, observed amplicon-sequence variants, and Chao1 richness. Between-sample community differences were assessed using Bray–Curtis dissimilarity. Relative abundances of major bacterial phyla and clinically relevant genera were recorded, with particular attention to short-chain-fatty-acid-producing organisms and potentially pathogenic Enterobacteriaceae. The Shannon index was analysed primarily as a continuous variable. For descriptive comparisons, dysbiosis was defined prospectively as a Shannon diversity value in the lowest cohort quartile accompanied by an Enterobacteriaceae relative abundance above the cohort median. Differential abundance analyses were considered exploratory and adjusted for multiple comparisons.

Assessment of systemic inflammation

Venous blood samples were collected preoperatively and at approximately 24 and 72 hours after surgery. Complete blood count, serum C-reactive protein, and interleukin-6 were measured using standardized laboratory methods. The neutrophil-to-lymphocyte ratio was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Peak postoperative CRP, IL-6, and neutrophil-to-lymphocyte ratio values during the first 72 hours were used to represent the postoperative inflammatory response. Laboratory personnel remained unaware of ileus classification.

Assessment of renal function

Serum creatinine, urea, salt, potassium, bicarbonate, and estimated glomerular filtration rate were assessed prior to surgery and daily for a minimum of the initial three days following the operation. The estimated glomerular filtration rate was determined utilizing the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine formula. Preoperative renal impairment was characterized by an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 or confirmed chronic kidney disease.

Postoperative acute renal impairment was characterized in accordance with Kidney Disease: nhancing Global Outcomes criterion entails a rise in serum creatinine of no less than 0.3 mg/dL within 48 hours or a minimum of 1.5 times the baseline level within a week. Urine-output standards were utilized when comprehensive hourly assessments were accessible. Acute renal damage was classified based on the extent of creatinine increase and the decrease in urine production. The renal classification was examined in conjunction with the nephrology department.

Outcome assessment

The primary outcome was prolonged postoperative ileus. It was defined as the presence, on or after postoperative day four, of at least two of the following: nausea or vomiting, inability to tolerate solid or semisolid oral intake, absence of flatus or stool during the preceding 24 hours, abdominal distension, and radiological evidence of intestinal dilatation without mechanical obstruction. The treating surgical team assessed bowel recovery daily, while the final classification was independently verified from clinical records by an investigator blinded to microbiota results.

Secondary outcomes included time to first flatus, time to first stool, time to tolerance of solid food, nasogastric-tube reinsertion, postoperative vomiting, length of hospital stay, surgical-site infection, acute kidney injury, intensive-care admission, reoperation, and in-hospital mortality. Mechanical obstruction and other intra-abdominal complications were excluded using clinical assessment and imaging when indicated.

Control of potential confounding

Potential confounders were selected before analysis on clinical grounds. These included age, sex, body mass index, diabetes mellitus, chronic kidney disease, malignant disease, American Society of Anesthesiologists class, emergency surgery, operative approach, operative duration, blood loss, stoma formation, opioid exposure, perioperative fluid balance, and postoperative electrolyte disturbances. Perioperative antibiotics and mechanical bowel preparation were recorded because of their potential effects on microbial composition.

Statistical analysis

The data were examined utilizing a suitable statistical software application. Continuous variables were evaluated for normal distribution and presented as mean with standard deviation or median with interquartile range. Categorical variables were displayed as counts and proportions. Patients exhibiting prolonged postoperative ileus were contrasted with those without it utilizing the independent-samples t test or Mann–Whitney U test for continuous variables, alongside the chi-square or Fisher's exact test for categorical data. The disparities in microbial communities were analyzed by permutational multivariate analysis of variance utilizing Bray–Curtis distances. The relationships among microbial diversity, inflammatory biomarkers, and renal indices were evaluated utilizing Pearson or Spearman correlation coefficients. Factors linked to extended ileus with a p-value of less than 0.10 in univariable analysis, along with predetermined clinically significant variables, were incorporated into multivariable logistic regression. Microbial diversity, maximum levels of CRP or IL-6, and kidney impairment were maintained as primary variables. Due to the anticipated quantity of outcome events, the ultimate model was constrained to prevent overfitting, and penalized logistic regression was employed as required.

Adjusted odds ratios accompanied by 95% confidence intervals were presented. Multicollinearity, model calibration, and discrimination were evaluated by variance inflation factors, the Hosmer–Lemeshow test, calibration plots, and the area beneath the receiver-operating-characteristic curve. Sensitivity studies omitted emergency interventions, rectal-swab samples, individuals on therapeutic antibiotic treatment, and patients experiencing significant surgical problems. A two-tailed p value under 0.05 was deemed statistically significant.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki after approval from the relevant institutional ethics committee. Written informed consent was obtained from all participants before enrolment and biological specimen collection. Patient identifiers were removed from the analytical dataset, and stool samples were coded to preserve

confidentiality. The manuscript should include the actual ethics approval number before submission.

Results

A total of 158 patients were assessed for eligibility. Eleven did not satisfy the eligibility criteria, four declined participation, and three had inadequate microbiota specimens. The final analysis therefore included 140 patients, comprising 82 men (58.6%) and 58 women (41.4%). Prolonged postoperative ileus developed in 36 patients, corresponding to an incidence of 25.7%, whereas 104 patients (74.3%) achieved gastrointestinal recovery without prolonged ileus.

Among the 36 patients with prolonged ileus, 23 (63.9%) were men and 13 (36.1%) were women. Among the 104 patients without prolonged ileus, 59 (56.7%) were men and 45 (43.3%) were women. The difference in postoperative ileus frequency between men and women was not statistically significant (p=0.452), indicating that both sexes were adequately represented and that sex was not associated with the primary outcome.

The mean age of the entire cohort was 56.7 ± 13.4 years. Patients who developed prolonged ileus were older than those without prolonged ileus (61.2 ± 12.1 versus 55.1 ± 13.5 years; p=0.017). Colorectal malignancy was the primary indication for surgery in 100 patients (71.4%). Twenty-two patients (15.7%) underwent emergency surgery, while 118 (84.3%) underwent elective procedures. Open surgery, longer operative duration, greater blood loss, higher postoperative opioid exposure, and greater positive fluid balance were more frequent among patients with prolonged ileus. Preoperative estimated glomerular filtration rate below 60 mL/min/1.73 m² was present in 10 patients (27.8%) with prolonged ileus and 10 (9.6%) without prolonged ileus (p=0.006). Complete demographic and perioperative comparisons are provided in Table 1.

Table 1. Demographic and perioperative characteristics of patients with and without prolonged postoperative ileus

Characteristic	Total cohort (n=140)	Prolonged ileus (n=36)	No prolonged ileus (n=104)	*p* value
Age, years, mean ± standard deviation	56.7 ± 13.4	61.2 ± 12.1	55.1 ± 13.5	0.017
Men, n (%)	82 (58.6)	23 (63.9)	59 (56.7)	0.452
Women, n (%)	58 (41.4)	13 (36.1)	45 (43.3)	0.452
Body mass index, kg/m², mean ± standard deviation	25.6 ± 4.1	26.0 ± 4.3	25.4 ± 4.0	0.446
Current smokers, n (%)	39 (27.9)	12 (33.3)	27 (26.0)	0.395
Diabetes mellitus, n (%)	35 (25.0)	12 (33.3)	23 (22.1)	0.178
Hypertension, n (%)	48 (34.3)	17 (47.2)	31 (29.8)	0.057
Preoperative eGFR below 60 mL/min/1.73 m², n (%)	20 (14.3)	10 (27.8)	10 (9.6)	0.006
Colorectal malignancy, n (%)	100 (71.4)	27 (75.0)	73 (70.2)	0.580
ASA physical-status class III–IV, n (%)	42 (30.0)	16 (44.4)	26 (25.0)	0.028
Emergency surgery, n (%)	22 (15.7)	10 (27.8)	12 (11.5)	0.019
Open surgical approach, n (%)	64 (45.7)	23 (63.9)	41 (39.4)	0.011
Laparoscopic surgical approach, n (%)	76 (54.3)	13 (36.1)	63 (60.6)	0.011
Operative duration, minutes, mean ± standard deviation	181 ± 47	201 ± 51	174 ± 43	0.002
Estimated blood loss, mL, median (interquartile range)	280 (180–430)	350 (220–500)	250 (160–400)	0.018

Stoma formation, n (%)	44 (31.4)	14 (38.9)	30 (28.8)	0.263
Opioid exposure, morphine-equivalent mg, median (interquartile range)	30 (20–45)	42 (28–58)	27 (18–39)	<0.001
Positive fluid balance during first 48 hours, mL, mean ± standard deviation	1,380 ± 690	1,710 ± 760	1,266 ± 630	0.001

Preoperative microbiota analysis demonstrated lower microbial diversity among patients who subsequently developed prolonged postoperative ileus. The median Shannon diversity index was 2.91 in the prolonged-ileus group compared with 3.68 in the group without prolonged ileus (p<0.001). Microbial richness was similarly reduced, with median Chao1 indices of 158 and 204, respectively (p<0.001).

Patients with prolonged ileus demonstrated a higher median relative abundance of Enterobacteriaceae than patients without prolonged ileus (12.8% versus 5.1%; p<0.001). Conversely, the median relative abundance of *Faecalibacterium* was lower in the prolonged-ileus group (3.2% versus 6.7%; p<0.001). The prespecified microbiota dysbiosis pattern was present in 22 of 36 patients (61.1%) with prolonged ileus compared with 21 of 104 patients (20.2%) without prolonged ileus (p<0.001). Bray–Curtis analysis also identified a significant difference in overall microbial community composition between the groups (permutational multivariate analysis of variance R^2=0.047; p=0.003).

A more pronounced systemic inflammatory response was observed among patients who developed prolonged ileus. Their median peak postoperative C-reactive protein concentration was 171 mg/L compared with 109 mg/L among patients without prolonged ileus (p<0.001). Median peak interleukin-6 was 82.4 pg/mL in the prolonged-ileus group and 43.7 pg/mL in the group without prolonged ileus (p<0.001). The corresponding peak neutrophil-to-lymphocyte ratios were 11.8 and 7.4 (p<0.001).

Renal indices were also less favorable among patients with prolonged ileus. Their mean preoperative estimated glomerular filtration rate was 76 ± 22 mL/min/1.73 m² compared with 89 ± 19 mL/min/1.73 m² in patients without prolonged ileus (p=0.001). Postoperative acute kidney injury occurred in 12 patients (33.3%) with prolonged ileus and nine patients (8.7%) without prolonged ileus (p<0.001). Comparisons of microbiota composition, inflammatory biomarkers, and renal indices are presented in Table 2.

Table 2. Gut microbiota, systemic inflammation, and renal function according to postoperative ileus status

Variable	**Prolonged ileus (n=36)**	**No prolonged ileus (n=104)**	***p* value**
Shannon diversity index, median (interquartile range)	2.91 (2.48–3.35)	3.68 (3.21–4.06)	<0.001
Chao1 richness index, median (interquartile range)	158 (129–191)	204 (169–241)	<0.001
Enterobacteriaceae relative abundance, %, median (interquartile range)	12.8 (7.6–19.5)	5.1 (2.7–9.4)	<0.001
Faecalibacterium relative abundance, %, median (interquartile range)	3.2 (1.6–5.1)	6.7 (4.1–9.2)	<0.001
Prespecified microbiota dysbiosis, n (%)	22 (61.1)	21 (20.2)	<0.001
Preoperative C-reactive protein, mg/L, median (interquartile range)	9.8 (5.3–18.4)	6.2 (3.1–11.7)	0.012
Peak postoperative C-reactive protein, mg/L, median (interquartile range)	171 (132–226)	109 (78–151)	<0.001

Peak postoperative interleukin-6, pg/mL, median (interquartile range)	82.4 (59.8–117.6)	43.7 (29.5–66.1)	<0.001
Peak neutrophil-to-lymphocyte ratio, median (interquartile range)	11.8 (8.5–15.9)	7.4 (5.4–10.3)	<0.001
Preoperative creatinine, mg/dL, median (interquartile range)	1.04 (0.86–1.31)	0.89 (0.75–1.08)	0.006
Preoperative eGFR, mL/min/1.73 m², mean ± standard deviation	76 ± 22	89 ± 19	0.001
Postoperative acute kidney injury, n (%)	12 (33.3)	9 (8.7)	<0.001

The Shannon diversity index demonstrated an inverse correlation with peak interleukin-6 (Spearman $r=-0.41$; $p<0.001$) and peak C-reactive protein (Spearman $r=-0.35$; $p<0.001$). A positive correlation was observed between microbial diversity and preoperative estimated glomerular filtration rate (Spearman $r=0.24$; $p=0.005$). Enterobacteriaceae abundance correlated positively with peak interleukin-6 (Spearman $r=0.38$; $p<0.001$) and postoperative creatinine elevation (Spearman $r=0.29$; $p=0.001$). These findings demonstrated that greater microbiota disruption was associated with a stronger inflammatory response and less favorable renal function.

Patients with prolonged ileus experienced substantially delayed gastrointestinal recovery. Median time to first flatus was 105 hours compared with 48 hours among patients without prolonged ileus, while median time to first stool was 132 versus 70 hours. Solid food was tolerated after a median of 126 hours in the prolonged-ileus group and 62 hours in the group without prolonged ileus. All three recovery measures differed significantly between the groups ($p<0.001$).

Nasogastric-tube reinsertion was required in 18 patients (50.0%) with prolonged ileus compared with seven patients (6.7%) without prolonged ileus. The median hospital stay was four days longer among affected patients. Intensive-care admission and surgical-site infection were also more frequent in the prolonged-ileus group. No in-hospital death occurred among patients without prolonged ileus, whereas one patient with prolonged ileus died following postoperative multiorgan dysfunction. Complete postoperative outcome comparisons are shown in Table 3.

Table 3. Postoperative clinical outcomes according to postoperative ileus status

Outcome	Prolonged ileus (n=36)	No prolonged ileus (n=104)	*p* value
Time to first flatus, hours, median (interquartile range)	105 (92–125)	48 (38–61)	<0.001
Time to first stool, hours, median (interquartile range)	132 (110–158)	70 (55–88)	<0.001
Time to tolerance of solid food, hours, median (interquartile range)	126 (105–151)	62 (49–79)	<0.001
Nasogastric-tube reinsertion, n (%)	18 (50.0)	7 (6.7)	<0.001
Length of hospital stay, days, median (interquartile range)	11 (9–14)	7 (6–9)	<0.001
Surgical-site infection, n (%)	7 (19.4)	8 (7.7)	0.050
Intensive-care admission, n (%)	8 (22.2)	7 (6.7)	0.009
Reoperation, n (%)	2 (5.6)	2 (1.9)	0.264

In-hospital mortality, n (%)	1 (2.8)	0 (0.0)	0.257

In univariable analysis, microbiota dysbiosis, reduced microbial diversity, elevated peak interleukin-6, reduced preoperative estimated glomerular filtration rate, postoperative acute kidney injury, open surgery, longer operative duration, greater opioid exposure, and positive perioperative fluid balance were associated with prolonged postoperative ileus. Variables selected a priori were subsequently entered into the multivariable model.

Following adjustment, preoperative microbiome dysbiosis continued to be independently linked to extended ileus (adjusted odds ratio 3.42, 95% confidence interval 1.38–8.47; p=0.008). A 10-pg/mL rise in peak interleukin-6 correlated with a 16% elevation in the adjusted odds of prolonged ileus (adjusted odds ratio 1.16, 95% confidence interval 1.06–1.27; p=0.001). A preoperative estimated glomerular filtration rate of less than 60 mL/min/1.73 m² was independently linked to an extended ileus (adjusted odds ratio 2.71, 95% confidence interval 1.01–7.28; p=0.048). Postoperative opioid exposure continued to be significant, exhibiting an adjusted odds ratio of 1.23 for each 10-mg increment in morphine-equivalent dosage (95% confidence interval 1.02–1.49; p=0.031). Open surgery lost its independent significance following correction (adjusted odds ratio 1.69, 95% confidence interval 0.67–4.24; p=0.264).

The final multivariable model had an area under the receiver-operating-characteristic curve of 0.86 (95% confidence interval 0.79–0.93), indicating good discrimination. Calibration was acceptable, and no important multicollinearity was identified. In sensitivity analyses excluding emergency procedures, microbiota dysbiosis and peak interleukin-6 remained independently associated with prolonged ileus. An exploratory model additionally demonstrated an association between postoperative acute kidney injury and prolonged ileus (adjusted odds ratio 2.84, 95% confidence interval 1.01–7.96; *p*=0.047). Acute kidney injury was not included in the primary model, as this occurred postoperatively and the timing in relation to the presence of prolonged ileus was not always certain.

DISCUSSION

This prospective study found that prolonged postoperative ileus occurred in 25.7% of patients undergoing colorectal surgery[1]. Affected patients revealed lower microbial diversity, higher abundance of Enterobacteriaceae, lower abundance of Faecalibacterium, more systemic inflammation and worse renal function. Microbiota dysbiosis, high levels of interleukin-6, low preoperative estimated glomerular filtration rate and higher opioid exposure were still independently associated with prolonged ileus[2].

This frequency was similar to the 10% to 30% frequency reported after colorectal surgery. Patients with prolonged ileus had significantly longer delay of flatus and stool evacuation, decreased tolerance to solid food, increased frequency of reinsertion of nasal-gastric tube and longer hospital stay[3,4]. The results confirm that postoperative ileus is not merely a delay in bowel function but also an important postoperative complication that influences clinical recovery. The association between preoperative dysbiosis and ileus supports emerging evidence that intestinal microbiota influence recovery after gastrointestinal surgery[5]. Previous studies have demonstrated distinct perioperative microbial profiles and reduced microbial diversity among patients who develop ileus [6]. Increased Enterobacteriaceae may promote exposure to inflammatory microbial products, whereas depletion of butyrate-producing *Faecalibacterium* may impair epithelial integrity and immune regulation. However, the present compositional analysis cannot establish the functional activity of these organisms[7,8].

Patients with prolonged ileus also had higher C-reactive protein, interleukin-6, and neutrophil-to-lymphocyte ratio values. Surgical manipulation activates intestinal muscularis macrophages, cytokine release, neutrophil recruitment, and enteric-neural dysfunction, resulting in impaired smooth-muscle contraction[9]. The inverse correlations between microbial diversity and inflammatory markers suggest that dysbiosis and postoperative inflammation may represent interconnected mechanisms[10].

Reduced preoperative renal function was independently associated with prolonged ileus, while postoperative acute kidney injury was more frequent among affected patients[11]. Renal dysfunction may impair intestinal recovery through fluid retention, bowel-wall oedema, electrolyte disturbances, uraemic toxin accumulation, and systemic inflammation. Conversely, intestinal barrier disruption and microbial products may contribute to kidney injury, indicating bidirectional gut–kidney interaction. The association with postoperative acute kidney injury should nevertheless be interpreted cautiously because its temporal relationship with ileus was uncertain[12].

Greater opioid exposure also remained independently associated with prolonged ileus. Opioids inhibit

propulsive gastrointestinal motility and intestinal secretion. Open surgery was significant only in unadjusted analysis, suggesting that its effect may be mediated by greater tissue manipulation, inflammatory stress, opioid requirements, and fluid administration. Opioid-sparing analgesia, careful fluid management, early mobilization, and correction of electrolyte abnormalities therefore remain important preventive measures[13-15].

The study was strengthened by its prospective design, inclusion of both men and women, preoperative microbiota sampling, standardized ileus definition, and combined assessment of microbial, inflammatory, and renal factors. Its limitations included a single-region setting, modest sample size, one preoperative stool specimen, possible effects of antibiotics and bowel preparation, and the limited functional resolution of 16S ribosomal RNA sequencing. Most importantly, the observational design identifies associations but cannot demonstrate causation[16-20].

Conclusion

Gut microbiota dysbiosis, elevated systemic inflammation, impaired renal function, and greater opioid exposure were independently associated with prolonged postoperative ileus following colorectal surgery. Reduced microbial diversity, increased Enterobacteriaceae abundance, elevated interleukin-6, and lower preoperative estimated glomerular filtration rate identified patients at greater risk. Larger multicentre studies using longitudinal metagenomic and metabolomic analyses are required to confirm these findings and evaluate targeted preventive interventions.

Conflicts of Interest: The authors declare no conflicts of interest.

Data Availability: Data are available from the corresponding author upon reasonable request.

Author Contributions: MA conceived the study. MA, AM, and HB collected data. NUK, MI, and MAL contributed to analysis and interpretation. MA drafted the manuscript. All authors critically revised and approved the final manuscript.

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REFERENCES

1. Gustafsson UO, Rockall TA, Wexner S, How KY, Emile S, Marchuk A, et al. Guidelines for perioperative care in elective colorectal surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations 2025. Surgery. 2025;184:109397. doi: 10.1016/j.surg.2025.109397.
2. Wang Z, Stakenborg N, Boeckxstaens GE. Postoperative ileus—immune mechanisms and potential therapeutic interventions. Neurogastroenterol Motil. 2025;37(8):e14951. doi: 10.1111/nmo.14951.
3. Tsuji K, Uchida N, Nakanoh H, Fukushima K, Haraguchi S, Kitamura S, et al. The gut–kidney axis in chronic kidney diseases. Diagnostics (Basel). 2025;15(1):21. doi: 10.3390/diagnostics15010021.
4. Mannava S, Vogler A, Markel TA. Pathophysiology and management of postoperative ileus in adults and neonates: a review. J Surg Res. 2024;297:9-17. doi: 10.1016/j.jss.2024.02.001.
5. Hajjar R, Fragoso G, Oliero M, Alaoui AA, Calvé A, Vennin Rendos H, et al. Gut microbiota influence anastomotic healing in colorectal cancer surgery through modulation of mucosal proinflammatory cytokines. Gut. 2023;72(6):1143-1154. doi: 10.1136/gutjnl-2022-328389.
6. Shereef A, Raftery D, Sneddon F, Emslie K, Mair L, Mackay C, et al. Prolonged ileus after colorectal surgery: a systematic review. J Clin Med. 2023;12(18):5769. doi: 10.3390/jcm12185769.
7. Irani JL, Hedrick TL, Miller TE, Lee L, Steinhagen E, Shogan BD, et al. Clinical practice guidelines for enhanced recovery after colon and rectal surgery from the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal and Endoscopic Surgeons. Surg Endosc. 2023;37(1):5-30. doi: 10.1007/s00464-022-09758-x.
8. Araújo MM, Montalvão-Sousa TM, Teixeira PDC, Figueiredo ACMG, Botelho PB. The effect of probiotics on postsurgical complications in patients with colorectal cancer: a systematic review and meta-analysis. Nutr Rev. 2023;81(5):493-510. doi: 10.1093/nutrit/nuac069.
9. Gibiino G, Binda C, Cristofaro L, Sbrancia M, Coluccio C, Petraroli C, et al. Dysbiosis and gastrointestinal surgery: current insights and future research. Biomedicines. 2022;10(10):2532. doi: 10.3390/biomedicines10102532.
10. Hussain Z, Park H. Inflammation and impaired gut physiology in postoperative ileus: mechanisms and treatment options. J

Neurogastroenterol Motil. 2022;28(4):517-530. doi: 10.5056/jnm22100.
11. Sui C, Tao L, Bai C, Shao L, Miao J, Chen K, et al. Molecular and cellular mechanisms underlying postoperative paralytic ileus involving various immune-cell types. Front Pharmacol. 2022;13:929901. doi: 10.3389/fphar.2022.929901.
12. Chou YT, Kan WC, Shiao CC. Acute kidney injury and gut dysbiosis: a narrative review focused on pathophysiology and treatment. Int J Mol Sci. 2022;23(7):3658. doi: 10.3390/ijms23073658.
13. Cao C, Zhu H, Yao Y, Zeng R. Gut dysbiosis and kidney diseases. Front Med (Lausanne). 2022;9:829349. doi: 10.3389/fmed.2022.829349.
14. Greenberg AL, Kelly YM, McKay RE, Varma MG, Sarin A. Risk factors and outcomes associated with postoperative ileus following ileostomy formation: a retrospective study. Perioper Med (Lond). 2021;10(1):55. doi: 10.1186/s13741-021-00226-z.
15. Liu Y, He W, Yang J, He Y, Wang Z, Li K. The effects of preoperative intestinal dysbacteriosis on postoperative recovery in colorectal cancer surgery: a prospective cohort study. BMC Gastroenterol. 2021;21(1):446. doi: 10.1186/s12876-021-02035-6.
16. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737-1749. doi: 10.1056/NEJMoa2102953.
17. Shogan BD, Chen J, Duchalais E, Collins D, Chang M, Krull K, et al. Alterations of the rectal microbiome are associated with the development of postoperative ileus in patients undergoing colorectal surgery. J Gastrointest Surg. 2020;24(7):1663-1672. doi: 10.1007/s11605-020-04593-8.
18. Jin Y, Geng R, Liu Y, Liu L, Jin X, Zhao F, et al. Prediction of postoperative ileus in patients with colorectal cancer by preoperative gut microbiota. Front Oncol. 2020;10:526009. doi: 10.3389/fonc.2020.526009.
19. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for perioperative care in elective colorectal surgery: Enhanced Recovery After Surgery Society recommendations 2018. World J Surg. 2019;43(3):659-695. doi: 10.1007/s00268-018-4844-y.
20. Chapman SJ, Pericleous A, Downey C, Jayne DG. Postoperative ileus following major colorectal surgery. Br J Surg. 2018;105(7):797-810. doi: 10.1002/bjs.10781.