

Exploring the clinical value of probiotics in the perioperative management of colorectal cancer: Meta-analysis with trial sequential analysis

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Abstract. Colorectal cancer (CRC) is the third most common malignant neoplasm, and there is currently no consensus on the clinical value of probiotics in perioperative CRC. A meta-analysis combined with a trial sequential analysis (TSA) was performed to assess the efficacy and safety of probiotics in the adjuvant treatment of CRC to provide an evidence-based recommendation for perioperative CRC. The present meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and the study protocol was registered with the International Prospective Register of Systematic Reviews (CRD42024510734). The meta-analysis demonstrated that probiotics significantly reduced the incidence of postoperative infections in patients who underwent CRC surgery (risk ratio, 0.54; 95% CI, 0.45-0.65; $P < 0.05$). Although the sample size was insufficient for the required information size ($n=2,897$), TSA results demonstrated that cumulative Z values exceeded both the conventional and TSA cut-offs, which indicated that this meta-analysis barely extended the probability of false positives. Meanwhile, probiotics reduced the mean number of days of hospitalization for patients with CRC (mean difference, -1.23; 95% CI, -2.18 to -0.28; $P < 0.05$). Notably, different genera of probiotics used contributed to

different outcomes, with subgroup analyses indicating that *Lactobacillus*, *Bifidobacterium*, combined *Lactobacillus* with *Bifidobacterium*, and multiple combination strains significantly reduced the incidence of postoperative infections in CRC, with statistically significant differences, whereas *Saccharomyces boulardii* alone did not confer a potential benefit. Overall, probiotics appeared to be effective in reducing postoperative infectious complications and shortening the length of hospital stay.

Introduction

The global burden of colorectal cancer (CRC) is substantial, with incidence rates rising, particularly in developing countries, where healthcare systems often struggle to provide adequate cancer care (1). CRC is the third most common malignant tumor worldwide and the second leading cause of cancer-related death following lung cancer (2). The International Agency for Research on Cancer estimates that the number of worldwide novel CRC cases and associated deaths will be ~3.2 and 1.6 million, respectively, in 2040 (3). The disease presents substantial challenges to public health, not only due to the physical and psychological burdens experienced by patients, but also due to the notable healthcare costs involved in its management (4).

Current CRC treatments, including surgery, chemotherapy and radiation therapy, are often constrained by serious side effects, such as adverse effects and high recurrence rates, and inconsistent efficacy across patients. These limitations underscore the urgent need for innovative adjunctive therapeutic strategies that can improve treatment outcomes while minimizing adverse effects (5,6). Postoperative infection, a common complication following surgery, profoundly impacts both surgical outcomes and patient prognosis; therefore, it remains a key focus for prevention and control during the perioperative period (7).

Recently, the use of probiotics as a supportive CRC treatment has gained attention due to their ability to modulate

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the gut microbiota and enhance immune responses (8). Probiotics are live microorganisms that provide health benefits to the host, particularly through their regulatory effects on the gut microbiome and immune system (9). Certain probiotic strains, such as *Lactobacillus rhamnosus* GG, *Bifidobacterium longum* and *Lactobacillus casei*, may help prevent CRC by inhibiting tumor growth and metastasis, reducing inflammation and improving the overall gut environment (10). Furthermore, probiotics have been found to support gut health and alleviate the adverse effects commonly associated with conventional cancer therapies, such as chemotherapy-induced gastrointestinal toxicity (11). The beneficial effects of probiotics may be mediated through mechanisms such as modulation of the intestinal microbiota, strengthening of the epithelial barrier function and regulation of systemic inflammatory responses (12). These attributes suggest that probiotics may not only improve the quality of life of patients with CRC but also contribute to enhanced treatment outcomes.

Despite a promising theoretical foundation, the clinical application of probiotics in CRC management remains inconsistent. A systematic review of the existing literature revealed mixed findings. A systematic review of the existing literature revealed mixed findings regarding the effects of probiotics on patients with CRC (13). Some studies reported beneficial effects, suggesting that probiotics may modify the gut microbiota, reduce inflammatory cytokines and secrete anticancer metabolites (14). Probiotics have also been revealed to modulate T-lymphocyte and dendritic cell activities (15). Furthermore, specific lactic acid-producing bacteria, valued for their immunomodulatory properties, have demonstrated efficacy for instance, combinations such as *Lactobacillus salivarius* and *Lactobacillus fermentum* with *Lactobacillus acidophilus* have been associated with reduced CRC cell proliferation (16). Other studies demonstrated no notable impact on disease progression or survival outcomes (17,18). This variability may stem from differences in study design, probiotic strain dosage regimens and patient populations, contributing to the heterogeneity of the results. Moreover, the absence of robust, high-quality randomized controlled trials (RCTs) limits the ability to draw definitive conclusions regarding the efficacy and safety of probiotics in this context (19). To address these gaps, the present meta-analysis and trial sequential analysis (TSA) were employed to systematically assess the available evidence on the use of probiotics as an adjunct to standard CRC therapies. Meta-analysis enables the synthesis of data across multiple studies, which provides a more comprehensive evaluation of treatment effects. In parallel, TSA can be used to estimate the required sample size to confirm the reliability of the findings, which reduces the risk of type I errors (20). The primary aim of the present study was to clarify the role of probiotics in enhancing the efficacy and safety of CRC treatment. By offering a thorough, evidence-based assessment, the present study aims to inform clinical practice and support the potential integration of probiotics into CRC management. Future research should focus on identifying the most effective probiotic strains and elucidating the underlying mechanisms through which these microorganisms influence tumor biology and patient outcomes (4).

Materials and methods

Study registration. The present study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and was registered with the International Prospective Register of Systematic Reviews under the identifier CRD42024510734 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024510734).

Literature search strategy. A systematic review was conducted by searching multiple databases, including PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Embase (<https://www.embase.com/>), Cochrane Central Register of Controlled Trials (<https://www.cochranelibrary.com/central/>), Allied and Complementary Medicine Database (<https://www.proquest.com/amed/>), the American Association for Cancer Research abstract database (<https://www.aacr.org/>) and China Biology Medicine disc (<http://www.sinomed.ac.cn>). The search covered all relevant articles published from the inception of each database until December 26, 2023, without language restrictions. The search strategy employed a combination of Medical Subject Headings terms (<https://meshb.nlm.nih.gov/>) and free-text keywords, including disease-related search terms such as 'CRC', 'colorectal tumor' and 'colorectal neoplasm'. Intervention terms were comprised of 'probiotics', '*Lactobacilli*', '*Bifidobacteria*', '*Lactococci*', 'yeast', '*Enterococci*', '*Bifidobacterium*', '*Lactobacillus*' and '*Saccharomyces*'. To identify relevant study designs, filters such as 'RCT', and 'placebo-controlled' were applied. Boolean operators (AND/OR) and proximity operators (NEAR/3) were used to enhance search sensitivity. The full search strategy, adapted to the syntax requirements of each database, is provided in Data S1.

Manual searches were additionally conducted to ensure literature saturation. These included screening the reference lists of the included studies and relevant review articles, as well as reviewing journals subscribed to by the People's Hospital of Putuo District library. Printed copies of conference proceedings from the National Conference on Clinical Nutrition (2021-2023), obtained during conference attendance were also reviewed.

Where applicable, the corresponding authors of potentially eligible studies were contacted via email to request the missing data. Any unresolved missing data were addressed using sensitivity analyses following the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3; section 16.1.2; <https://training.cochrane.org/handbook/archive/v6.3/chapter-16>).

Study inclusion and exclusion criteria. Publicly accessible RCTs that investigated the efficacy of probiotic-assisted treatment in patients with CRC who underwent open, laparoscopic or robotic CRC surgery were included in this study. Sex and ethnicity were not restricted in the present study. In the RCTs, the treatment group was treated with any dose and type of probiotic preparation including *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, and multi-strain combinations, and the control group was treated with a placebo. The efficacy and safety of the primary outcome measures, including the incidence of postoperative infections and mean number of hospitalization days, were explored. Studies in which the

patients had advanced CRC who could not undergo surgery, received other organ resections or had a combination of other malignant tumors or gastrointestinal diseases were excluded. Studies that could not extract the primary outcome data and used probiotics combined with other adjunctive therapies, in addition to studies on the pharmacokinetics of probiotics without long-term follow-up outcome data were also excluded.

Literature screening and data extraction. Two researchers conducted a thorough review of the literature, extracted the data and cross-checked their findings. In the event of discrepancies, they engaged in discussions to resolve them or sought assistance from a third party for adjudication. Data extraction was performed using a customized form, which encompassed essential information, such as the authors of the included studies, publication dates, characteristics of the study subjects, details of interventions, elements of bias assessment and outcome measures of interest. During data extraction, the probiotic genus (or species/strain) used in each intervention arm was recorded for every included study. The subgroup analyses (*Lactobacillus*, *Bifidobacterium*, *Saccharomyces* and multi-strain combinations) were then defined based on the predominant probiotic genus or formulation type that consistently emerged from this extracted data across the included studies.

Quality assessment. The risk of bias in the studies included in the analysis was independently assessed by two investigators and subsequently verified. The assessment of bias in the included studies was conducted using the RCT risk of bias assessment tool recommended by the Cochrane Handbook (21). This evaluation considered multiple factors, such as the randomization method, allocation concealment, blinding procedures for patients and investigators, blinding of outcome assessors, completeness of outcome data, selective reporting of study results and identification of other potential sources of bias such as industry sponsorship bias and geographic/ethnic heterogeneity.

Statistical analysis. Statistical analysis was performed utilizing RevMan software (version 5.4; The Cochrane Collaboration), with the mean difference (MD) employed as the effect size for continuous variables and the risk ratio (RR) for dichotomous variables, each presented with 95% CIs. Heterogeneity among the study outcomes was assessed using the χ^2 test ($\alpha=0.1$) in conjunction with the I^2 statistic to measure the extent of heterogeneity.

Meta-analysis was performed with a random-effects model. In instances of significant statistical heterogeneity within the findings of the incorporated studies, the origin of heterogeneity was explored through subgroup analysis.

Publication bias was evaluated using funnel plots. Additionally, TSA was performed using TSA software (version 0.9; Copenhagen Clinical Trials Centre in Denmark) (22). TSA, a form of cumulative meta-analysis, addresses the issue of random errors (both false-negative and false-positive outcomes) that can occur in conventional meta-analysis during repeated updates. Furthermore, TSA helps determine the sample size required to achieve a reliable conclusion. TSA analysis excluded zero-event studies (studies with no infection events in both groups). The cumulative

Z-curve constituted the core graphical output of TSA. This curve plotted the cumulative Z-scores (standard normal deviates) derived from sequentially incorporating trial data as they accumulate over time, thereby tracking the evolving strength of evidence for or against the intervention effect. TSA employed this curve in conjunction with pre-specified monitoring boundaries to assess potential early stopping points. Benefit (efficacy) boundaries are defined such that if the cumulative Z-curve crosses above this boundary, it provides statistically significant evidence favoring the intervention effect, allowing for an early conclusion of benefit. Conversely, crossing a predefined futility boundary suggests a lack of clinically meaningful effect. The region between these boundaries represents a zone of insufficient evidence, indicating that more data are required. A crucial parameter is the Required Information Size (RIS), which estimates the total number of participants needed to detect (or reject) a predefined target intervention effect (such as, a 15% relative risk reduction) with a prespecified power (typically 80-90%) while controlling the Type I error rate (typically 5%). The RIS determines the maximum extent of the X-axis (representing cumulative information size) on the TSA graph. Decision rules based on the cumulative Z-curve position relative to the boundaries are: i) If $Z >$ Upper boundary, firm evidence of benefit is concluded; ii) if $Z <$ Lower boundary, firm evidence of futility (or harm) is concluded; iii) if Z remains between the boundaries, evidence is deemed inconclusive, necessitating further trials.

Results

Literature search results. The search strategy initially retrieved 3,265 documents. After removing duplicates and conducting a preliminary assessment of titles and abstracts, 2,880 documents remained. Scrutiny of the full texts further narrowed down the total to 64 documents for rescreening, which ultimately identified 21 studies suitable for quantitative meta-analysis and TSA (23-43). These studies included 1,602 patients with CRC who had undergone surgery or were scheduled to undergo surgery. The literature screening process and outcomes are displayed in Fig. 1.

Basic characteristics of included studies. Table I presents the fundamental characteristics of the included studies. The detailed information includes the country of origin, age range of the participants, sample size, specific intervention measures and duration of administration.

Meta-analysis results

Incidence of postoperative infection. The incidence of postoperative infection was examined in 21 studies that investigated the efficacy and safety of probiotics as adjuvant therapy for CRC. A random-effects meta-analysis demonstrated a significantly lower incidence of postoperative infection in the probiotic group compared with that in the placebo group (RR, 0.54; 95% CI, 0.45-0.65; $P<0.05$) (Fig. 2). Numerically, the infection rate was 14.8% (119/805) in probiotic groups vs. 29.1% (232/797) in controls. Given the various genera of probiotics used in the included studies, a subgroup analysis based on probiotic species was conducted, which revealed that using multiple strains (RR, 0.61; 95% CI, 0.46-0.83; $P<0.05$),

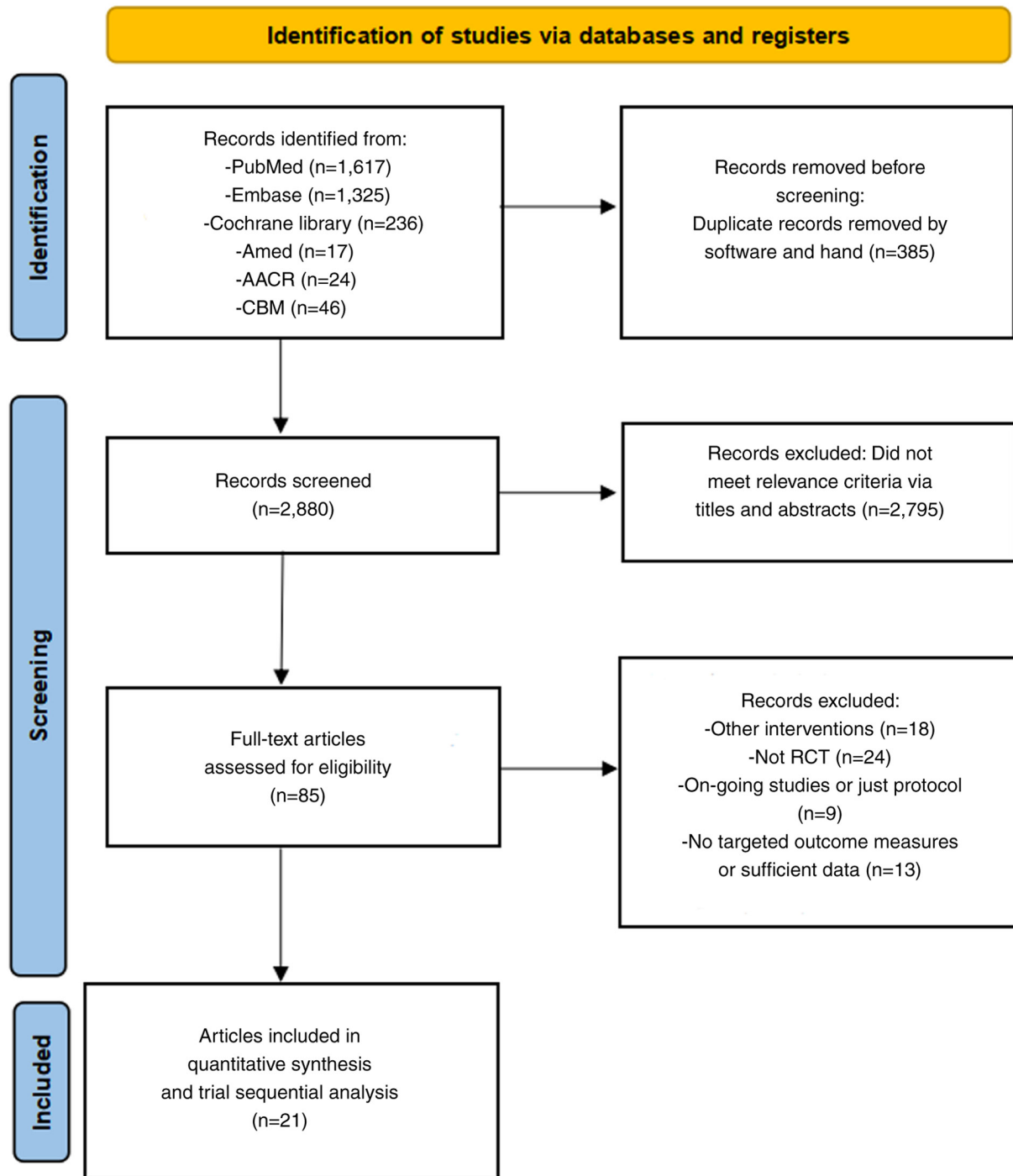


Figure 1. PRISMA flowchart detailing literature search and screening strategy. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, randomized controlled trial; AACR, American Association for Cancer Research; CBM, China Biology Medicine disc.

Lactobacillus species (RR, 0.43; 95% CI, 0.25-0.74; $P<0.05$), *Bifidobacterium* species (RR, 0.48; 95% CI, 0.31-0.76; $P<0.05$) and a combination of *Lactobacillus* and *Bifidobacterium* species (RR, 0.53; 95% CI, 0.36-0.77; $P<0.05$) significantly reduced the incidence of postoperative infections compared with the placebo group. However, no significant difference in the incidence of postoperative infections of the single strains of *Saccharomyces* (RR, 0.34; 95% CI, 0.08-1.41; $P>0.05$) was found compared with that in placebo group.

Mean length of hospitalization. The length of hospitalization was reported in nine of the RCTs. A random-effects

meta-analysis indicated that probiotics significantly reduced the length of hospital stay compared with that in the placebo group (MD, -1.23; 95% CI, -2.18 to -0.28; $P<0.05$) (Fig. 3). However, when analyzing the genera of probiotics used, there was no significant reduction in the number of days of hospitalization for any genus except for those using *Lactobacillus* species (MD, -1.70; 95% CI, -3.12 to -0.28; $P<0.05$).

TSA of probiotics in adjuvant therapy for CRC. TSA results indicated that the cumulative Z-curve crossed both the traditional and trial sequential monitoring boundaries for

Table I. Basic characteristics of included studies.

First author, year	Country	Sample size, n		Age (range), years	Interventions	Duration of administration	(Refs.)
		T	C				
Xia <i>et al</i> , 2010	China	30	30	67.3 (37-82)	<i>Lactobacillus casei</i> , <i>Lactobacillus acidophilus</i>	>5 days preoperatively	(38)
Zhang <i>et al</i> , 2010	China	30	30	T, 66.7 (41-83); C, 63.0 (39-81)	<i>Bifidobacterium</i>	For 5 days preoperatively	(42)
Liu <i>et al</i> , 2011	China	50	50	T, 65.3±11.0; C, 65.7±9.9	<i>Lactobacillus plantarum</i> , <i>Lactobacillus acidophilus</i> and <i>Bifidobacterium longum</i>	For 6 days preoperatively and 10 days postoperatively	(28)
Zhang <i>et al</i> , 2012	China	30	30	T, 67.5 (45-87); C, 61.5 (46-82)	<i>Bifidobacterium longum</i> , <i>Lactobacillus acidophilus</i> and <i>Enterococcus faecalis</i>	For 3-5 days preoperatively	(43)
Liu <i>et al</i> , 2013	China	75	75	T, 62.28±12.41; C, 66.06±11.02	<i>Lactobacillus plantarum</i> , <i>Lactobacillus acidophilus</i> and <i>Bifidobacterium longum</i>	For 6 days preoperatively and 10 days postoperatively	(29)
Pellino <i>et al</i> , 2013	Italy	10	8	T, 71.5±2.1; C, 72.9±1.6	<i>Streptococcus thermophilus</i> , <i>Bifidobacterium longum</i> , <i>Bifidobacterium breve</i> , <i>Bifidobacterium infantis</i> , <i>Lactobacillus acidophilus</i> , <i>Lactobacillus plantarum</i> , <i>Lactobacillus paracasei</i> , <i>Lactobacillus delbrueckii</i> <i>subsp. bulgaricus</i>	For 1 day to 4 weeks after discontinuing antibiotics postoperatively	(34)
Mangell <i>et al</i> , 2012	Sweden	32	32	T, 74 (70-80); C, 70 (64-79)	<i>Lactobacillus plantarum</i>	For 8 days preoperatively and 5 days postoperatively	(31)
Chen <i>et al</i> , 2014	China	35	35	T, 60.3±17.2; C, 59.8±18.7	<i>Clostridium typhimurium</i> and <i>Bifidobacterium infantis</i>	For 5 days preoperatively and 7 days postoperatively	(24)
Sadahiro <i>et al</i> , 2014	Japan	100	95	T, 67±9; C, 66±12	<i>Bifidobacteria</i>	For 7 days preoperatively and 5-10 days postoperatively	(36)
Consoli <i>et al</i> , 2016	Brazil	15	18	T, 51 (28-76); C, 59 (17-83)	<i>Saccharomyces boulardii</i>	For at least 7 days preoperatively	(25)
Liu <i>et al</i> , 2015	China	66	68	T, 65.62±18.18; C, 60.16±16.20	<i>Lactobacillus plantarum</i> , <i>Lactobacillus acidophilus</i> and <i>Bifidobacterium longum</i>	For 6 days preoperatively and 10 days postoperatively	(30)
Mizuta <i>et al</i> , 2016	Japan	31	29	T, 68.9±10.4; C, 71.2±9.5	<i>Bifidobacterium longum</i>	For 7-14 days preoperatively and 14 days postoperatively	(32)
Yang <i>et al</i> , 2016	China	30	30	T, 63.90± 2.25; C, 62.17±11.06	<i>Bifidobacterium longum</i> , <i>Lactobacillus acidophilus</i> and <i>Enterococcus faecalis</i>	For 5 days preoperatively to 7 days postoperatively	(40)
Kotzampassi <i>et al</i> , 2015	Greece	84	80	T, 65.9±11.5; C, 66.4±11.9	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus plantarum</i> , <i>Bifidobacterium lactis</i> and <i>Saccharomyces boulardii</i>	From the day of surgery to 14 days postoperatively	(27)
Tan <i>et al</i> , 2016	Malaysia	20	20	T, 64.3±14.5; C, 68±11.9	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus lactis</i> , <i>Bifidobacterium bifidum</i> , <i>Bifidobacterium longum</i> and <i>Bifidobacterium infantis</i>	For 8 days preoperatively	(37)

Table I. Continued.

First author, year	Country	Sample size, n		Age (range), years	Interventions	Duration of administration	(Refs.)
		T	C				
Bajramagic <i>et al</i> , 2019	Bosnia and Herzegovina	39	39	NA	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus plantarum</i> , <i>Lactobacillus rhamnosus</i> , <i>Bifidobacterium lactis</i> , <i>Bifidobacterium bifidum</i> , <i>Bifidobacterium breve</i> , <i>Streptococcus thermophilus</i>	For 3 days preoperatively to 30 days postoperatively	(23)
Xu <i>et al</i> , 2019	China	30	30	T, 61.03±15.28; C, 62.35±13.71	<i>Bifidobacterium longum</i> , <i>Lactobacillus acidophilus</i> and <i>Enterococcus faecalis</i>	For 7 consecutive days preoperatively	(39)
Zaharuddin <i>et al</i> , 2019	Malaysia	27	25	T, 67.33±9.44; C, 66.5±8.57	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus lactis</i> , <i>Lactobacillus casei subsp</i> , <i>Bifidobacterium longum</i> , <i>Bifidobacterium bifidum</i> and <i>Bifidobacterium infantis</i>	For 4 weeks postoperatively to 6 months	(41)
Park <i>et al</i> , 2020	Korea	29	31	T, 60.1±10.37; C, 61.03±7.02	<i>Bifidobacterium animalis subsp. Lactis</i> , <i>Lactobacillus casei</i> , and <i>Lactobacillus plantarum</i>	For 7 days preoperatively to 21 days postoperatively	(33)
Rodríguez-Padilla <i>et al</i> , 2021	Spain	34	35	T, 65 (45-81); C, 68 (41-80)	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus plantarum</i> , <i>Lactobacillus paracasei</i> , <i>Lactobacillus delbrueckii subsp. bulgaricus</i> ., <i>Bifidobacterium breve</i> , <i>Bifidobacterium longum</i> , <i>Bifidobacterium infantis</i> , <i>Streptococcus thermophilus</i>	For 20 days preoperatively every second day	(35)
Huang <i>et al</i> , 2023	China	50	50	T, 57.7±11.9; C, 62.1±10.5	<i>Bifidobacterium infants</i> , <i>Lactobacillus acidophilus</i> , <i>Enterococcus faecalis</i> , <i>Bifidobacterium cereus</i>	From the third postoperative day to the end of the first 6 weeks	(26)

T, the test group who received probiotics; C, the control group who received standard care or placebo; NA, not applicable.

benefit (Fig. 4), which supports the fact that probiotics are effective in the prevention of postoperative infections. Although the RIS (2,897 participants) was not reached, the results suggested no need for further RCTs to confirm this finding.

Risk of bias and publication bias assessment. The results of the methodological quality assessment, which illustrate the risk of bias in the included studies, are presented in Fig. S1. The funnel plot, constructed using data on postoperative infection rates, revealed an asymmetrical distribution of studies around the funnel, which indicated the potential presence of publication bias. Publication bias analysis is depicted in Fig. S2.

Discussion

In the realm of cancer research, there is a growing focus on the interplay between diet, gut microbiota and CRC (44). The human microbiota, which consists of ~100 trillion microorganisms, forms an intricate ecosystem that comprises bacteria, viruses, eukaryotes and archaea. This ecosystem serves a key role in facilitating nutrient absorption, bolstering host immunity against infections, fortifying the intestinal immune system and regulating host metabolism (45). Notably, the composition of the microbiome differs between healthy individuals and those diagnosed with CRC. The bacteria implicated in CRC to date

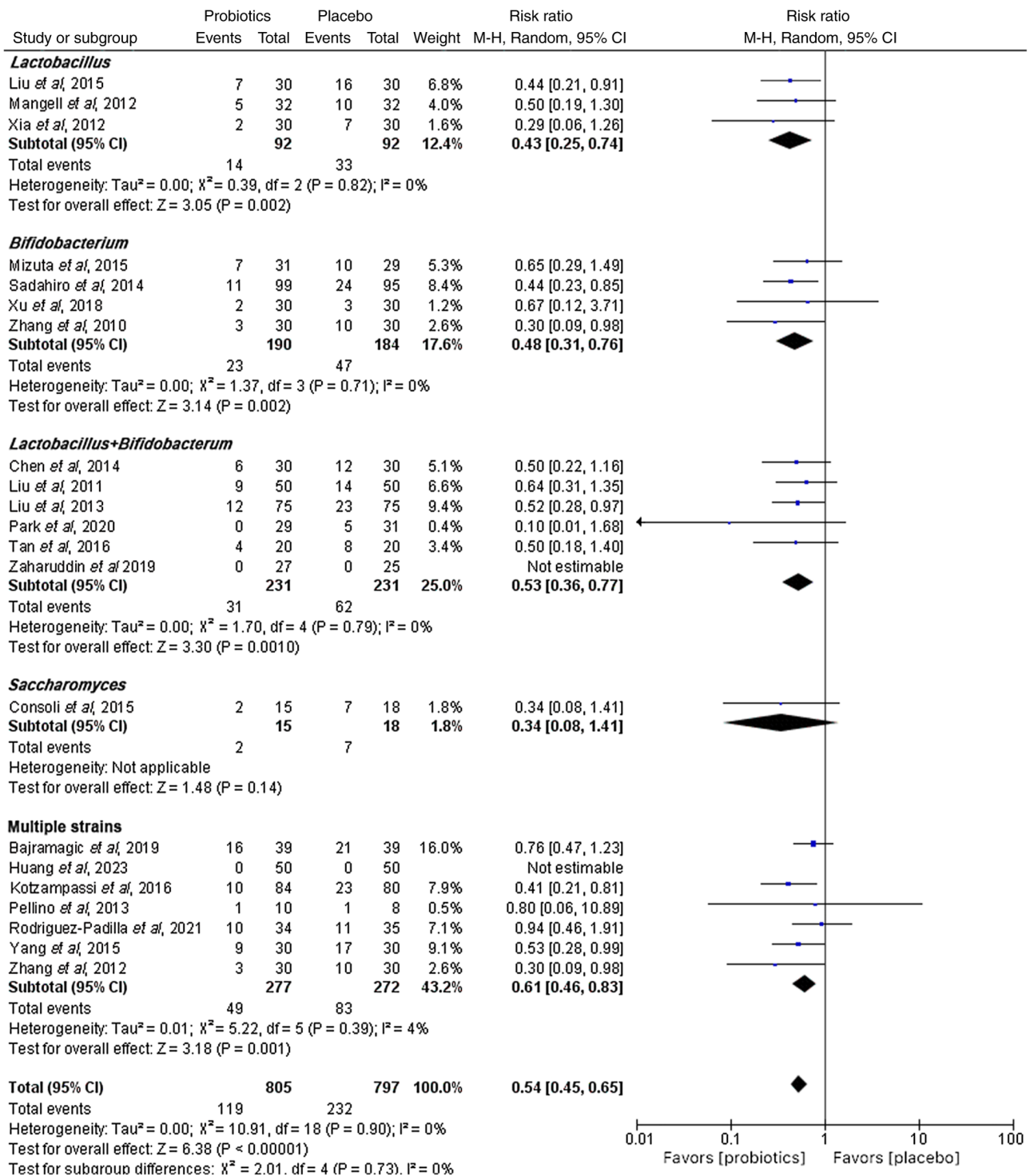


Figure 2. Meta-analysis of probiotics for the incidence of postoperative infections.

include *Fusobacterium nucleatum*, *Enterococcus faecalis*, *Streptococcus gallolyticus*, enterotoxigenic *Bacteroides fragilis*, *Escherichia coli*, *Peptostreptococcus* spp. and *Ruminococcus* spp. Conversely, species such as *Lactobacillus* spp., *Bifidobacterium* spp., *Faecalibacterium* spp., *Roseburia* spp., *Clostridium* spp., *Granulicatella* spp., *Streptococcus thermophilus* and other members of the Lachnospiraceae family are diminished in patients with CRC (46). Based on existing research, persistent dysbiosis in gut microbiota diversity hinders the efficacy of chemotherapy and promotes CRC

development and progression. Therefore, the regulation of gut microbiota has emerged as a novel strategy for managing CRC progression (47,48).

Probiotics, recognized as potential agents that influence the composition and functionality of human gut microbiota, can provide therapeutic advantages in patients with CRC when administered in appropriate dosages (49). Current clinical evidence indicates that effective dosing typically ranges between 10^9 and 10^{11} colony-forming units per day, contingent upon specific probiotic strains, disease status and therapeutic

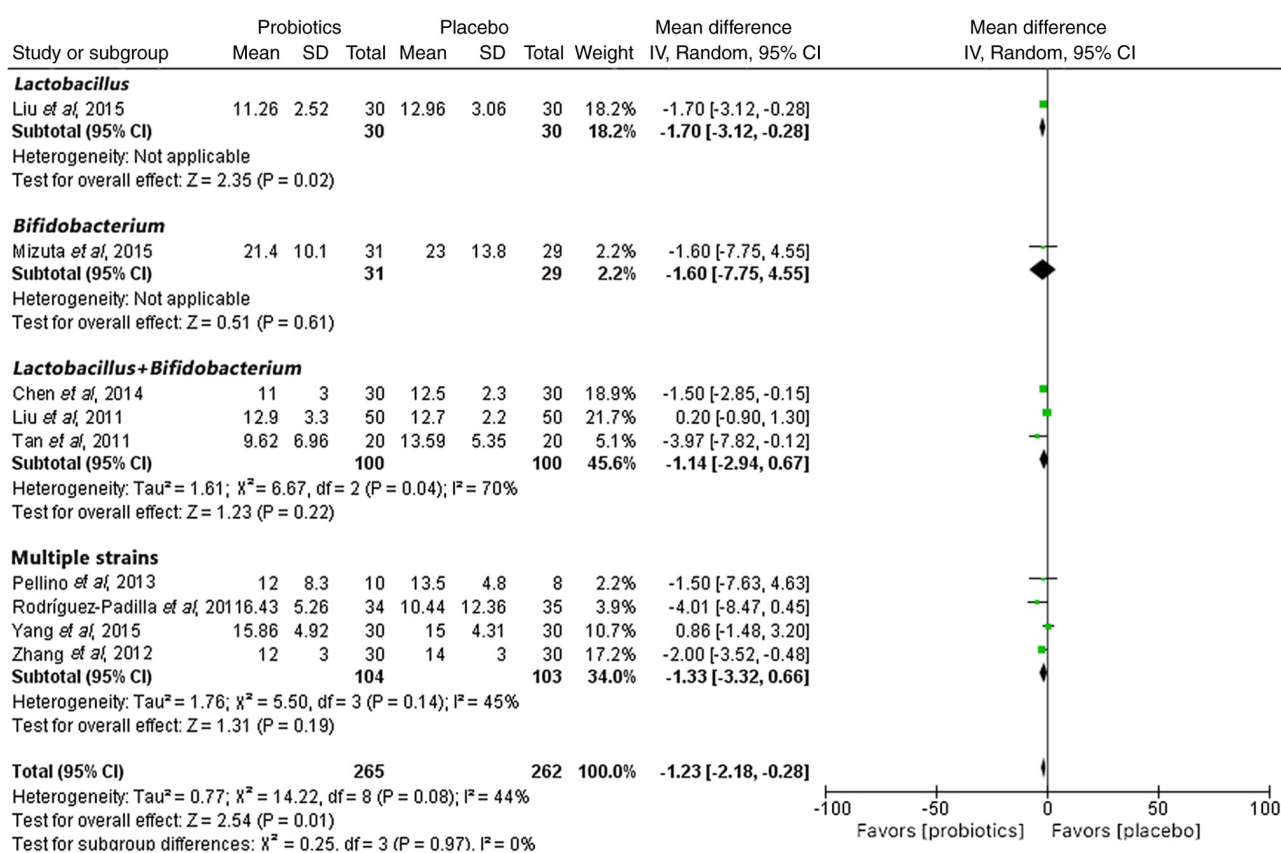


Figure 3. Meta-analysis of probiotics for mean hospitalization days.

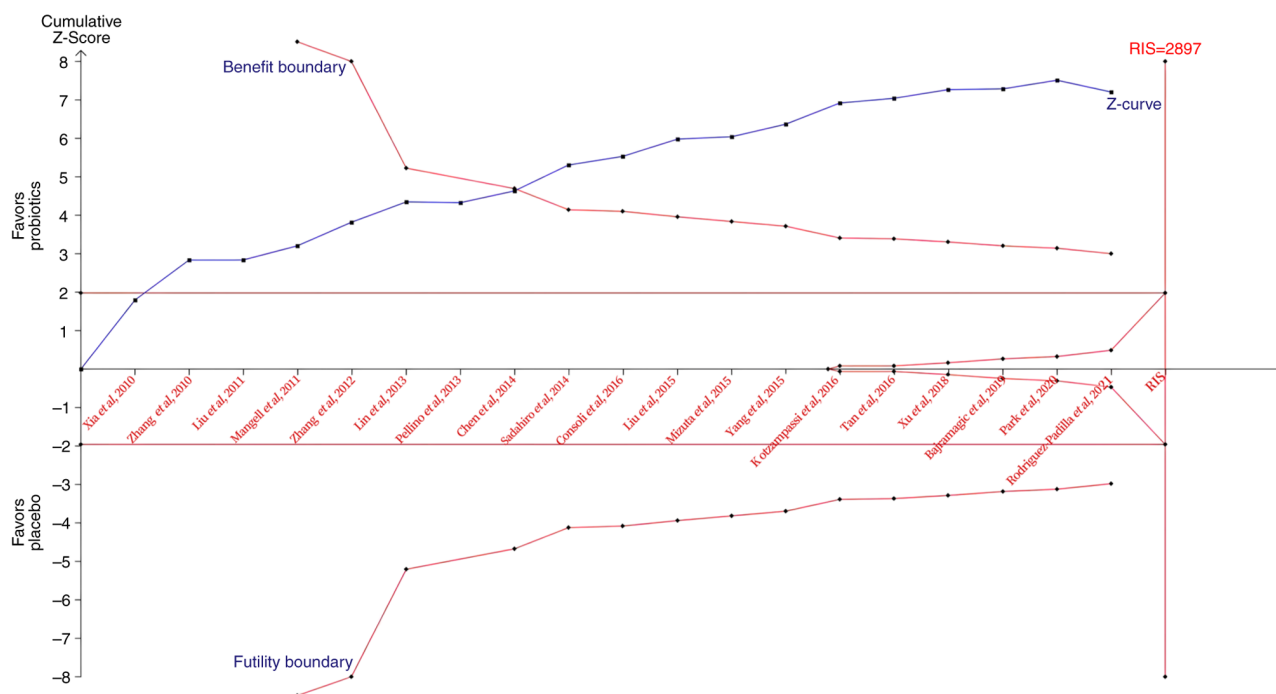


Figure 4. Trial sequential analysis results for probiotics for the incidence of postoperative infections. RIS, required information size.

objectives. Rigorous dose-finding studies remain necessary to establish standardized protocols for CRC management (50-52). The advantageous impacts of probiotics, which act in a species- or strain-specific manner, encompass the preservation

of a healthy microbiome, reversal of dysbiosis, prevention of pathogenic infections (such as, rotavirus-induced diarrhea and *Clostridioides difficile* infections) and mucosal adhesion of pathogens, and stabilization and enhancement of intestinal

barrier function (53-56). Probiotic bacteria may confer these advantages through the production of anti-carcinogenic, anti-inflammatory, anti-mutagenic and other biologically notable compounds, such as short-chain fatty acids, which are frequently associated with gastrointestinal disorders, including CRC (57). Another potential mechanism of anticancer activity is the enhancement or restoration of natural killer (NK) cell activity. NK cells serve a key role in regulating immunity against both cancer and infections, with higher NK cell activity being associated with a reduced risk of cancer. The ability of probiotics to boost NK cell activity appears to be connected to their production of IL-12 (58).

It is well established that postoperative complications following CRC surgeries notably impact treatment efficacy, recurrence rates and overall survival in patients. Minimizing postoperative infection is key for the improvement of surgical and long-term oncological outcomes. Numerous meta-analyses have indicated the potential advantages of probiotics in mitigating postoperative complications among patients with CRC. Persson *et al* (59) focused on diarrhea as the primary outcome, reporting an odds ratio (OR) of 0.42 (95% CI, 0.31-0.55; $P < 0.05$). An *et al* (60) examined perioperative mortality, yielding an RR of 0.17 (95% CI, 0.02-1.38; $P < 0.05$), as well as overall postoperative complications, yielding an RR of 0.45 (95% CI, 0.27-0.76; $P < 0.05$). Araújo *et al* (61) investigated various complications, including ileus, which is impairment of intestinal motility (OR, 0.13; 95% CI, 0.02-0.78; $P < 0.05$), diarrhea (OR, 0.32; 95% CI, 0.15-0.69; $P < 0.05$), abdominal collection (OR, 0.35; 95% CI, 0.13-0.92; $P < 0.05$), sepsis (OR, 0.41; 95% CI, 0.22-0.80; $P < 0.05$), pneumonia (OR, 0.39; 95% CI, 0.19-0.83; $P < 0.05$) and surgical site infection (OR, 0.53; 95% CI, 0.36-0.78; $P < 0.05$). Chen *et al* (62) assessed total postoperative infections (OR, 0.31; 95% CI, 0.15-0.64; $P < 0.05$) and surgical site infections (OR, 0.62; 95% CI, 0.39-0.99; $P < 0.05$). There was no notable rise in adverse events associated with probiotic use (63).

In the present study, the effectiveness and safety of probiotics was examined in the prevention of postoperative infections by incorporating unique methodological features, notably the use of RRs instead of ORs to reduce the potential overestimation of adverse effects associated with OR. The present study involved a more extensive and detailed analysis, including subgroup and TSA analyses, to evaluate evidence credibility. These results indicated that probiotics may notably and positively influence the reduction of postoperative infectious complications. Postoperative infection represents a multifaceted challenge that was intentionally not explored in depth within the present study. Nevertheless, postoperative infection was identified as a primary outcome due to its substantial clinical importance, as these infections contribute to increased mortality rates and elevate both direct and indirect healthcare expenditures. The placebo group exhibited a postoperative infection incidence of 29.1% (232/797), whereas the probiotic group demonstrated ~60% lower odds of infection in patients with CRC. As a result, this outcome may indirectly underscore the potential advantages of probiotics to clinicians. In future research, we plan to utilize Mendelian randomization to investigate the association between gut microbiota and CRC prognosis. Additionally, the potential advantages of probiotics in decreasing the mean length of hospital stay

for patients with CRC was investigated. The probiotic group experienced a decrease in the mean number of hospitalization days by 1 day, which led to potential cost savings in healthcare. However, it is well established that length of hospital stay is influenced by various confounding factors, including patient comorbidities (for example, diabetes or coronary artery disease), psychological conditions (for example, anxiety or depression) and the choice of surgical approach. To mitigate the effects of these confounders, a random-effects model was utilized. Furthermore, subgroup analyses based on surgical techniques were performed and aimed to standardize hospitalization duration by employing hospitalization costs. However, this cost-based adjustment was not achievable due to the lack of available data. Future research can include cost-related outcomes to assess the economic benefits of probiotics from a health economics perspective.

Furthermore, subgroup analysis indicated that the effectiveness of various probiotic types in the prevention of postoperative infections was evident in the combination of multiple strains, *Lactobacillus* species, *Bifidobacterium* species, and the combination of *Lactobacillus* and *Bifidobacterium* species, but not in single strains of *Saccharomyces*. Additionally, smaller studies with shorter durations tended to exhibit exaggerated effect sizes compared with larger and longer studies. Accordingly, caution should be exercised when interpreting the results of small, short-duration studies.

The variability in probiotic types, duration of administration, study design and outcomes presents a challenge in conducting TSA. While this variability was considered in the present analysis, the assumptions regarding the results of future large trials were based on the expectation of consistency with existing trial findings. This assumption appears to be justified for probiotics, given the coherence observed among the results of large RCTs.

Despite not reaching the RIS of 2,897, the cumulative Z-curve crossed the boundaries, which allowed a conclusion to be reached without the need for further trials. To the best of our knowledge, the present study represents the first application of TSA to assess the effect of probiotics on the incidence of postoperative infections, which thereby enhances the validity of these findings. However, the clinical application of probiotics in CRC management poses several challenges. Variability in study designs, probiotic formulations and patient populations complicates the interpretation and comparison of the results. Moreover, the optimal strains, dosages and duration of probiotic therapy have not yet been defined. The limitations of the present study are largely attributed to the heterogeneity of the included trials. Several studies featured relatively small sample sizes, which may have compromised the robustness and generalizability of their findings. Additionally, the lack of long-term follow-up data limits the ability to evaluate the sustained effects of probiotics on CRC outcomes. Variations in patient demographics and clinical settings further introduce potential statistical biases, which make it more difficult to draw definitive conclusions from the aggregated data.

In the past decade, research has increasingly demonstrated the complex interplay between gut microbiota and immune responses in maintaining physiological balance and influencing the development, progression and treatment outcomes of various diseases, including cancer (64-67). Leveraging the

gut mycobiome for diagnostic, prognostic and therapeutic purposes in cancer and other disorders (such as inflammatory bowel disease, metabolic diseases and autoimmune conditions) demonstrates its potential in precision medicine. Future research should prioritize large multicentre trials with standardized protocols to strengthen the evidence for the use of probiotics as adjunctive therapy in CRC management.

Future therapeutic strategies targeting the microbiome or drawing inspiration from it should be designed to modulate gut bacteria synergistically to enhance the effectiveness of probiotics in clinical settings (68). Consequently, probiotics have the potential to serve as a preventive measure for CRC and to enhance treatment, thereby improving clinical outcomes for patients with CRC in the future. The future of probiotic research in CRC should focus on developing personalized treatment strategies and conducting in-depth mechanistic studies. Tailoring probiotic interventions to individual patient profiles and uncovering the specific mechanisms through which probiotics exert their effects will be key to realizing their full potential as adjunctive therapies. Continued investigation in these areas will not only enhance the current understanding of probiotics but also pave the way for more effective targeted treatment strategies to potentially improve outcomes for patients with CRC in the future.

In conclusion, probiotics demonstrate potential as an effective strategy for the prevention of postoperative infectious complications. The current meta-analysis with TSA suggested that probiotics are efficacious in the prevention of postoperative infections in patients undergoing colorectal resection. Therefore, integrating probiotics into routine perioperative care for CRC surgery may offer notable benefits for patients in the future. However, further large-scale RCTs are required to investigate the optimal composition, timing, duration and dosing schedule of probiotics, particularly in patients with immunodeficiency and dysbiosis who may be advised against probiotic use.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YZ, JH and WS conceptualized and designed the study, conducted the statistical analysis and edited the manuscript. YZ, JH, QX, FZ, YY and HY conducted data collection and wrote the manuscript. FZ and WS are responsible for the interpretation of the research results and confirm the authenticity

of all the raw data. FZ reviewed and gave final approval of the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of People's Hospital of Putuo District (Zhoushan, China; grant no. 2024014KYLW).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Dang HX, Krasnick BA, White BS, Grossman JG, Strand MS, Zhang J, Cabanski CR, Miller CA, Fulton RS, Goedegebuure SP, *et al*: The clonal evolution of metastatic colorectal cancer. *Sci Adv* 6: eaay9691, 2020.
2. GBD 2021 Diseases and Injuries Collaborators: Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: A systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 403: 2133-2161, 2024.
3. Morgan E, Arnold M, Gini A, Lorenzoni V, Cabasag CJ, Laversanne M, Vignat J, Ferlay J, Murphy N and Bray F: Global burden of colorectal cancer in 2020 and 2040: Incidence and mortality estimates from GLOBOCAN. *Gut* 72: 338-344, 2023.
4. Saffar KN, Larypoor M and Torbati MB: Analyzing of colorectal cancer-related genes and microRNAs expression profiles in response to probiotics *Lactobacillus acidophilus* and *Saccharomyces cerevisiae* in colon cancer cell lines. *Mol Biol Rep* 51: 122, 2024.
5. Türk S, Yılmaz A, Safari Baesmat A, Malkan UY, Ucar G and Türk C: The probiotic-induced dysregulation of immune-related genes in colon cells and relation with colorectal cancer. *Cell Mol Biol (Noisy-le-grand)* 69: 37-45, 2023.
6. Siegel RL, Wagle NS, Cercek A, Smith RA and Jemal A: Colorectal cancer statistics, 2023. *CA Cancer J Clin* 73: 233-254, 2023.
7. Matsuda A, Maruyama H, Akagi S, Inoue T, Uemura K, Kobayashi M, Shiomi H, Watanabe M, Arai H, Kojima Y, *et al*: Do postoperative infectious complications really affect long-term survival in colorectal cancer surgery? A multicenter retrospective cohort study. *Ann Gastroenterol Surg* 7: 110-120, 2022.
8. Guo J, Zhou B, Niu Y, Liu L and Yang L: Engineered probiotics introduced to improve intestinal microecology for the treatment of chronic diseases: present state and perspectives. *J Diabetes Metab Disord* 22: 1029-1038, 2023.
9. Kim SH and Lim YJ: The role of microbiome in colorectal carcinogenesis and its clinical potential as a target for cancer treatment. *Intest Res* 20: 31-42, 2023.
10. Wang X, Pan L, Wang F, Long F, Yang B and Tang D: Interventional effects of oral microecological agents on perioperative indicators of colorectal cancer: A meta-analysis. *Front Oncol* 13: 1229177, 2023.
11. Khorashadizadeh S, Abbasifar S, Yousefi M, Fayedeh F and Moodi Ghalibaf A: The role of microbiome and probiotics in chemo-radiotherapy-induced diarrhea: A narrative review of the current evidence. *Cancer Rep (Hoboken)* 7: e70029, 2024.
12. He Z, Xie H, Xu H, Wu J, Zeng W, He Q, Jobin C, Jin S and Lan P: Chemotherapy-induced microbiota exacerbates the toxicity of chemotherapy through the suppression of interleukin-10 from macrophages. *Gut Microbes* 16: 2319511, 2024.

13. Imanbayev N, Iztleuov Y, Bekmukhambetov Y, Abdelazim IA, Donayeva A, Amanzholykyz A, Aigul Z, Aigerim I and Aslan Y: Colorectal cancer and microbiota: Systematic review. *Prz Gastroenterol* 16: 380-396, 2024.
14. Sanders ME, Merenstein DJ, Reid G, Gibson GR and Rastall RA: Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. *Nat Rev Gastroenterol Hepatol* 16: 605-616, 2019.
15. Azcárate-Peril MA, Sikes M and Bruno-Bárcena JM: The intestinal microbiota, gastrointestinal environment and colorectal cancer: A putative role for probiotics in prevention of colorectal cancer? *Am J Physiol Gastrointest Liver Physiol* 301: G401-G424, 2011.
16. Paolillo R, Romano Carratelli C, Sorrentino S, Mazzola N and Rizzo A: Immunomodulatory effects of *Lactobacillus plantarum* on human colon cancer cells. *Int Immunopharmacol* 9: 1265-1271, 2009.
17. Yuan L, Zhang S, Li H, Yang F, Mushtaq N, Ullah S, Shi Y, An C and Xu J: The influence of gut microbiota dysbiosis to the efficacy of 5-Fluorouracil treatment on colorectal cancer. *Biomed Pharmacother* 108: 184-193, 2018.
18. Kumar A, Pramanik J, Batta K, Bama P, Gaur M, Rustagi S, Prajapati BG and Bhattacharya S: Impact of metallic nanoparticles on gut microbiota modulation in colorectal cancer: A review. *Cancer Innov* 3: e150, 2024.
19. Zhao J, Liao Y, Wei C, Ma Y, Wang F, Chen Y, Zhao B, Ji H, Wang D and Tang D: Potential ability of probiotics in the prevention and treatment of colorectal cancer. *Clin Med Insights Oncol* 17: 11795549231188225, 2023.
20. Wu J, Ma X, Wang X, Zhu G, Wang H, Zhang Y and Li J: Efficacy and safety of compound kushen injection for advanced colorectal cancer: A systematic review and meta-analysis of randomized clinical trials with trial sequential analysis. *Integr Cancer Ther* 23: 15347354241258458, 2024.
21. Higgins JP, Savovic J and Page MJ: Chapter 8: Assessing risk of bias in a randomized trial. In: *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, *et al* (eds). Cochrane, 2021. Available from: training.cochrane.org/handbook.
22. Weng H, Li S and Zeng XT: Application of the trial sequential analysis soft ware for meta-analysis. *Chin J Evid-Based Med* 16: 604-611, 2016 (In Chinese).
23. Bajramagic S, Hodzic E, Mulabdic A, Holjan S, Smajlovic SV and Rovcanin A: Usage of probiotics and its clinical significance at surgically treated patients suffering from colorectal carcinoma. *Med Arch* 73: 316-320, 2019.
24. Chen H, Xia Y, Shi C, Liang Y, Yang Y and Qin H: Effects of perioperative probiotics administration on patients with colorectal cancer. *Chin J Clin Nutr* 22: 8, 2014 (In Chinese).
25. Consoli ML, da Silva RS, Nicoli JR, Bruña-Romero O, da Silva RG, de Vasconcelos Generoso S and Correia MI: Randomized clinical trial: Impact of oral administration of *saccharomyces boulardii* on gene expression of intestinal cytokines in patients undergoing colon resection. *JPEN J Parenter Enteral Nutr* 40: 1114-1121, 2016.
26. Huang F, Li S, Chen W, Han Y, Yao Y, Yang L, Li Q, Xiao Q, Wei J, Liu Z, *et al*: Postoperative Probiotics administration attenuates gastrointestinal complications and gut microbiota dysbiosis caused by chemotherapy in colorectal cancer patients. *Nutrients* 15: 356, 2023.
27. Kotzampassi K, Stavrou G, Damoraki G, Georgitsi M, Basdanis G, Tsaousi G and Giamarellos-Bourboulis EJ: A Four-Probiotics regimen reduces postoperative complications after colorectal surgery: A randomized, double-blind, placebo-controlled study. *World J Surg* 39: 2776-2783, 2015.
28. Liu Z, Qin H, Yang Z, Xia Y, Liu W, Yang J, Jiang Y, Zhang H, Yang Z, Wang Y and Zheng Q: Randomised clinical trial: The effects of perioperative probiotic treatment on barrier function and post-operative infectious complications in colorectal cancer surgery - a double-blind study. *Aliment Pharmacol Ther* 33: 50-63, 2011.
29. Liu ZH, Huang MJ, Zhang XW, Wang L, Huang NQ, Peng H, Lan P, Peng JS, Yang Z, Xia Y, *et al*: The effects of perioperative probiotic treatment on serum zonulin concentration and subsequent postoperative infectious complications after colorectal cancer surgery: A double-center and double-blind randomized clinical trial. *Am J Clin Nutr* 97: 117-126, 2013.
30. Liu Z, Li C, Huang M, Tong C, Zhang X, Wang L, Peng H, Lan P, Zhang P, Huang N, *et al*: Positive regulatory effects of perioperative probiotic treatment on postoperative liver complications after colorectal liver metastases surgery: A double-center and double-blind randomized clinical trial. *BMC Gastroenterol* 15: 34, 2015.
31. Mangell P, Thorlacius H, Syk I, Ahnér S, Molin G, Olsson C and Jeppsson B: *Lactobacillus plantarum* 299v does not reduce enteric bacteria or bacterial translocation in patients undergoing colon resection. *Dig Dis Sci* 57: 1915-1924, 2012.
32. Mizuta M, Endo I, Yamamoto S, Inokawa H, Kubo M, Uda T, Sogabe O, Maeda H, Shirakawa K, Okazaki E, *et al*: Perioperative supplementation with bifidobacteria improves postoperative nutritional recovery, inflammatory response, and fecal microbiota in patients undergoing colorectal surgery: A prospective, randomized clinical trial. *Biosci Microbiota Food Health* 35: 77-87, 2016.
33. Park JJ, Lee JH, Kye BH, Oh HK, Cho YB, Kim YT, Kim JY, Sung NY, Kang SB, Seo JM, *et al*: Effects of probiotics on the symptoms and surgical outcomes after anterior Resection of colon cancer (POSTCARE): A randomized, double-blind, placebo-controlled trial. *J Clin Med* 9: 2181, 2020.
34. Pellino G, Sciaudone G, Candilio G, Camerlingo A, Marcellinaro R, De Fatico S, Rocco F, Canonico S, Riegler G and Selvaggi F: Early postoperative administration of probiotics versus placebo in elderly patients undergoing elective colorectal surgery: A double-blind randomized controlled trial. *BMC Surg* 13 (Suppl 2): S57, 2013.
35. Rodríguez-Padilla Á, Morales-Martín G, Pérez-Quintero R, Gómez-Salgado J, Balongo-García R and Ruiz-Frutos C: Postoperative ileus after stimulation with probiotics before ileostomy closure. *Nutrients* 13: 626, 2021.
36. Sadahiro S, Suzuki T, Tanaka A, Okada K, Kamata H, Ozaki T and Koga Y: Comparison between oral antibiotics and probiotics as bowel preparation for elective colon cancer surgery to prevent infection: Prospective randomized trial. *Surgery* 155: 493-503, 2014.
37. Tan CK, Said S, Rajandram R, Wang Z, Roslani AC and Chin KF: Pre-surgical administration of microbial cell preparation in colorectal cancer patients: A randomized controlled trial. *World J Surg* 40: 1985-1992, 2016.
38. Xia Y, Yang Z, Chen HQ and Qin HL: Effect of bowel preparation with probiotics on intestinal barrier after surgery for colorectal cancer. *Zhonghua Wei Chang Wai Ke Za Zhi* 13: 528-531, 2010 (In Chinese).
39. Xu Q, Xu P, Cen Y and Li W: Effects of preoperative oral administration of glucose solution combined with postoperative probiotics on inflammation and intestinal barrier function in patients after colorectal cancer surgery. *Oncol Lett* 18: 694-698, 2019.
40. Yang Y, Xia Y, Chen H, Hong L, Feng J, Yang J, Yang Z, Shi C, Wu W, Gao R, *et al*: The effect of perioperative probiotics treatment for colorectal cancer: short-term outcomes of a randomized controlled trial. *Oncotarget* 7: 8432-8440, 2016.
41. Zaharuddin L, Mokhtar NM, Muhammad Nawawi KN and Raja Ali RA: A randomized double-blind placebo-controlled trial of probiotics in post-surgical colorectal cancer. *BMC Gastroenterol* 19: 131, 2019.
42. Zhang W, Du P, Chen D, Cui L and Ying C: Effect of viable bifidobacterium supplement on the immune status and inflammatory response in patients undergoing resection for colorectal cancer. *Chin J Gastrointest Surg* 13: 40-40, 2010.
43. Zhang JW, Du P, Gao J, Yang BR, Fang WJ and Ying CM: Preoperative probiotics decrease postoperative infectious complications of colorectal cancer. *Am J Med Sci* 343: 199-205, 2012.
44. Yu J, Nong C, Zhao J, Meng L and Song J: An integrative bioinformatic analysis of microbiome and transcriptome for predicting the risk of colon adenocarcinoma. *Dis Markers* 2022: 7994074, 2022.
45. Chang H, Lei L, Zhou Y, Ye F and Zhao G: Dietary flavonoids and the risk of colorectal cancer: An updated meta-analysis of epidemiological studies. *Nutrients* 10: 950, 2018.
46. Al-Nemari R, Al-Senaidey A, Semlali A, Ismael M, Badjah-Hadj-Ahmed AY and Ben Bacha A: GC-MS profiling and assessment of antioxidant, antibacterial, and anticancer properties of extracts of *Annona squamosa* L. leaves. *BMC Complement Med Ther* 20: 296, 2020.
47. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinetz TV, Prieto PA, Vicente D, Hoffman K, Wei SC, *et al*: Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science* 359: 97-103, 2018.
48. Wong CC and Yu J: Gut microbiota in colorectal cancer development and therapy. *Nat Rev Clin Oncol* 20: 429-452, 2023.
49. Sun L, Zhu Z, Jia X, Ying X, Wang B, Wang P, Zhang S and Yu J: The difference of human gut microbiome in colorectal cancer with and without metastases. *Front Oncol* 12: 982744, 2022.

50. Zhang W, An Y, Qin X, Wu X, Wang X, Hou H, Song X, Liu T, Wang B, Huang X and Cao H: Gut microbiota-derived metabolites in colorectal cancer: The bad and the challenges. *Front Oncol* 11: 739648, 2021.
51. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ, Salminen S, *et al*: Expert consensus document. The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* 11: 506-514, 2014.
52. Suez J, Zmora N, Segal E and Elinav E: The pros, cons, and many unknowns of probiotics. *Nat Med* 25: 716-729, 2019.
53. Sonnenburg JL and Bäckhed F: Diet-microbiota interactions as moderators of human metabolism. *Nature* 535: 56-64, 2016.
54. Szajewska H and Kołodziej M: Systematic review with meta-analysis: *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea. *Aliment Pharmacol Ther* 42: 793-801, 2015.
55. Szajewska H, Guarino A, Hojsak I, Indrio F, Kolacek S, Shamir R, Vandenplas Y and Weizman Z: European Society for Pediatric Gastroenterology, Hepatology, and Nutrition: Use of probiotics for management of acute gastroenteritis: A position paper by the ESPGHAN Working Group for Probiotics and Prebiotics. *J Pediatr Gastroenterol Nutr* 58: 531-539, 2014.
56. Cani PD and Jordan BF: Gut microbiota-mediated inflammation in obesity: A link with gastrointestinal cancer. *Nat Rev Gastroenterol Hepatol* 15: 671-682, 2018.
57. Huang HC, Cai BH, Suen CS, Lee HY, Hwang MJ, Liu FT and Kannagi R: BGN/TLR4/NF- κ B mediates epigenetic silencing of immunosuppressive siglec ligands in colon cancer cells. *Cells* 9: 397, 2020.
58. Wu R, Shen Q, Li P and Shang N: Sturgeon chondroitin sulfate restores the balance of gut microbiota in colorectal cancer bearing mice. *Int J Mol Sci* 23: 3723, 2022.
59. Persson JE, Viana P, Persson M, Relvas JH and Danielski LG: Perioperative or postoperative probiotics reduce treatment-related complications in adult colorectal cancer patients undergoing surgery: A systematic review and meta-analysis. *J Gastrointest Cancer* 55: 740-748, 2024.
60. An S, Kim K, Kim MH, Jung JH and Kim Y: Perioperative probiotics application for preventing postoperative complications in patients with colorectal cancer: A systematic review and meta-analysis. *Medicina (Kaunas)* 58: 1644, 2022.
61. Araújo MM, Montalvão-Sousa TM, Teixeira PDC, Figueiredo ACMG and Botelho PB: The effect of probiotics on postsurgical complications in patients with colorectal cancer: A systematic review and meta-analysis. *Nutr Rev* 81: 493-510, 2023.
62. Chen C, Wen T and Zhao Q: Probiotics used for postoperative infections in patients undergoing colorectal cancer surgery. *Biomed Res Int* 2020: 5734718, 2020.
63. Chen Y, Qi A, Teng D, Li S, Yan Y, Hu S and Du X: Probiotics and synbiotics for preventing postoperative infectious complications in colorectal cancer patients: A systematic review and meta-analysis. *Tech Coloproctol* 26: 425-436, 2022.
64. Jaye K, Li CG and Bhuyan DJ: The complex interplay of gut microbiota with the five most common cancer types: From carcinogenesis to therapeutics to prognoses. *Crit Rev Oncol Hematol* 165: 103429, 2021.
65. Iida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA, Molina DA, Salcedo R, Back T, Cramer S, *et al*: Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. *Science* 342: 967-970, 2013.
66. Routy B, LeChatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, Fluckiger A, Messaoudene M, Rauber C, Roberti MP, *et al*: Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science* 359: 91-97, 2018.
67. Belkaid Y and Hand TW: Role of the microbiota in immunity and inflammation. *Cell* 157: 121-41, 2014.
68. Zhang F, Aschenbrenner D, Yoo JY and Zuo T: The gut mycobiome in health, disease, and clinical applications in association with the gut bacterial microbiome assembly. *Lancet Microbe* 3: e969-e983, 2022.



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