

ORIGINAL ARTICLE

Integrated Public Health Evaluation of Gut Microbiota, Inflammatory Biomarkers, and Nutritional Status in Patients Undergoing Colorectal Cancer Surgery

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ABSTRACT

Background: Colorectal cancer (CRC) remains a major global health concern, with postoperative complications contributing significantly to morbidity and delayed recovery. Recent evidence suggests a close interrelationship between gut microbiota imbalance, systemic inflammation, and nutritional status influencing surgical outcomes.

Objective: To assess the integrated role of gut microbiota composition, inflammatory biomarkers, and nutritional status in predicting postoperative complications among patients undergoing colorectal cancer surgery.

Methods: A prospective observational study was conducted at the Department of Gastroenterology and Hepatology, MTI-Hayatabad Medical Complex, Peshawar, Pakistan, from June 2022 to March 2023. One hundred CRC patients scheduled for elective colorectal resection were enrolled. Preoperative stool samples were analyzed using 16S rRNA sequencing for microbial diversity. Serum CRP, IL-6, and TNF- α were measured by ELISA, while nutritional status was assessed using BMI and serum albumin levels. Postoperative outcomes were followed for 30 days. Statistical analyses were performed using SPSS v26, and multivariate regression identified predictors of complications.

Results: Patients with gut dysbiosis (low Bifidobacterium and Lactobacillus) had significantly higher IL-6 and CRP levels ($p < 0.001$). Hypoalbuminemic patients (<3.5 g/dL) experienced more postoperative infections (28%) and longer hospital stays. IL-6, low albumin, and reduced microbiota diversity independently predicted complications.

Conclusion: An integrated assessment of gut microbiota, inflammatory biomarkers, and nutritional health provides valuable predictive insight into surgical outcomes. Optimizing microbial balance, reducing inflammation, and improving nutrition before surgery may enhance recovery and reduce postoperative morbidity in colorectal cancer patients.

Keywords: Colorectal cancer, Gut microbiota, Inflammatory biomarkers, IL-6, CRP, Nutritional status, Postoperative complications

INTRODUCTION

Colorectal cancer (CRC) remains one of the most prevalent malignancies worldwide and a major cause of cancer-related morbidity and mortality. Globally, it ranks as the third most commonly diagnosed cancer and the second leading cause of cancer deaths, accounting for over 1.9 million new cases and 900,000 deaths annually¹. In Pakistan and other low- to middle-income countries, its incidence has been steadily increasing due to changing dietary habits, sedentary lifestyles, and limited access to preventive healthcare. Despite advancements in surgical and oncological management, postoperative complications such as infection, anastomotic leakage, and delayed wound healing continue to pose significant clinical challenges, impacting both recovery time and overall survival².

Growing evidence indicates that the gut microbiota the complex community of microorganisms residing in the gastrointestinal tract plays a pivotal role in colorectal cancer pathogenesis and postoperative recovery³. A balanced gut microbial ecosystem maintains intestinal integrity, modulates immune responses, and regulates inflammation through microbial metabolites like short-chain fatty acids (SCFAs). In contrast, dysbiosis characterized by the depletion of beneficial species (Lactobacillus, Bifidobacterium) and overgrowth of pathogenic taxa (Enterobacteriaceae, Fusobacterium) is associated with mucosal inflammation, impaired immune regulation, and tumor progression. The surgical stress and perioperative antibiotic use often further disrupt microbial equilibrium, predisposing patients to postoperative complications⁴.

Simultaneously, systemic inflammation acts as both a driver and a consequence of tumor biology and surgical stress⁵.

Elevated levels of inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) have been correlated with poor surgical outcomes, including delayed anastomotic healing and increased infection risk. IL-6, in particular, serves as a key mediator in the acute-phase response, linking the inflammatory cascade to catabolic metabolism and immune suppression. Persistent inflammation may also alter the gut microbiota composition, establishing a vicious cycle that hinders recovery⁶.

Nutritional status represents another critical determinant of postoperative prognosis. Malnutrition and cachexia, common among CRC patients, reduce physiological reserves, compromise immune competence, and impair wound repair mechanisms⁷. Indicators such as body mass index (BMI), serum albumin, and prealbumin are widely used to assess nutritional health. Low serum albumin levels, in particular, have been consistently associated with increased postoperative morbidity and prolonged hospitalization. Furthermore, nutritional deficiencies may influence microbial diversity and immune modulation, suggesting an intricate interplay among diet, microbiota, and inflammation⁸.

Despite substantial research on each of these domains individually, few studies have holistically examined the interconnection between gut microbiota composition, systemic inflammation, and nutritional status in the context of colorectal cancer surgery. An integrated evaluation of these parameters could provide valuable insights into predicting postoperative outcomes and tailoring preoperative optimization strategies. Understanding this triad may open avenues for targeted interventions, including microbiota modulation through probiotics, anti-inflammatory therapies, and nutritional rehabilitation, thereby improving surgical recovery and overall patient survival^{9,10}.

Therefore, the present study aims to investigate the integrated relationship between gut microbiota diversity,

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inflammatory biomarkers, and nutritional status among patients undergoing colorectal cancer surgery. By correlating these factors with postoperative outcomes, this study seeks to identify predictive indicators that can enhance risk stratification and guide comprehensive perioperative management strategies for improved clinical outcomes¹¹.

MATERIALS AND METHODS

Study Design and Setting: This prospective observational study was conducted in the Department of Gastroenterology and Hepatology, Medical Teaching Institution – Hayatabad Medical Complex (MTI-HMC), Peshawar, Pakistan, from June 2022 to March 2023. The research aimed to evaluate the integrated relationship between gut microbiota composition, systemic inflammatory biomarkers, and nutritional status in patients undergoing colorectal cancer surgery. Ethical clearance was obtained from the Institutional Review Board. Written informed consent was obtained from each participant prior to inclusion in the study.

Study Population and Sampling Technique: A total of 100 patients diagnosed with histologically confirmed colorectal adenocarcinoma and scheduled for elective surgical resection were recruited through consecutive non-probability sampling from both inpatient and outpatient departments of Gastroenterology and Hepatology. Patients aged between 30 and 75 years, with no prior chemotherapy or radiotherapy, were considered eligible. Exclusion criteria included individuals with inflammatory bowel disease, irritable bowel syndrome, chronic liver or renal dysfunction, autoimmune disorders, and those who had received antibiotics, probiotics, or prebiotics within the four weeks preceding sampling. Patients with severe malnutrition requiring parenteral nutrition or those unwilling to provide consent were also excluded from participation.

Clinical and Demographic Data Collection: Detailed demographic and clinical information including age, gender, body mass index (BMI), comorbidities, and tumor characteristics were recorded using a standardized proforma. Preoperative assessments comprised complete blood count, liver and renal function tests, colonoscopy findings, and histopathological verification. Nutritional and inflammatory parameters were evaluated before surgery, and postoperative complications were monitored for 30 days after the procedure.

Gut Microbiota Profiling: Fresh stool samples were collected from each patient one to three days prior to surgery using sterile containers. The samples were immediately transported to the microbiology research laboratory under cold chain conditions and stored at -80°C until processing. Genomic DNA was extracted using the QIAamp DNA Stool Mini Kit (Qiagen, Germany). The bacterial 16S rRNA gene (V3–V4 region) was amplified through polymerase chain reaction and sequenced using the Illumina MiSeq platform. Bioinformatic analysis was performed with the QIIME 2 pipeline, and operational taxonomic units (OTUs) were defined at 97% sequence similarity. Microbial diversity was evaluated using Shannon and Simpson indices. Dysbiosis was defined as reduced alpha diversity, depletion of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, and an overgrowth of pathogenic taxa including *Enterobacteriaceae* and *Fusobacterium*.

Assessment of Inflammatory Biomarkers: Peripheral venous blood samples were collected preoperatively after an overnight fast. The serum was separated by centrifugation at 3000 rpm for 10 minutes and stored at -20°C until analysis. Serum C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Abcam, UK) according to the manufacturer's instructions. The results were expressed as mg/L for CRP and pg/mL for IL-6 and TNF-α. Elevated levels of these biomarkers were considered indicative of a heightened systemic inflammatory response.

Nutritional Assessment: The nutritional status of all patients was assessed through a combination of anthropometric and

biochemical parameters. Body mass index (BMI) was calculated using the standard formula (weight in kilograms divided by height in meters squared). Serum albumin and prealbumin were determined using an automated biochemistry analyzer (Beckman Coulter AU480). In addition, micronutrient levels including vitamin D, ferritin, and zinc were measured using immunoassay techniques. Based on serum albumin and BMI values, patients were categorized into three groups:

- **Well-nourished:** Serum albumin ≥ 3.5 g/dL and BMI ≥ 20 kg/m²
- **Moderately malnourished:** Albumin 3.0–3.4 g/dL or BMI 18–19.9 kg/m²
- **Severely malnourished:** Albumin < 3.0 g/dL or BMI < 18 kg/m²

This classification allowed comparison of nutritional adequacy with postoperative outcomes and inflammatory markers. **Postoperative Monitoring and Outcome Evaluation:** All patients were observed for 30 days following surgery to assess postoperative outcomes. Complications including wound infections, anastomotic leakage, sepsis, delayed bowel motility, or prolonged hospitalization were systematically recorded. The Clavien-Dindo classification system was employed to grade the severity of postoperative complications. Duration of hospital stay, need for re-operation, and readmission rates were documented.

Statistical Analysis: Data were analyzed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean \pm standard deviation (SD), whereas categorical variables were summarized as frequencies and percentages. The Student's t-test and one-way ANOVA were applied to compare quantitative variables across study groups. The Pearson correlation coefficient was used to explore relationships among gut microbiota diversity indices, inflammatory biomarkers, and nutritional parameters. To identify independent predictors of postoperative complications, a multivariate logistic regression model was applied. A p-value of < 0.05 was considered statistically significant for all analyses.

RESULTS

Demographic and Clinical Characteristics: A total of 100 patients undergoing colorectal cancer surgery were included in this study. The mean age of participants was 56.4 ± 9.8 years, with a male-to-female ratio of 1.3:1 (57 males and 43 females). The majority of patients (62%) were between 50 and 65 years of age. The mean body mass index (BMI) was 24.5 ± 3.2 kg/m². Among the study group, 39% of patients were classified as malnourished based on serum albumin and BMI criteria, while 61% were well-nourished. The most common comorbidities included type 2 diabetes mellitus (27%), hypertension (22%), and anemia (18%). Baseline demographic and clinical details are presented in Table 1. As shown in Table 1, nearly two-fifths of the study population were malnourished prior to surgery. These patients generally exhibited lower BMI and serum albumin values, highlighting nutritional vulnerability that could influence postoperative outcomes.

Table 1: Demographic and Baseline Clinical Characteristics of Study Participants

Variable	Mean \pm SD / n (%)
Total Patients	100
Age (years)	56.4 ± 9.8
Gender (Male/Female)	57 (57%) / 43 (43%)
BMI (kg/m ²)	24.5 ± 3.2
Well-nourished	61 (61%)
Malnourished	39 (39%)
Serum Albumin (g/dL)	3.48 ± 0.41
Diabetes Mellitus	27 (27%)
Hypertension	22 (22%)
Anemia	18 (18%)

Gut Microbiota Composition and Diversity: Preoperative stool analysis revealed marked alterations in gut microbial composition

among colorectal cancer patients. The Shannon diversity index was significantly lower in patients who later developed postoperative complications (mean 1.78 ± 0.42) compared to those who recovered without complications (mean 2.45 ± 0.37 ; $p < 0.001$). Patients with dysbiosis demonstrated a relative depletion of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, and an increased abundance of pathogenic taxa, particularly *Enterobacteriaceae* and *Fusobacterium nucleatum*.

Moreover, reduced microbial diversity correlated strongly with elevated inflammatory markers, suggesting an interplay between dysbiosis and systemic inflammation. These findings underscore the significant role of the gut microbiome in determining host inflammatory status and recovery trajectory after surgery.

Table 2: Inflammatory and Nutritional Biomarkers in Colorectal Cancer Patients

Parameter	Overall Mean \pm SD	Without Complications (n=77)	With Complications (n=23)	p-value
CRP (mg/L)	12.6 ± 4.1	10.8 ± 3.2	17.1 ± 4.3	<0.001
IL-6 (pg/mL)	18.4 ± 6.7	15.9 ± 5.2	26.3 ± 7.1	<0.001
TNF- α (pg/mL)	9.3 ± 3.8	8.6 ± 3.1	11.5 ± 4.2	0.007
Serum Albumin (g/dL)	3.48 ± 0.41	3.58 ± 0.38	3.12 ± 0.29	<0.001
BMI (kg/m ²)	24.5 ± 3.2	25.2 ± 2.9	22.8 ± 3.1	0.009

Association Between Microbiota, Inflammatory Markers, and Nutritional Status: Correlation analysis revealed significant interactions among gut microbiota diversity, inflammatory biomarkers, and nutritional indicators. The Shannon diversity index exhibited a strong negative correlation with IL-6 ($r = -0.61$, $p < 0.001$) and CRP ($r = -0.54$, $p < 0.001$), indicating that reduced microbial diversity is associated with elevated systemic inflammation. Serum albumin positively correlated with microbial diversity ($r = 0.58$, $p < 0.001$), emphasizing the interdependence between nutritional balance and intestinal microbial health.

Furthermore, patients with low albumin (<3.5 g/dL) showed markedly higher IL-6 levels (mean 25.8 pg/mL) than those with normal albumin levels (mean 14.7 pg/mL), suggesting that hypoalbuminemia is a potential marker of systemic inflammation and poor microbial integrity.

Postoperative Complications and Outcomes: Out of 100 patients, 23 (23%) developed postoperative complications within 30 days of surgery. The most frequent complications included surgical site infection (11%), anastomotic leakage (6%), and prolonged ileus (4%). The mean length of hospital stay was 9.8 ± 3.1 days for uncomplicated cases and 16.5 ± 4.7 days for complicated cases ($p < 0.001$).

Patients with dysbiosis and high IL-6 levels experienced a longer duration of hospitalization and delayed wound healing. Inflammatory markers and nutritional deficiencies were the most significant contributors to poor postoperative outcomes. As demonstrated in Table 3, microbial diversity, inflammatory load, and nutritional deficiency were significant predictors of surgical outcomes. Patients with dysbiosis (lower Shannon index), elevated IL-6, and hypoalbuminemia were more prone to postoperative morbidity and prolonged recovery.

Table 3: Postoperative Outcomes in Relation to Biomarkers and Microbiota Diversity

Parameter	No Complications (n=77)	Complications (n=23)	p-value
Mean Shannon Index	2.45 ± 0.37	1.78 ± 0.42	<0.001
CRP (mg/L)	10.8 ± 3.2	17.1 ± 4.3	<0.001
IL-6 (pg/mL)	15.9 ± 5.2	26.3 ± 7.1	<0.001
Albumin (g/dL)	3.58 ± 0.38	3.12 ± 0.29	<0.001
Hospital Stay (days)	9.8 ± 3.1	16.5 ± 4.7	<0.001

Multivariate Regression Analysis for Predictors of Postoperative Complications: A multivariate logistic regression model was employed to identify independent predictors of postoperative complications. Elevated IL-6 levels, hypoalbuminemia, and reduced microbiota diversity emerged as statistically significant independent predictors. As illustrated in

Inflammatory Biomarkers: The mean preoperative serum C-reactive protein (CRP) level was 12.6 ± 4.1 mg/L, while interleukin-6 (IL-6) averaged 18.4 ± 6.7 pg/mL and tumor necrosis factor- α (TNF- α) was 9.3 ± 3.8 pg/mL. Patients who experienced postoperative complications demonstrated significantly higher IL-6 and CRP concentrations compared to those without complications ($p < 0.001$). Elevated inflammatory markers were most commonly observed in individuals with microbial imbalance and low albumin levels. Table 2 provides a summary of the inflammatory and nutritional biomarker data. As depicted in Table 2, both CRP and IL-6 levels were significantly higher in patients who developed postoperative infections, while serum albumin and BMI values were notably lower in the same group. This inverse relationship indicates that nutritional depletion amplifies systemic inflammation, thereby increasing the likelihood of adverse surgical outcomes.

Table 4, IL-6, low albumin, and microbial dysbiosis independently predicted the likelihood of postoperative complications. Among these, IL-6 was the strongest predictor, followed by serum albumin and microbiota diversity index.

Table 4: Multivariate Logistic Regression Analysis of Predictors for Postoperative Complications

Predictor	β Coefficient	Odds Ratio (95% CI)	p-value
IL-6 > 20 pg/mL	1.21	3.4 (1.6–7.2)	0.001
Serum Albumin < 3.5 g/dL	1.08	2.9 (1.5–5.7)	0.003
Shannon Index < 2.0	0.97	2.6 (1.3–5.3)	0.006
Elevated CRP (>10 mg/L)	0.85	2.3 (1.1–4.8)	0.02

The results of this study demonstrate that patients with altered gut microbiota and systemic inflammation experienced poorer surgical outcomes, including higher complication rates and prolonged recovery. Malnutrition further exacerbated inflammatory responses, establishing a multidimensional interplay among nutritional health, microbial ecology, and immune regulation.

The integrated assessment of these three parameters microbiota, inflammation, and nutrition proved to be a valuable tool for identifying at-risk patients prior to colorectal cancer surgery. Collectively, these findings highlight the importance of preoperative interventions targeting microbial restoration and nutritional optimization to improve postoperative prognosis in colorectal cancer patients.

DISCUSSION

This study provides an integrated evaluation of gut microbiota composition, systemic inflammatory biomarkers, and nutritional status in patients undergoing colorectal cancer (CRC) surgery at MTI-Hayatabad Medical Complex, Peshawar⁹. The findings strongly support the hypothesis that these three physiological dimensions are interlinked and collectively influence surgical outcomes. Specifically, patients exhibiting microbial dysbiosis, elevated inflammatory markers (particularly IL-6 and CRP), and hypoalbuminemia were at a significantly higher risk of postoperative complications such as wound infections, anastomotic leakage, and prolonged hospital stay¹⁰⁻¹².

The observed reduction in microbial diversity among CRC patients, particularly the depletion of beneficial genera (*Lactobacillus* and *Bifidobacterium*) and enrichment of pathogenic taxa (*Fusobacterium* and *Enterobacteriaceae*), aligns with previous studies highlighting the critical role of gut microbiota in maintaining intestinal homeostasis and modulating the immune response¹³. Dysbiosis may impair mucosal integrity, promote bacterial translocation, and activate Toll-like receptor-mediated inflammatory

pathways, which in turn elevate systemic cytokines such as IL-6 and TNF- α . This pro-inflammatory milieu disrupts postoperative healing and increases the susceptibility to infection¹⁴.

Our findings are consistent with the work of Wang et al. (2022) and Xie et al. (2023), who reported that altered gut microbial diversity is associated with enhanced postoperative inflammation and poorer recovery among CRC patients. The negative correlation between the Shannon diversity index and IL-6 levels ($r = -0.61$) observed in this study reinforces the notion that microbial imbalance directly contributes to immune dysregulation^{15,16}.

The elevation of CRP and IL-6 among patients with postoperative complications further underscores the importance of inflammatory biomarkers as reliable predictors of adverse surgical outcomes. IL-6 acts as a central mediator of the acute-phase response and induces hepatic synthesis of CRP, amplifying inflammation and tissue catabolism¹⁷. Persistently elevated IL-6 levels have been linked to anastomotic leakage, delayed wound healing, and increased mortality in colorectal surgery. The strong predictive value of IL-6 found in this study ($p = 0.001$, OR = 3.4) mirrors findings from Matsuo et al. (2023), where IL-6 was identified as an independent determinant of postoperative morbidity¹⁸.

Nutritional status also emerged as a key determinant of surgical recovery. Approximately 39% of the patients were malnourished prior to surgery, with significantly lower albumin and BMI values. Serum albumin < 3.5 g/dL was associated with higher rates of infection and longer hospital stays, consistent with earlier observations by Kim et al. (2021) and Arends et al. (2021). Hypoalbuminemia not only reflects protein depletion but also indicates an ongoing inflammatory and catabolic state. Moreover, nutritional deficiencies can impair immune function, reduce collagen synthesis, and weaken epithelial barrier repair all of which contribute to poor postoperative outcomes^{19,20}.

Importantly, the integration of microbiota, inflammation, and nutrition presents a comprehensive framework for preoperative risk assessment. Individually, each parameter offers valuable information, but their combined evaluation yields superior predictive accuracy²¹. Multivariate analysis in this study demonstrated that IL-6, low serum albumin, and reduced microbiota diversity were independent predictors of postoperative complications. This supports the concept that a disturbed gut-immune-nutrition axis predisposes patients to surgical morbidity²².

The clinical implications of these findings are significant. Targeted preoperative interventions, such as probiotic and prebiotic supplementation, dietary optimization, and anti-inflammatory modulation, could restore microbial equilibrium and improve immune and metabolic resilience. Several randomized controlled trials have already demonstrated that perioperative probiotic therapy reduces infection rates, enhances gut barrier integrity, and shortens hospital stays in colorectal surgery patients²³. Future research should explore personalized microbiome and nutrition-based strategies to enhance postoperative recovery, especially in low- and middle-income settings where CRC burden and malnutrition prevalence remain high²⁴.

Nonetheless, this study has certain limitations. First, it was conducted in a single tertiary-care center, which may limit generalizability. Second, although 16S rRNA sequencing provides valuable insight into microbial composition, metagenomic or metabolomic profiling could offer a deeper understanding of functional microbial changes. Lastly, long-term outcomes such as recurrence or survival were not evaluated, which could be addressed in future longitudinal studies^{19,25}.

Overall, the integration of microbial, inflammatory, and nutritional parameters represents a promising approach for risk stratification and perioperative management in colorectal cancer surgery¹³.

CONCLUSION

This study demonstrates that altered gut microbiota, elevated inflammatory biomarkers (especially IL-6 and CRP), and poor nutritional status significantly increase the risk of postoperative complications in colorectal cancer surgery. Integrating these parameters into preoperative evaluation can help identify high-risk patients and improve outcomes. Optimizing gut health, controlling inflammation, and enhancing nutrition should be key components of perioperative care to promote faster recovery and reduce surgical morbidity.

Authors' Contributions:

AUR¹ conceived and supervised the study design.

MT² performed data collection and statistical analysis.

FR³ contributed to methodology and manuscript drafting.

AM⁴ assisted in data interpretation and results preparation.

MAK⁵ reviewed and edited the manuscript.

SF⁶ finalized the discussion and approved the final version.

All authors read and approved the final manuscript.

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Data Availability: Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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