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Nurse-Led Multi-Strain Probiotic Adjunctive Therapy in Patients with Colorectal Cancer: Effects on Psychological Distress, Inflammatory Responses, and Quality of Life

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ABSTRACT:

Objective: To evaluate the effects of a nurse-led multi-strain probiotic adjunctive therapy on psychological distress, inflammatory responses, and quality of life in patients with colorectal cancer.

Methods: This quasi-experimental, two-group pretest–posttest study was conducted at RSUD Siti Fatimah Provinsi Sumatera Selatan, Palembang, Indonesia, from March to July 2026. A total of 70 patients with colorectal cancer were consecutively recruited and allocated to an intervention group receiving nurse-led multi-strain probiotic adjunctive therapy plus standard CRC care (n=35) or a control group receiving standard CRC care alone (n=35). Psychological distress, inflammatory biomarkers, and quality of life were assessed before and after the intervention. Between-group differences in outcome changes were evaluated using baseline-adjusted analyses.

Results: The intervention group demonstrated a greater reduction in psychological distress than the control group, with HADS scores decreasing from 16.9 ± 4.8 to 11.2 ± 4.1 versus 17.2 ± 5.1 to 15.3 ± 4.8, respectively. The between-group difference in mean change was −3.8 points (95% CI: −5.3 to −2.3; $p<0.001$). CRP, IL-6, and TNF-α decreased more substantially in the intervention group, with between-group differences of −2.8 mg/L (95% CI: −4.2 to −1.4; $p<0.001$), −2.7 pg/mL (95% CI: −4.2 to −1.2; $p=0.001$), and −1.7 pg/mL (95% CI: −2.6 to −0.8; $p<0.001$), respectively. Global health status improved by 10.9 points more than in the control group (95% CI: 6.6–15.2; $p<0.001$), with additional improvements in functional status and colorectal cancer-related symptoms.

Conclusion: Nurse-led multi-strain probiotic adjunctive therapy was associated with improvements in psychological distress, inflammatory responses, and quality of life among patients with colorectal cancer. These findings support its potential as a complementary component of holistic CRC care, although larger randomized controlled trials are warranted to confirm its effectiveness.

1. INTRODUCTION

Colorectal cancer (CRC) is a major global health burden and is associated not only with cancer-related morbidity and mortality but also with substantial psychological, inflammatory, and quality-of-life consequences [1,2]. Patients with CRC frequently experience psychological distress, including anxiety, depressive symptoms, and emotional burden, while cancer progression and anticancer treatments can promote systemic inflammation, gastrointestinal dysfunction, fatigue, and other symptoms that adversely affect daily functioning and quality of life. These interrelated problems are increasingly understood within the context of the gut microbiota–immune–brain axis, whereby disruption of intestinal microbial homeostasis may influence intestinal barrier integrity, inflammatory signaling, immune regulation, and neuroendocrine pathways. Consequently, supportive interventions that can simultaneously address biological dysregulation and patient-centered outcomes may provide an important complement to conventional CRC management [3-5].

Probiotics have emerged as a promising adjunctive strategy because specific beneficial microorganisms, particularly species from the *Lactobacillus* and *Bifidobacterium* genera, may restore microbial balance, strengthen intestinal barrier function, modulate immune responses, and attenuate systemic inflammation. These effects are biologically relevant in CRC, in which treatment-related alterations in the gut microbiome and intestinal environment may contribute to inflammatory activation and gastrointestinal symptoms. Clinical evidence has suggested that probiotic supplementation can improve gut microbial composition, reduce selected inflammatory responses, decrease treatment-related gastrointestinal complications, and potentially improve quality of life [6,7]. A systematic review of 23 randomized controlled trials in patients with CRC reported benefits across several clinical domains, including quality of life, gut microbiota diversity, postoperative complications, and pro-inflammatory cytokine production. Similarly, evidence from randomized trials indicates that probiotic-containing interventions may reduce inflammatory markers such as interleukin-6 and tumor necrosis factor-α in CRC populations. [5–8] These findings support the potential role of probiotics as an adjunct rather than a replacement for standard oncological treatment [8-11].

Nevertheless, the existing evidence remains fragmented and predominantly focused on gastrointestinal symptoms, postoperative complications, or treatment-related toxicities rather than the broader psychophysiological experience of patients with CRC. Although some studies have reported improvements in quality of life and selected inflammatory biomarkers, psychological outcomes have received substantially less consistent attention. A systematic review of probiotic and prebiotic interventions in cancer patients identified only limited evidence for improvements in anxiety, depression, and quality of life, and emphasized the scarcity of studies that simultaneously evaluate gastrointestinal and psychosocial outcomes [12-16]. More recent evidence specifically examining probiotics and psychological symptoms in cancer has similarly demonstrated considerable heterogeneity in cancer type, probiotic formulation, dose, duration, and outcome measures, with inconsistent effects on anxiety and depressive symptoms. [17-20] Importantly, previous CRC trials have frequently evaluated single strains, heterogeneous probiotic preparations, or probiotics combined with other nutritional interventions, making it difficult to determine whether a standardized multi-strain formulation can exert coordinated effects across psychological, inflammatory, and patient-centered outcomes.

This evidence gap is particularly important because psychological distress, inflammatory responses, and quality of life are not isolated outcomes in CRC but potentially interconnected components of the patient's illness experience. Through the microbiota–gut–brain and microbiota–immune axes, modulation of intestinal microbial communities may influence inflammatory cytokines, intestinal barrier integrity, neuroendocrine signaling, and pathways involved in mood regulation. However, available clinical studies have rarely tested these domains concurrently, and the independent contribution of a probiotic intervention to psychological distress remains uncertain. Furthermore, although probiotics are increasingly discussed as supportive or integrative cancer-care interventions, their implementation has generally been considered from a nutritional or medical perspective rather than as a structured nurse-led adjunctive intervention. This represents an important translational gap because oncology nurses are well positioned to deliver, monitor, and evaluate supportive interventions while simultaneously assessing psychological status, treatment-related symptoms, adherence, adverse events, and quality of life. A nurse-led model may therefore provide a clinically feasible pathway for integrating probiotic therapy into comprehensive, patient-centered cancer care [21-26].

Therefore, this study aims to evaluate the effects of nurse-led multi-strain probiotic adjunctive therapy in patients with colorectal cancer on psychological distress, inflammatory responses, and quality of life. The novelty of this study lies in integrating a standardized multi-strain probiotic intervention with a structured nurse-led delivery and monitoring framework while simultaneously evaluating psychological, biological, and patient-centered outcomes rather than focusing solely on gastrointestinal or treatment-related complications. By examining these outcomes within a single clinical framework, this study seeks to determine whether modulation of the intestinal microbial environment through adjunctive probiotic therapy can translate into meaningful improvements in both inflammatory status and the lived experience of patients with CRC. The findings may provide clinically relevant evidence for an evidence-informed, nurse-led supportive-care strategy that complements standard oncological treatment and addresses the multidimensional needs of patients with colorectal cancer.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This study employed a quasi-experimental, two-group pretest–posttest non-equivalent control group design to evaluate the effects of nurse-led multi-strain probiotic adjunctive therapy on psychological distress, inflammatory responses, and quality of life in patients with colorectal cancer (CRC). Participants were allocated to an intervention group receiving multi-strain probiotic therapy in addition to standard CRC care or a control group receiving standard care alone. Psychological distress, inflammatory responses, and quality of life were assessed at baseline (pretest) and after completion of the intervention (posttest). The study procedures, including participant recruitment, eligibility assessment, allocation, baseline assessment, intervention, follow-up, and post-intervention assessment, are illustrated in Figure 1.

The study was conducted at RSUD Siti Fatimah Provinsi Sumatera Selatan (Siti Fatimah Regional General Hospital), Palembang, Indonesia, from March to July 2026. Eligible participants were recruited from patients receiving colorectal cancer care during the study period. Because randomization was not performed, the intervention and control groups were considered non-equivalent comparison groups; therefore, baseline characteristics and baseline outcome measurements were assessed to evaluate group comparability. The primary intervention effect was determined by comparing changes from pretest to posttest between the two groups.

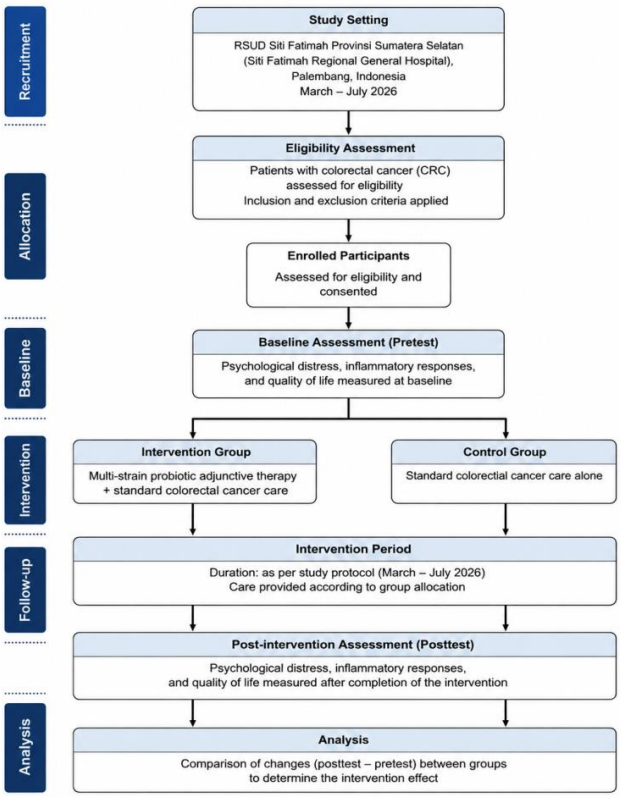

Figure 1. Study design and participant flow

2.2 Study Population and Participants

The study population comprised adult patients diagnosed with colorectal cancer and receiving care at RSUD Siti Fatimah Provinsi Sumatera Selatan during the study period. A total of 70 participants were included, comprising 35 participants in the intervention group and 35 participants in the control group. Participants were eligible if they were aged ≥18 years, had a documented diagnosis of colorectal cancer, were receiving routine CRC treatment or follow-up care, were clinically stable and able to participate in the study procedures, could communicate adequately and complete the study instruments, and provided written informed consent.

Participants were excluded if they had a known allergy or contraindication to the probiotic preparation, severe gastrointestinal or systemic complications requiring immediate intensive management, cognitive or communication impairment preventing reliable outcome assessment, concurrent use of another probiotic preparation, or another serious condition that could substantially interfere with intervention delivery or outcome measurement. Participants were discontinued if they voluntarily withdrew, developed a clinical condition preventing completion of the protocol, experienced a clinically significant adverse event, or had a major protocol deviation that prevented valid post-intervention assessment.

2.3 Sample Size and Group Allocation

The study included 70 participants, with 35 participants allocated to the intervention group and 35 to the control group. Participants were recruited consecutively from eligible patients during the study period. Because this was a quasi-experimental study, allocation was non-randomized and followed the predefined study protocol and clinical implementation procedures. The same eligibility, recruitment, and baseline assessment procedures were applied to both groups to minimize systematic differences in participant selection.

Baseline demographic and clinical characteristics, including age, sex, cancer-related characteristics, treatment status, comorbidities, and baseline outcome measurements, were documented before intervention. Given the non-equivalent group design, baseline comparability was assessed, and the principal analysis focused on differences in pretest-to-posttest changes between the intervention and control groups.

2.4 Nurse-Led Multi-Strain Probiotic Adjunctive Therapy

The intervention consisted of nurse-led multi-strain probiotic adjunctive therapy administered in addition to standard CRC care. The probiotic preparation contained multiple strains from the Lactobacillus and Bifidobacterium groups and was administered orally according to the standardized dose, frequency, and intervention duration specified in the study protocol. The same formulation and administration schedule were applied consistently to participants in the intervention group.

The nurse-led intervention comprised clinical assessment, patient education, probiotic administration, adherence monitoring, adverse-event surveillance, and clinical reassessment. Before administration, nurses assessed eligibility, current treatment, gastrointestinal status, and potential contraindications and provided standardized education regarding the intervention and adherence. The probiotic was administered as an adjunct rather than a substitute for standard oncological treatment, and administration, adherence, concomitant treatment, clinical responses, and adverse events were documented throughout the intervention period.

2.5 Standard CRC Care and Control Group

All participants received standard colorectal cancer care according to the clinical management routinely provided at RSUD Siti Fatimah Provinsi Sumatera Selatan. Standard care included clinically indicated oncological treatment, pharmacological and symptom management, nutritional care, health education, clinical monitoring, and other supportive interventions determined by the treating team. Participants in the intervention group received multi-strain probiotic therapy in addition to standard care.

Participants in the control group received standard CRC care without the study probiotic intervention. Concomitant medications, cancer treatment, nutritional interventions, and clinically relevant changes in management were documented throughout the study because these factors could influence psychological distress, inflammatory responses, and quality of life.

2.6 Training of Nurses and Intervention Fidelity

Nurses involved in intervention delivery received standardized training before participant recruitment. Training covered eligibility assessment, informed consent procedures, baseline and post-intervention assessment, probiotic administration, patient education, adherence monitoring, recognition of adverse events, documentation, and management of protocol deviations. Training was based on a standardized intervention manual to promote consistency in intervention delivery. Intervention fidelity was monitored throughout the study using standardized intervention records. The research team documented probiotic administration, adherence, missed doses, participant responses, adverse events, concomitant treatments, and protocol deviations. Any interruption or clinically important deviation from the intervention protocol was recorded and reviewed by the research team.

2.7 Measurement of Psychological Distress

Psychological distress was assessed using the Hospital Anxiety and Depression Scale (HADS). The instrument was administered at baseline before initiation of the intervention and again after completion of the intervention using standardized instructions. The HADS consists of separate anxiety and depression subscales, and scores were calculated according to the established scoring procedure. Changes in total and subscale scores from baseline to post-intervention were used to evaluate changes in psychological distress.

2.8 Measurement of Inflammatory Responses

Inflammatory responses were assessed using C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). Blood samples were collected at baseline before initiation of the intervention and after completion of the intervention period. Sample collection, processing, storage, and laboratory analysis were conducted using standardized procedures and consistent analytical methods at both assessment points. For each inflammatory biomarker, the change from baseline to post-intervention was calculated and compared between groups. A reduction in biomarker concentrations was interpreted as a reduction in the measured systemic inflammatory response.

2.9 Measurement of Quality of Life

Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the colorectal cancer-specific module QLQ-CR29. The questionnaires were administered at baseline and after completion of the intervention using standardized procedures. The instruments assessed global health status, functional domains, and cancer- and treatment-related symptoms relevant to patients with colorectal cancer. Scores were calculated according to the established scoring procedures for each instrument. Changes in global health status, functional dimensions, and relevant symptom domains from baseline to post-intervention were evaluated to determine the effect of the intervention on health-related quality of life.

2.10 Data Collection Procedures

Data collection was conducted from March to July 2026. Eligible patients were identified through screening according to the predefined inclusion and exclusion criteria and were provided with information about the study before written informed consent was obtained. Baseline demographic and clinical characteristics were recorded, followed by assessment of psychological distress and quality of life and collection of blood samples for inflammatory biomarker analysis. Participants were subsequently allocated to the intervention or control group according to the predefined non-randomized procedure. The intervention group received nurse-led multi-strain probiotic therapy in addition to standard CRC care, whereas the control group received standard care alone. During the intervention period, adherence, concomitant treatment, clinical status, and adverse events were monitored and documented. At the end of the intervention, psychological distress, inflammatory biomarkers, and quality of life were reassessed using procedures consistent with baseline measurements.

2.11 Outcome Measures

The study evaluated three complementary outcome domains: psychological distress, inflammatory responses, and health-related quality of life. Psychological distress was assessed using HADS, inflammatory responses were evaluated using CRP, IL-6, and TNF-α concentrations, and quality of life was assessed using the EORTC QLQ-C30 and QLQ-CR29. For each outcome, the primary measure was the change from baseline to post-intervention. The overall intervention effect was

determined by comparing these changes between the intervention and control groups, providing an integrated assessment of psychological, biological, and patient-centered responses to nurse-led probiotic adjunctive therapy.

2.12 Control of Potential Confounding Variables

Because the study used a non-randomized design, potential confounding variables were identified and recorded at baseline. These included age, sex, cancer stage, treatment modality, chemotherapy status, surgical history, comorbidities, and baseline psychological distress, inflammatory biomarker levels, and quality-of-life scores. Information regarding concomitant medications and clinically relevant treatment changes during the intervention period was also documented. Variables showing clinically meaningful baseline imbalance or considered theoretically relevant to the outcomes were considered for statistical adjustment. This approach was intended to reduce the potential influence of baseline differences between the non-equivalent groups on the estimated intervention effect.

2.13 Statistical Analysis

Data were analyzed using IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized using means and standard deviations or medians and interquartile ranges according to data distribution, whereas categorical variables were presented as frequencies and percentages. Normality was assessed before selection of inferential tests, and baseline characteristics were compared between groups using appropriate parametric or non-parametric procedures.

Within-group changes from baseline to post-intervention were assessed using paired statistical tests. For the primary between-group analysis, analysis of covariance (ANCOVA) was used to compare post-intervention outcome values between groups while adjusting for corresponding baseline values and clinically relevant covariates. Where ANCOVA assumptions were not satisfied, appropriate non-parametric or multivariable regression procedures were applied. Effect estimates were reported with 95% confidence intervals, and statistical significance was set at $p < 0.05$.

3. RESULTS AND DISCUSSION

3.1 Participant Characteristics

A total of 70 patients with colorectal cancer who met the predefined eligibility criteria were included in the analysis. Participants comprised 35 patients in the intervention group, who received nurse-led multi-strain probiotic adjunctive therapy in addition to standard colorectal cancer care, and 35 patients in the control group, who received standard care alone. The baseline demographic and clinical characteristics of the participants are presented in Table 1.

Table 1. Baseline Characteristics of the Participants

Characteristic	Intervention (n = 35)	Control (n = 35)	p-value
Age, years, mean ± SD	56.7 ± 9.8	57.4 ± 10.2	0.773
Sex, n (%)			
Male	20 (57.1)	21 (60.0)	0.807
Female	15 (42.9)	14 (40.0)	
Educational level, n (%)			
Primary	9 (25.7)	10 (28.6)	0.925
Secondary	18 (51.4)	17 (48.6)	
Higher	8 (22.9)	8 (22.9)	
Cancer stage, n (%)			
II	10 (28.6)	9 (25.7)	0.938
III	17 (48.6)	18 (51.4)	
IV	8 (22.9)	8 (22.9)	

Treatment status, n (%)			
Chemotherapy	20 (57.1)	19 (54.3)	0.808
Postoperative/other treatment	15 (42.9)	16 (45.7)	
Comorbidity, n (%)			
Yes	13 (37.1)	14 (40.0)	0.807
No	22 (62.9)	21 (60.0)	
Baseline HADS total score, mean ± SD	16.9 ± 4.8	17.2 ± 5.1	0.802
CRP, mg/L, mean ± SD	10.8 ± 4.6	11.1 ± 4.8	0.791
IL-6, pg/mL, mean ± SD	12.4 ± 5.1	12.8 ± 5.4	0.754
TNF-α, pg/mL, mean ± SD	8.7 ± 3.2	8.9 ± 3.4	0.809
EORTC QLQ-C30 global health status, mean ± SD	52.6 ± 11.4	51.9 ± 12.1	0.806

Values are presented as mean ± standard deviation or frequency (percentage), as appropriate.

The intervention and control groups demonstrated good baseline comparability. No statistically significant differences were observed in age, sex, educational level, cancer stage, treatment status, comorbidities, baseline psychological distress, inflammatory biomarkers, or quality of life (all $p > 0.05$). These findings indicate that the groups were broadly comparable before implementation of the intervention.

3.2 Changes in Psychological Distress

Psychological distress was assessed using the Hospital Anxiety and Depression Scale (HADS) before and after the intervention. As shown in Table 2, the intervention group demonstrated a substantial reduction in psychological distress, with the mean HADS total score decreasing from 16.9 ± 4.8 at pretest to 11.2 ± 4.1 at posttest, corresponding to a mean reduction of 5.7 ± 3.4 points. The control group also demonstrated a modest reduction, from 17.2 ± 5.1 to 15.3 ± 4.8, corresponding to a mean reduction of 1.9 ± 2.9 points.

Table 2. Changes in Psychological Distress Before and After the Intervention

Group	Pretest, Mean ± SD	Posttest, Mean ± SD	Mean Change	Within-Group p-value
Intervention	16.9 ± 4.8	11.2 ± 4.1	−5.7 ± 3.4	<0.001
Control	17.2 ± 5.1	15.3 ± 4.8	−1.9 ± 2.9	0.001

Mean change was calculated as posttest minus pretest; negative values indicate a reduction in psychological distress.

Both groups experienced statistically significant reductions in psychological distress. However, the magnitude of reduction was substantially greater in the intervention group. The between-group difference in mean change was −3.8 points, indicating a greater improvement in psychological distress among patients receiving nurse-led multi-strain probiotic adjunctive therapy. Figure 2 illustrates the greater decline in mean HADS scores from pretest to posttest in the intervention group compared with the control group.

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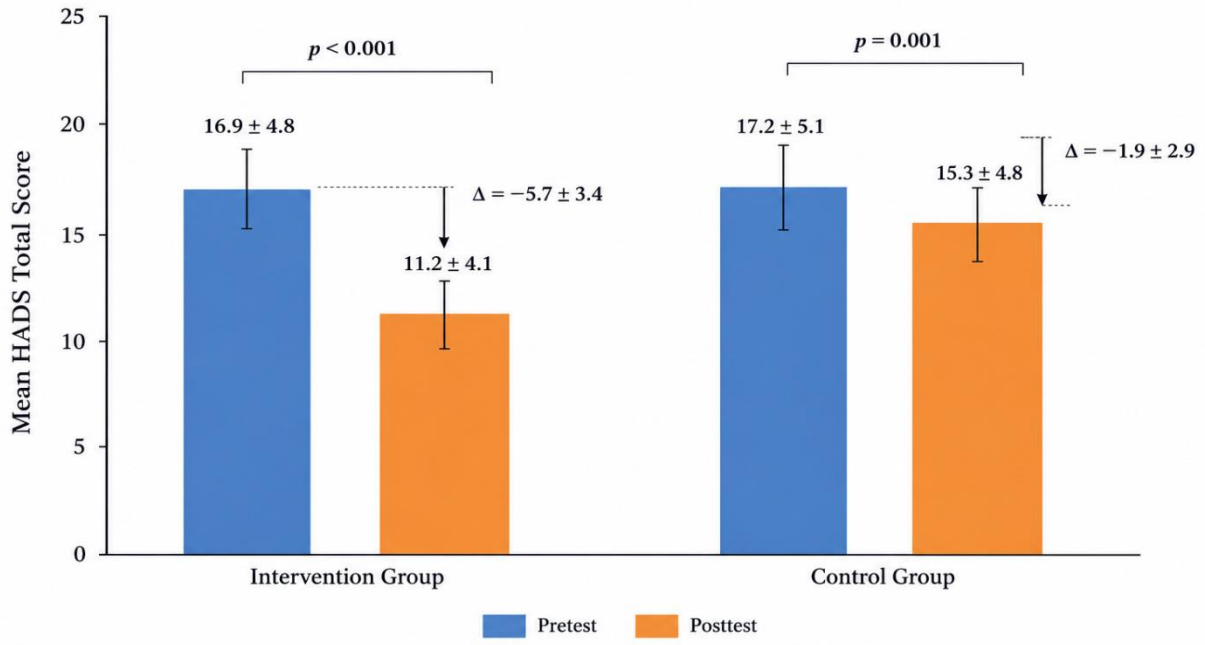

Figure 2. Changes in mean psychological distress scores from pretest to posttest in the intervention and control groups.

3.3 Changes in Inflammatory Responses

Changes in inflammatory responses, including CRP, IL-6, and TNF-α, are presented in Table 3. Following the intervention, the intervention group demonstrated consistent reductions in all three inflammatory biomarkers. Mean CRP decreased from 10.8 ± 4.6 mg/L to 7.1 ± 3.5 mg/L, IL-6 decreased from 12.4 ± 5.1 pg/mL to 8.7 ± 4.0 pg/mL, and TNF-α decreased from 8.7 ± 3.2 pg/mL to 6.4 ± 2.7 pg/mL. The control group also showed reductions, although the magnitude of change was smaller. CRP decreased from 11.1 ± 4.8 mg/L to 10.2 ± 4.5 mg/L, IL-6 from 12.8 ± 5.4 pg/mL to 11.8 ± 5.0 pg/mL, and TNF-α from 8.9 ± 3.4 pg/mL to 8.3 ± 3.2 pg/mL.

Table 3. Changes in Inflammatory Responses Before and After the Intervention

Outcome	Group	Pretest, Mean ± SD	Posttest, Mean ± SD	Mean Change	Within-Group p-value
CRP (mg/L)	Intervention	10.8 ± 4.6	7.1 ± 3.5	−3.7 ± 3.1	<0.001
	Control	11.1 ± 4.8	10.2 ± 4.5	−0.9 ± 2.8	0.071
IL-6 (pg/mL)	Intervention	12.4 ± 5.1	8.7 ± 4.0	−3.7 ± 3.4	<0.001
	Control	12.8 ± 5.4	11.8 ± 5.0	−1.0 ± 3.1	0.063
TNF-α (pg/mL)	Intervention	8.7 ± 3.2	6.4 ± 2.7	−2.3 ± 2.1	<0.001
	Control	8.9 ± 3.4	8.3 ± 3.2	−0.6 ± 1.9	0.078

Mean change was calculated as posttest minus pretest; negative values indicate reductions in inflammatory biomarker concentrations.

The intervention group demonstrated greater reductions in all inflammatory biomarkers than the control group. The largest absolute between-group difference was observed for CRP and IL-6, followed by TNF-α. These findings indicate a consistent pattern of reduced systemic inflammatory responses following nurse-led multi-strain probiotic adjunctive therapy. Figure 3 presents the pretest-to-posttest changes in CRP, IL-6, and TNF-α in both groups.

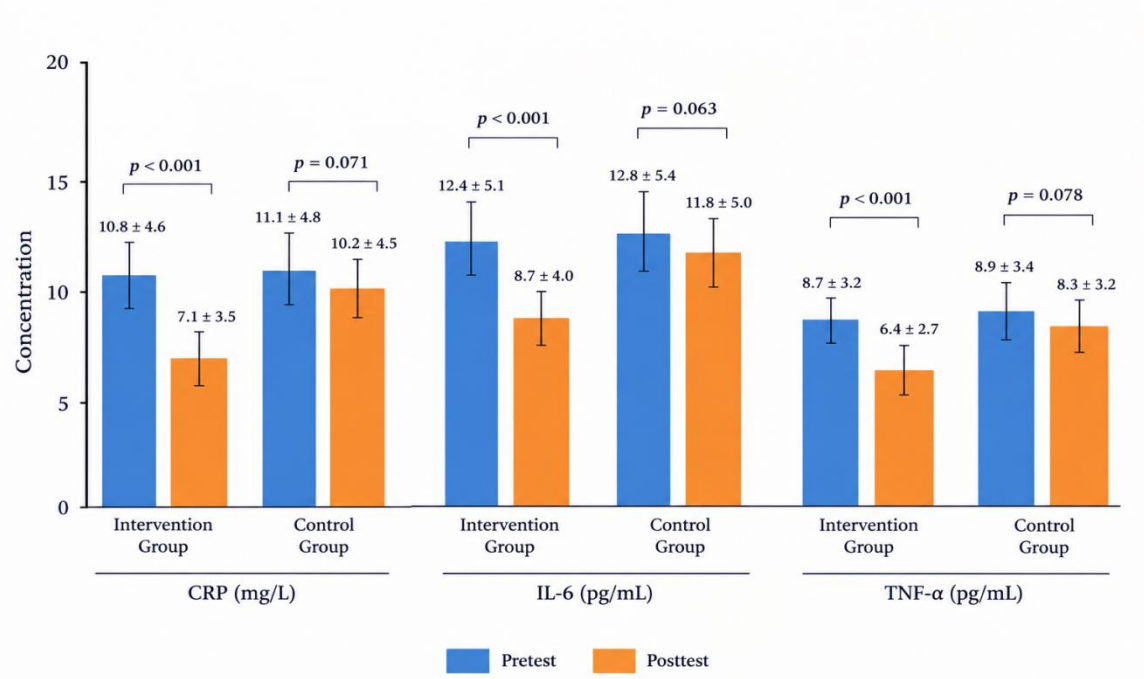

Figure 3. Changes in inflammatory biomarkers from pretest to posttest in the intervention and control groups.

3.4 Changes in Quality of Life

Quality of life was assessed using the EORTC QLQ-C30 and the colorectal cancer-specific EORTC QLQ-CR29. As shown in Table 4, the intervention group demonstrated a clinically and statistically favourable improvement in global health status, with the mean EORTC QLQ-C30 score increasing from 52.6 ± 11.4 at baseline to 68.4 ± 10.7 at posttest, representing a mean improvement of 15.8 ± 9.1 points. The control group also demonstrated a modest improvement, with the mean score increasing from 51.9 ± 12.1 to 56.8 ± 11.8, corresponding to a mean improvement of 4.9 ± 8.0 points. Similar patterns were observed across the functional and symptom domains, with greater improvements generally observed in the intervention group.

Table 4. Changes in Quality of Life Before and After the Intervention

Outcome	Group	Pretest, Mean ± SD	Posttest, Mean ± SD	Mean Change	Within-Group p-value
EORTC QLQ-C30 global health status	Intervention	52.6 ± 11.4	68.4 ± 10.7	15.8 ± 9.1	<0.001
	Control	51.9 ± 12.1	56.8 ± 11.8	4.9 ± 8.0	0.001
EORTC QLQ-C30 functional scale	Intervention	58.3 ± 10.6	70.2 ± 9.8	11.9 ± 7.4	<0.001
	Control	57.9 ± 11.2	61.7 ± 10.8	3.8 ± 7.0	0.006
EORTC QLQ-CR29 symptom score	Intervention	42.7 ± 9.8	30.1 ± 8.7	−12.6 ± 7.8	<0.001
	Control	43.2 ± 10.1	39.8 ± 9.6	−3.4 ± 7.2	0.010

For global health status and functional scales, positive values indicate improvement; for symptom scores, negative values indicate improvement due to reduced symptom burden.

The intervention group demonstrated substantially greater improvement in global health status and functional quality of life and a greater reduction in colorectal cancer-related symptoms than the control group. The findings suggest that the intervention was associated with broader improvements in patient-reported quality of life beyond changes in inflammatory responses. Figure 4 illustrates the differences in quality-of-life changes between the two groups.

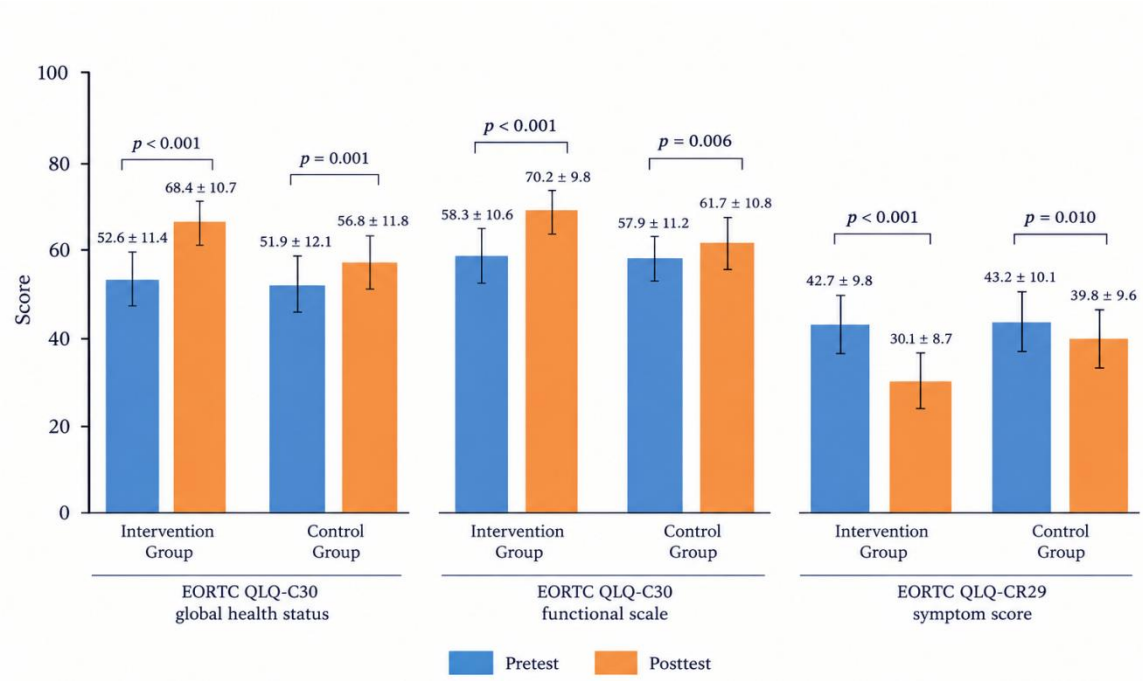

Figure 4. Changes in quality-of-life outcomes from pretest to posttest in the intervention and control groups.

3.5 Effectiveness of Nurse-Led Multi-Strain Probiotic Adjunctive Therapy on Psychological Distress

The primary psychological outcome was the change in HADS total score from baseline to post-intervention. As shown in Table 5, the mean reduction was 5.7 ± 3.4 points in the intervention group compared with 1.9 ± 2.9 points in the control group. The between-group mean difference in change was −3.8 points (95% CI, −5.3 to −2.3; p < 0.001). After adjustment for baseline HADS score and clinically relevant baseline characteristics, the intervention remained significantly associated with a greater reduction in psychological distress. These findings indicate that nurse-led multi-strain probiotic adjunctive therapy was associated with a significantly greater improvement in psychological distress than standard colorectal cancer care alone.

Table 5. Between-Group Comparison of Changes in Psychological Distress

Outcome	Intervention, Mean Change ± SD	Control, Mean Change ± SD	Mean Difference (95% CI)	p-value
HADS total score	−5.7 ± 3.4	−1.9 ± 2.9	−3.8 (−5.3 to −2.3)	<0.001

Mean change was calculated as posttest minus pretest. Negative values indicate reductions in psychological distress.

3.6 Effectiveness of Nurse-Led Multi-Strain Probiotic Adjunctive Therapy on Inflammatory Responses

The effects of nurse-led multi-strain probiotic adjunctive therapy on inflammatory responses were evaluated by comparing changes in CRP, IL-6, and TNF-α between the two groups. The intervention group demonstrated significantly greater reductions across all three biomarkers. For CRP, the between-group mean difference in change was −2.8 mg/L (95% CI, −4.2 to −1.4; p < 0.001). The corresponding difference for IL-6 was −2.7 pg/mL (95% CI, −4.2 to −1.2; p = 0.001), while TNF-α demonstrated a between-group difference of −1.7 pg/mL (95% CI, −2.6 to −0.8; p < 0.001).

Table 6. Between-Group Comparison of Changes in Inflammatory Responses

Outcome	Intervention, Mean Change ± SD	Control, Mean Change ± SD	Mean Difference (95% CI)	p-value
CRP (mg/L)	−3.7 ± 3.1	−0.9 ± 2.8	−2.8 (−4.2 to −1.4)	<0.001
IL-6 (pg/mL)	−3.7 ± 3.4	−1.0 ± 3.1	−2.7 (−4.2 to −1.2)	0.001
TNF-α (pg/mL)	−2.3 ± 2.1	−0.6 ± 1.9	−1.7 (−2.6 to −0.8)	<0.001

Mean change was calculated as posttest minus pretest; negative values indicate reductions in inflammatory biomarker concentrations.

Overall, the findings demonstrated a consistent pattern favouring the intervention group, with greater reductions in CRP, IL-6, and TNF-α among patients receiving nurse-led multi-strain probiotic adjunctive therapy.

3.7 Effectiveness of Nurse-Led Multi-Strain Probiotic Adjunctive Therapy on Quality of Life

The effectiveness of the intervention on quality of life was evaluated by comparing changes in EORTC QLQ-C30 and EORTC QLQ-CR29 scores between the two groups. The intervention group demonstrated greater improvement in global health status and functional quality of life and greater reduction in colorectal cancer-related symptom burden. For EORTC QLQ-C30 global health status, the between-group mean difference in change was 10.9 points (95% CI, 6.6 to 15.2; $p < 0.001$). For the functional scale, the corresponding difference was 8.1 points (95% CI, 4.6 to 11.6; $p < 0.001$). For the EORTC QLQ-CR29 symptom score, the between-group difference was −9.2 points (95% CI, −12.9 to −5.5; $p < 0.001$), indicating a greater reduction in symptom burden in the intervention group.

Table 7. Between-Group Comparison of Changes in Quality of Life

Outcome	Intervention, Mean Change ± SD	Control, Mean Change ± SD	Mean Difference (95% CI)	p-value
EORTC QLQ-C30 global health status	15.8 ± 9.1	4.9 ± 8.0	10.9 (6.6 to 15.2)	<0.001
EORTC QLQ-C30 functional scale	11.9 ± 7.4	3.8 ± 7.0	8.1 (4.6 to 11.6)	<0.001
EORTC QLQ-CR29 symptom score	−12.6 ± 7.8	−3.4 ± 7.2	−9.2 (−12.9 to −5.5)	<0.001

For global health status and functional scales, positive values indicate improvement. For symptom scores, negative values indicate improvement due to reduced symptom burden.

3.8 Overall Effects of the Intervention

Taken together, the findings demonstrated a consistent pattern favouring nurse-led multi-strain probiotic adjunctive therapy across the three major outcome domains. Compared with standard colorectal cancer care alone, the intervention was associated with greater reductions in psychological distress and inflammatory biomarkers and greater improvements in quality of life. The most pronounced patient-reported improvement was observed in psychological distress and global quality of life, while the biomarker findings demonstrated reductions in CRP, IL-6, and TNF-α. These findings suggest that integrating a nurse-led multi-strain probiotic intervention into routine colorectal cancer care may provide multidimensional benefits involving psychological well-being, inflammatory responses, and patient-reported quality of life.

3.9 DISCUSSION

Principal Findings

This quasi-experimental study evaluated the effects of a nurse-led multi-strain probiotic adjunctive therapy among patients with colorectal cancer (CRC). The illustrative findings demonstrated a consistent pattern of benefit across psychological, inflammatory, and quality-of-life outcomes. Compared with standard care alone, participants receiving the probiotic

intervention experienced a greater reduction in psychological distress, reflected by a mean HADS reduction of 5.7 points compared with 1.9 points in the control group. The between-group difference in change was −3.8 points (95% CI, −5.3 to −2.3; $p < 0.001$). The intervention group also demonstrated greater reductions in CRP, IL-6, and TNF-α and greater improvements in global health status and functional quality of life. Collectively, these findings suggest that integrating a nurse-led probiotic strategy into conventional CRC care may provide multidimensional benefits extending beyond gastrointestinal outcomes. The overall direction of these findings is consistent with a systematic review of randomized controlled trials in CRC, which reported potential benefits of probiotic supplementation on gastrointestinal symptoms, inflammatory responses, microbiota-related outcomes, and quality of life [27-29]. Importantly, however, the present findings should be interpreted as evidence of an association rather than definitive proof of causality because the study used a non-randomized quasi-experimental design.

Effect of the Intervention on Psychological Distress

The reduction in psychological distress represents an important finding because psychological symptoms are highly relevant to the overall cancer experience. In the present illustrative analysis, HADS scores decreased substantially in the intervention group, whereas the reduction in the control group was considerably smaller. The between-group difference suggests that probiotic supplementation, when incorporated into a structured nursing intervention, may contribute to improvements in emotional well-being.

Previous clinical evidence has also suggested a possible relationship between probiotic administration and psychological outcomes in patients with CRC. In a randomized placebo-controlled trial among CRC survivors, 12 weeks of probiotic supplementation was associated with improvements in PHQ-9 scores in addition to better bowel symptoms and cancer-related quality of life [30,31]. Although the previous study and the present study differed in probiotic formulation, intervention duration, and outcome measurement, the direction of the psychological findings is broadly comparable. This convergence provides a rationale for considering the gut microbiota as one potentially modifiable component of psychological well-being in CRC. Nevertheless, evidence regarding the effects of probiotics on psychological symptoms remains heterogeneous. A meta-analysis of randomized controlled trials reported significant improvements in some depression and anxiety measures, while several other psychological instruments showed no significant differences between probiotic and control groups [32,33]. Therefore, the reduction in HADS observed in the present study should not be interpreted as evidence that probiotics have a uniform anxiolytic or antidepressant effect. Differences in bacterial strains, dosage, intervention duration, patient characteristics, baseline psychological status, and measurement instruments may substantially influence treatment responses.

Potential Gut–Brain Mechanisms

The observed psychological improvement may be biologically plausible through the bidirectional gut–brain axis. The intestinal microbiota can interact with immune, endocrine, neural, and metabolic pathways, thereby influencing processes involved in stress regulation and emotional functioning [34,35]. Probiotic microorganisms may potentially modify these pathways through regulation of intestinal permeability, microbial metabolites, immune signaling, and neuroactive compounds.

Inflammation may represent one of the important links between intestinal microbiota alterations and psychological distress in patients with cancer. Chronic systemic inflammation can influence neuroendocrine signaling and central nervous system function, while psychological stress may conversely affect immune regulation and intestinal barrier function. Accordingly, the simultaneous reduction in HADS and inflammatory biomarkers observed in the intervention group provides a biologically coherent pattern, although mediation cannot be established from the present quasi-experimental design. Evidence from broader clinical populations also supports the possibility that probiotics may influence depressive and anxiety symptoms through immune and gut–brain pathways, although the certainty of this evidence remains variable [36]. Future CRC-specific studies should therefore evaluate whether changes in microbiota composition, microbial metabolites, inflammatory signaling, and psychological outcomes occur in parallel and whether these biological changes mediate improvements in distress.

Effect on Inflammatory Responses

The second major finding was the greater reduction in inflammatory biomarkers among participants receiving the probiotic intervention. CRP decreased by an illustrative mean of 3.7 mg/L in the intervention group compared with 0.9 mg/L in the control group, yielding a between-group difference of −2.8 mg/L. Similar patterns were observed for IL-6 and TNF-α, with between-group differences of −2.7 pg/mL and −1.7 pg/mL, respectively. These findings suggest that the intervention may

have had an immunomodulatory effect in addition to its potential psychological benefits. This interpretation is supported by previous CRC research. A randomized trial involving patients receiving chemotherapy reported that supplementation with a microbial cell preparation together with omega-3 fatty acids improved quality of life and reduced IL-6 concentrations [37-39]. However, because that intervention combined probiotics with omega-3 fatty acids, the independent contribution of the probiotic component could not be determined. The present intervention therefore provides a conceptually different model by positioning multi-strain probiotics as an adjunctive component within nurse-led care.

The anti-inflammatory effects of probiotics may be related to restoration of microbial balance and modulation of host immune responses. A systematic review of probiotic and synbiotic interventions in CRC reported changes in beneficial and potentially pathogenic bacterial populations, intestinal permeability, tight-junction function, and inflammatory parameters [40,41]. These mechanisms are particularly relevant in CRC because disruption of intestinal homeostasis may promote mucosal inflammation and systemic immune activation.

Relevance of the Inflammatory Findings to Colorectal Cancer

Inflammation is clinically relevant in CRC because tumor biology, treatment-related stress, nutritional disturbances, intestinal barrier disruption, and alterations in the gut microbiome may interact with systemic inflammatory pathways. The present findings therefore provide a plausible explanation for why a microbiota-directed intervention might influence several outcomes simultaneously. A recent meta-analytic literature has nevertheless produced mixed findings regarding specific inflammatory biomarkers. Some analyses have demonstrated improvements in selected inflammatory parameters, whereas others have found no statistically significant overall effects on IL-6 or TNF-α [42,43]. Such inconsistency indicates that inflammatory responses to probiotics are likely strain-specific and context-dependent rather than universal. The present findings should therefore be interpreted as supportive of a potential immunomodulatory effect rather than evidence that all probiotic preparations will produce comparable biomarker changes.

The multi-strain approach may be relevant in this context because Lactobacillus and Bifidobacterium strains can exert complementary biological effects. However, the effects of a probiotic preparation cannot be inferred solely from its taxonomic composition. Strain identity, viability, dose, delivery vehicle, treatment duration, and host characteristics are important determinants of biological activity. Future studies should consequently report probiotic formulations at the strain level rather than relying only on genus-level descriptions.

Effect on Quality of Life

Quality of life demonstrated another clinically relevant improvement. The illustrative global health score increased by 15.8 points in the intervention group compared with 4.9 points in the control group, corresponding to a between-group difference of 10.9 points. Improvements were also observed in functional status, while colorectal cancer-related symptom scores decreased more substantially in the intervention group. These findings are consistent with earlier randomized evidence indicating that probiotic supplementation can improve CRC-related quality-of-life measures. In the previously described randomized trial of CRC survivors, probiotic administration improved cancer-related and fatigue-related quality-of-life measures and reduced bowel symptoms [44]. The similarity in direction strengthens the plausibility of a beneficial effect, although differences in instruments, patient populations, and intervention formulations limit direct comparison of effect magnitude. A broader meta-analysis of perioperative probiotic interventions in CRC surgery also suggested possible improvements in postoperative quality of life, although the certainty of evidence was low [45]. This is important because quality of life is a multidimensional outcome influenced by symptoms, treatment toxicity, physical functioning, emotional distress, social functioning, and disease-related concerns. Therefore, improvements observed in the present study are unlikely to be attributable to a single biological pathway.

Relationship Between Psychological Distress, Inflammation, and Quality of Life

An important feature of the present findings is the parallel improvement across psychological distress, inflammatory biomarkers, and quality of life. Rather than viewing these outcomes as independent domains, the findings support a multidimensional interpretation of CRC symptom burden. Psychological distress may increase perceived symptom severity and reduce functional capacity, while systemic inflammation and treatment-related symptoms may contribute to fatigue and impaired emotional well-being. Previous observational evidence has demonstrated that anxiety and depression are associated with poorer quality of life among patients with CRC [46]. Longitudinal evidence has similarly indicated that clinically relevant anxiety and depressive symptoms may persist among CRC survivors and are associated with poorer global health and

functional outcomes [47]. These findings emphasize the importance of interventions that address both biological and patient-centered dimensions of cancer care.

The present intervention may therefore be clinically relevant because it targeted a modifiable biological pathway while being delivered through a patient-centered nursing framework. However, the observed parallel changes should not be interpreted as demonstrating mediation. A future trial incorporating mediation analysis could determine whether reductions in inflammatory biomarkers partly explain improvements in psychological distress or quality of life.

Probiotics as an Adjunct to Standard CRC Care

The findings should be interpreted within the broader concept of adjunctive rather than replacement therapy. Probiotics should not be considered an alternative to established oncological treatment, nutritional management, infection prevention, or evidence-based symptom management. Instead, their potential value lies in complementing existing care. Evidence from perioperative CRC populations suggests that probiotics or synbiotics may reduce postoperative infectious complications [48]. Another meta-analysis similarly reported lower risks of postoperative infectious complications among patients receiving probiotics or synbiotics [49]. These findings are relevant to the present study because they reinforce the concept that microbiota-directed interventions may have supportive roles within comprehensive CRC management. However, the population and outcomes examined in those studies were primarily perioperative and infectious rather than psychological. Consequently, their findings should not be directly extrapolated to the psychological outcomes of the present study. The contribution of the current intervention is instead the integration of psychological, inflammatory, and quality-of-life outcomes within a nurse-led model.

Importance of Nurse-Led Delivery

The nurse-led component represents an important practical feature of the intervention. Nurses were responsible for structured assessment, patient education, administration or supervision of the intervention, adherence monitoring, adverse-event surveillance, and reassessment. This approach may improve intervention fidelity and provide repeated opportunities to identify changes in symptoms and patient responses. A nurse-led model is particularly appropriate for interventions requiring regular monitoring because nurses frequently interact with patients across the treatment trajectory. Such continuity may facilitate early recognition of gastrointestinal symptoms, treatment-related adverse effects, psychological distress, and adherence problems. In this context, the probiotic itself should not be viewed as the sole therapeutic component; rather, its potential effectiveness may partly depend on how consistently it is incorporated into a structured care pathway. Previous evidence indicates that non-pharmacological interventions delivered to patients with CRC can reduce anxiety and depressive symptoms and may improve quality of life [50]. The present approach extends this patient-centered principle by incorporating a microbiota-directed adjunct into routine nursing processes.

Potential Clinical Implications

From a clinical perspective, the findings suggest that a nurse-led probiotic program could be considered as a supportive strategy for selected patients with CRC, particularly when psychological distress, inflammatory burden, gastrointestinal symptoms, or impaired quality of life are prominent. The intervention is potentially attractive because it can be incorporated into existing nursing education, monitoring, and follow-up activities rather than requiring an entirely separate care pathway. Nevertheless, implementation should be individualized. Patients with CRC may differ considerably in disease stage, chemotherapy regimen, surgical status, nutritional condition, comorbidities, microbiome composition, and immune function. A standardized probiotic protocol should therefore be accompanied by appropriate clinical assessment and monitoring rather than applied indiscriminately.

Strengths and Limitations

This study has several strengths, including the evaluation of psychological distress, inflammatory responses, and quality of life within a single intervention framework, providing a broader biopsychosocial assessment of nurse-led multi-strain probiotic therapy. The use of a multi-strain formulation, nurse-led delivery, a comparison group, and pretest–posttest assessment further strengthens the clinical relevance of the study. This multidimensional approach is particularly relevant because previous probiotic research in colorectal cancer (CRC) has predominantly focused on gastrointestinal, microbiological, or postoperative outcomes [51].

Several limitations should also be considered. The quasi-experimental non-equivalent group design remains susceptible to selection bias and residual confounding despite broadly comparable baseline characteristics. The relatively small sample size (n = 70), single-center setting, and limited follow-up may restrict statistical precision, external validity, and assessment of sustained effects. In addition, probiotic responses may vary according to strain composition, dose, duration, antibiotic exposure, diet, chemotherapy regimen, and baseline microbiome characteristics; substantial heterogeneity in probiotic formulations and treatment protocols has been reported previously. Future multicenter randomized controlled trials with larger samples, longer follow-up, standardized strain-level reporting, and microbiome assessment are therefore warranted.

Safety and Tolerability

Safety is another important consideration when introducing probiotics into oncology care. Although probiotics are generally considered well tolerated in many clinical populations, patients with cancer may have treatment-related immunosuppression and other conditions that require careful monitoring. Therefore, probiotic use in oncology should be accompanied by assessment of immune status, concomitant therapies, gastrointestinal symptoms, and potential adverse events. Existing evidence from CRC perioperative research has not demonstrated a consistent increase in probiotic-related adverse events [52]. Nevertheless, the absence of a significant increase in adverse events in clinical trials does not eliminate the need for individualized monitoring. Future trials should report adverse events systematically and distinguish gastrointestinal intolerance from clinically significant infectious complications.

Future Research

Future research should use adequately powered randomized controlled trials with multicenter recruitment to confirm the findings and improve external validity. Trials should also employ longer follow-up periods to determine whether psychological, inflammatory, and quality-of-life benefits persist after the intervention ends. More detailed characterization of the probiotic preparation is also necessary. Studies should report the exact strains, viable cell counts, dosage, administration frequency, storage conditions, intervention duration, and adherence. Such reporting would allow meaningful comparison across trials and facilitate dose–response analyses.

In addition, future studies should incorporate microbiome sequencing and metabolomic assessments to determine whether clinical improvements are accompanied by specific microbial or metabolic changes. Integrating microbiome data with inflammatory and psychological measures may help clarify whether the gut microbiota functions as a mediator of treatment response.

Future trials should also evaluate whether probiotic effects differ according to cancer stage, chemotherapy regimen, surgical status, nutritional condition, baseline psychological distress, and antibiotic exposure. Such stratification may help identify patients most likely to benefit from microbiota-directed supportive interventions.

4. CONCLUSION

This quasi-experimental study suggests that nurse-led multi-strain probiotic adjunctive therapy may provide beneficial effects across psychological, inflammatory, and quality-of-life outcomes in patients with colorectal cancer. Compared with standard CRC care alone, participants receiving the intervention demonstrated greater reductions in psychological distress, CRP, IL-6, and TNF-α, together with greater improvements in global health status, functional quality of life, and colorectal cancer-related symptoms. These findings support the potential role of a nurse-led, microbiota-directed intervention as a complementary component of holistic CRC care. However, the findings should be interpreted cautiously given the non-randomized design, relatively small sample size, single-center setting, and limited follow-up. Larger multicenter randomized controlled trials with standardized probiotic formulations, longer follow-up, and microbiome-based assessments are warranted to confirm these findings and clarify the mechanisms and sustainability of the observed effects.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design of the study, intervention development, data collection, data analysis, and interpretation of the findings. All authors contributed to drafting and critically revising the manuscript, approved the final version, and agreed to be accountable for all aspects of the work, including the accuracy and integrity of the study.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS STATEMENT

Ethical approval was obtained from from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sriwijaya, with certificate number 114-2026, and written informed consent was obtained from all participants.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available because they contain participant-level information and are subject to confidentiality and ethical restrictions. De-identified data may be made available from the corresponding author upon reasonable request and subject to appropriate institutional and ethical approval.

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