# 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.

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## 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

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 $\chi^2$ 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),

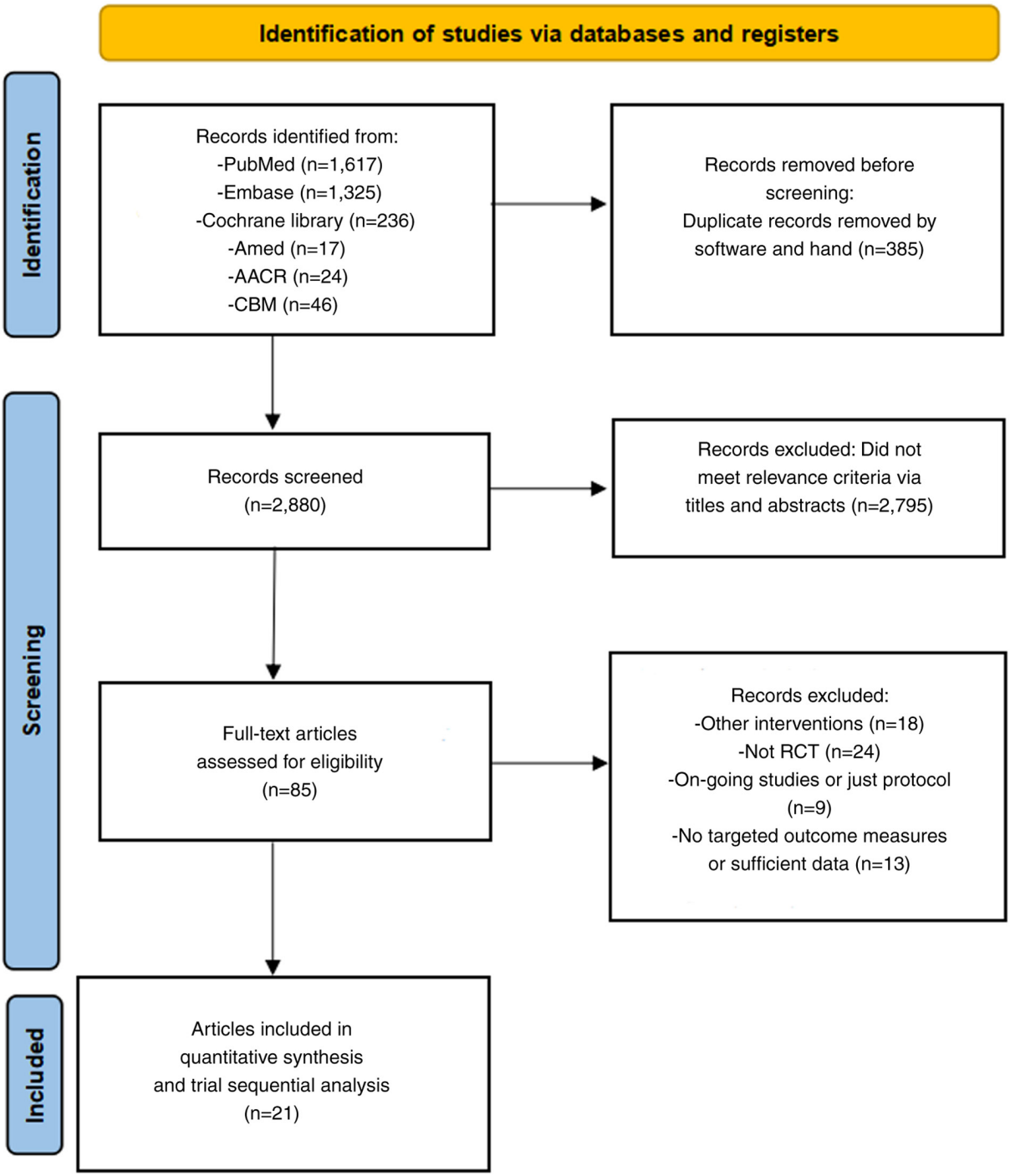



Figure 1. PRISMA flowchart detailing literature search and screening strategy. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, randomized controlled trial; AACR, American Association for Cancer Research; CBM, China Biology Medicine disc.

*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 *et al*, 2010 | China | 30 | 30 | 67.3 (37-82) | *Lactobacillus casei*, *Lactobacillus acidophilus* | >5 days preoperatively | (38) |
| Zhang *et al*, 2010 | China | 30 | 30 | T, 66.7 (41-83); C, 63.0 (39-81) | *Bifidobacterium* | For 5 days preoperatively | (42) |
| Liu *et al*, 2011 | China | 50 | 50 | T, 65.3±11.0; C, 65.7±9.9 | *Lactobacillus plantarum*, *Lactobacillus acidophilus* and *Bifidobacterium longum* | For 6 days preoperatively and 10 days postoperatively | (28) |
| Zhang *et al*, 2012 | China | 30 | 30 | T, 67.5 (45-87); C, 61.5 (46-82) | *Bifidobacterium longum*, *Lactobacillus acidophilus* and *Enterococcus faecalis* | For 3-5 days preoperatively | (43) |
| Liu *et al*, 2013 | China | 75 | 75 | T, 62.28±12.41; C, 66.06±11.02 | *Lactobacillus plantarum*, *Lactobacillus acidophilus* and *Bifidobacterium longum* | For 6 days preoperatively and 10 days postoperatively | (29) |
| Pellino *et al*, 2013 | Italy | 10 | 8 | T, 71.5±2.1; C, 72.9±1.6 | *Streptococcus thermophilus*, *Bifidobacterium longum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus delbrueckii subsp. bulgaricus* | For 1 day to 4 weeks after discontinuing antibiotics postoperatively | (34) |
| Mangell *et al*, 2012 | Sweden | 32 | 32 | T, 74 (70-80); C, 70 (64-79) | *Lactobacillus plantarum* | For 8 days preoperatively and 5 days postoperatively | (31) |
| Chen *et al*, 2014 | China | 35 | 35 | T, 60.3±17.2; C, 59.8±18.7 | *Clostridium typhimurium* and *Bifidobacterium infantis* | For 5 days preoperatively and 7 days postoperatively | (24) |
| Sadahiro *et al*, 2014 | Japan | 100 | 95 | T, 67±9; C, 66±12 | *Bifidobacteria* | For 7 days preoperatively and 5-10 days postoperatively | (36) |
| Consoli *et al*, 2016 | Brazil | 15 | 18 | T, 51 (28-76); C, 59 (17-83) | *Saccharomyces boulardii* | For at least 7 days preoperatively | (25) |
| Liu *et al*, 2015 | China | 66 | 68 | T, 65.62±18.18; C, 60.16±16.20 | *Lactobacillus plantarum*, *Lactobacillus acidophilus* and *Bifidobacterium longum* | For 6 days preoperatively and 10 days postoperatively | (30) |
| Mizuta *et al*, 2016 | Japan | 31 | 29 | T, 68.9±10.4; C, 71.2±9.5 | *Bifidobacterium longum* | For 7-14 days preoperatively and 14 days postoperatively | (32) |
| Yang *et al*, 2016 | China | 30 | 30 | T, 63.90± 2.25; C, 62.17±11.06 | *Bifidobacterium longum*, *Lactobacillus acidophilus* and *Enterococcus faecalis* | For 5 days preoperatively to 7 days postoperatively | (40) |
| Kotzampassi *et al*, 2015 | Greece | 84 | 80 | T, 65.9±11.5; C, 66.4±11.9 | *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Bifidobacterium lactis and Saccharomyces boulardii* | From the day of surgery to 14 days postoperatively | (27) |
| Tan *et al*, 2016 | Malaysia | 20 | 20 | T, 64.3±14.5; C, 68±11.9 | *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus lactis*, *Bifidobacterium bifidum*, *Bifidobacterium longum and Bifidobacterium infantis* | 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 *et al*, 2019 | Bosnia and Herzegovina | 39 | 39 | NA | *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus rhamnosus, Bifidobacterium lactis, Bifidobacterium bifidum, Bifidobacterium breve, Streptococcus thermophiles* | For 3 days preoperatively to 30 days postoperatively | (23) |
| Xu *et al*, 2019 | China | 30 | 30 | T, 61.03±15.28; C, 62.35±13.71 | *Bifidobacterium longum, Lactobacillus acidophilus* and *Enterococcus faecalis* | For 7 consecutive days preoperatively | (39) |
| Zaharuddin *et al*, 2019 | Malaysia | 27 | 25 | T, 67.33±9.44; C, 66.5±8.57 | *Lactobacillus acidophilus, Lactobacillus lactis, Lactobacillus casei subsp, Bifidobacterium longum, Bifidobacterium bifidum and Bifidobacterium infantis* | For 4 weeks postoperatively to 6 months | (41) |
| Park *et al*, 2020 | Korea | 29 | 31 | T, 60.1±10.37; C, 61.03±7.02 | *Bifidobacterium animalis subsp. Lactis, Lactobacillus casei,* and *Lactobacillus plantarum* | For 7 days preoperatively to 21 days postoperatively | (33) |
| Rodríguez-Padilla *et al*, 2021 | Spain | 34 | 35 | T, 65 (45-81); C, 68 (41-80) | *Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii subsp. bulgaricus., Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Streptococcus thermophilus* | For 20 days preoperatively every second day | (35) |
| Huang *et al*, 2023 | China | 50 | 50 | T, 57.7±11.9; C, 62.1±10.5 | *Bifidobacterium infants, Lactobacillus acidophilus, Enterococcus faecalis, Bifidobacterium cereus* | 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

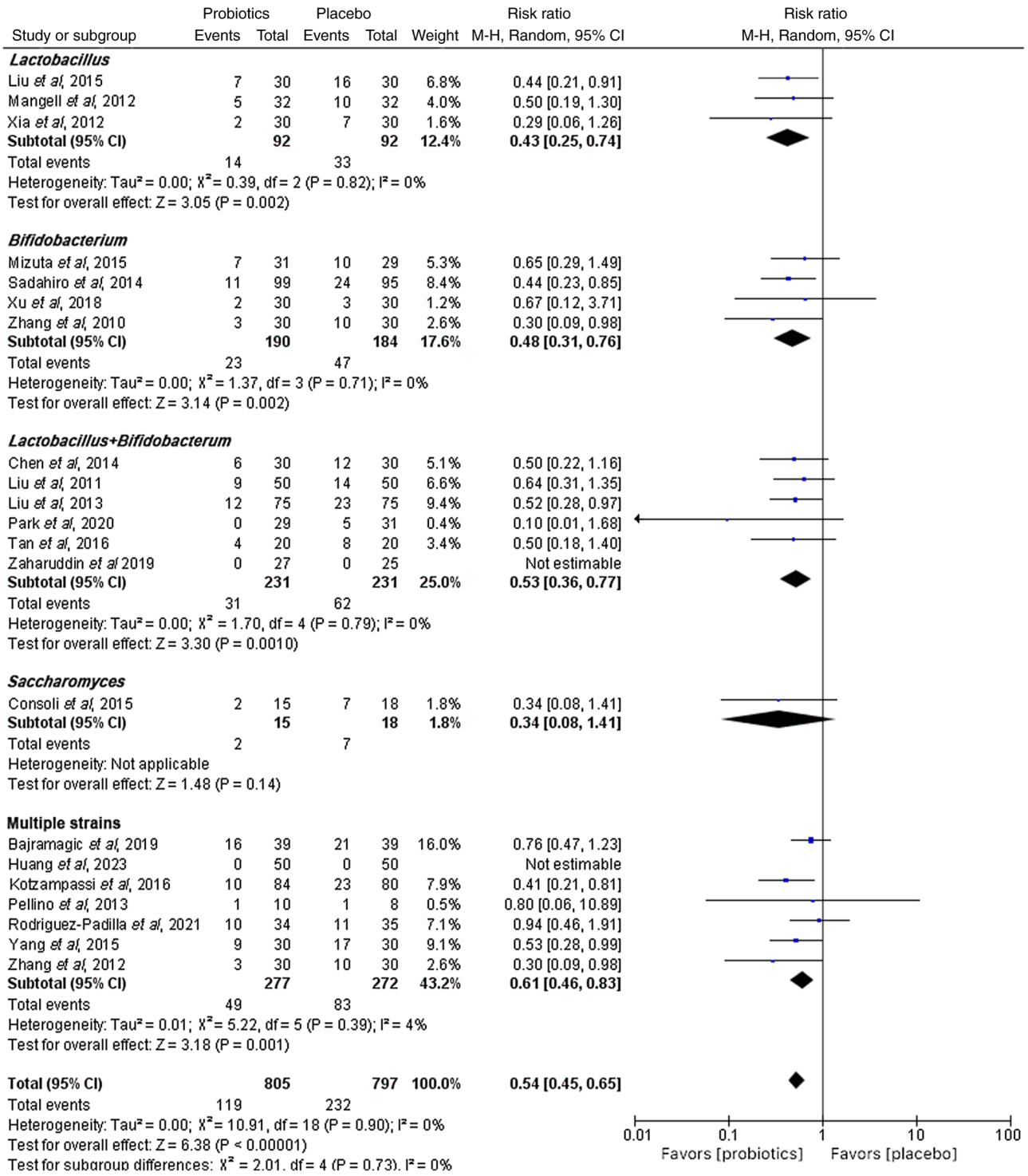



Figure 2. Meta-analysis of probiotics for the incidence of postoperative infections.

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

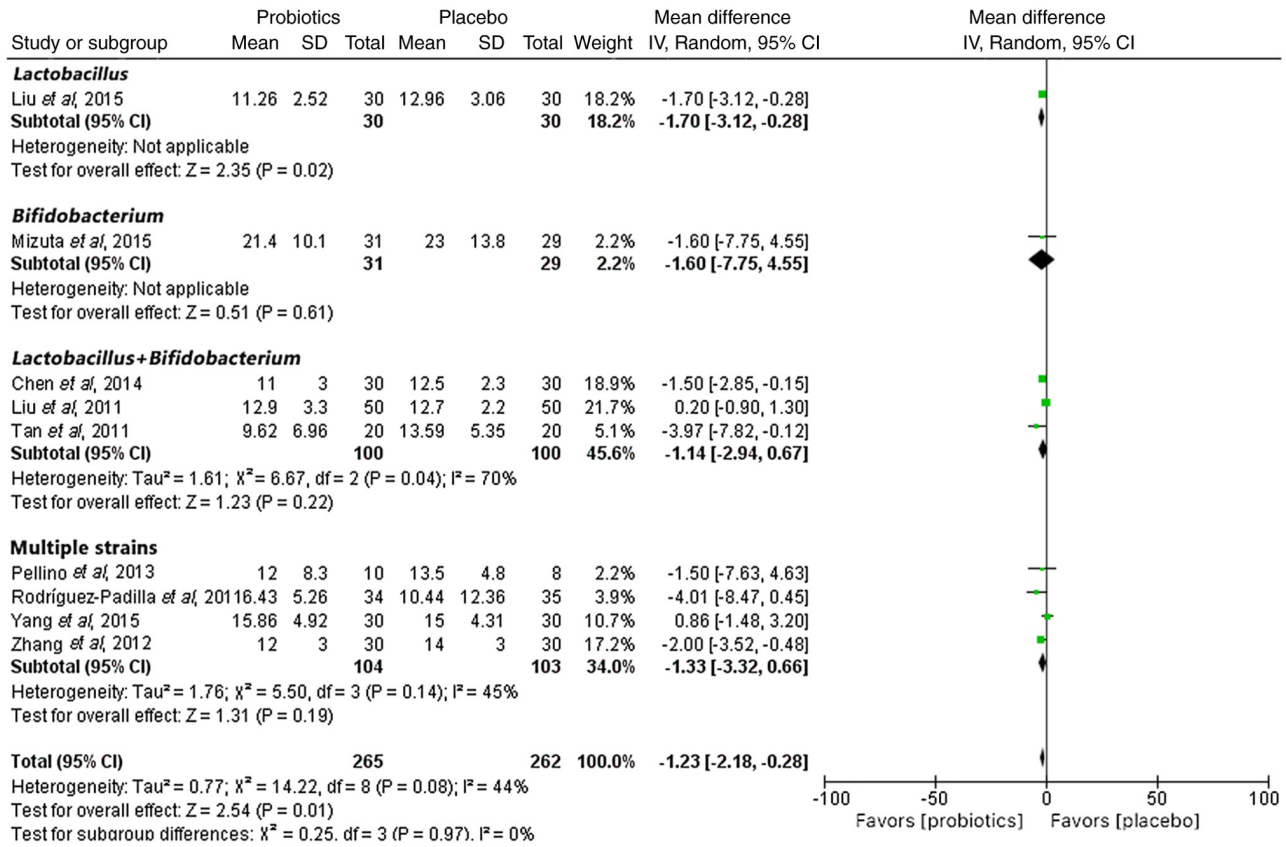



Figure 3. Meta-analysis of probiotics for mean hospitalization days.

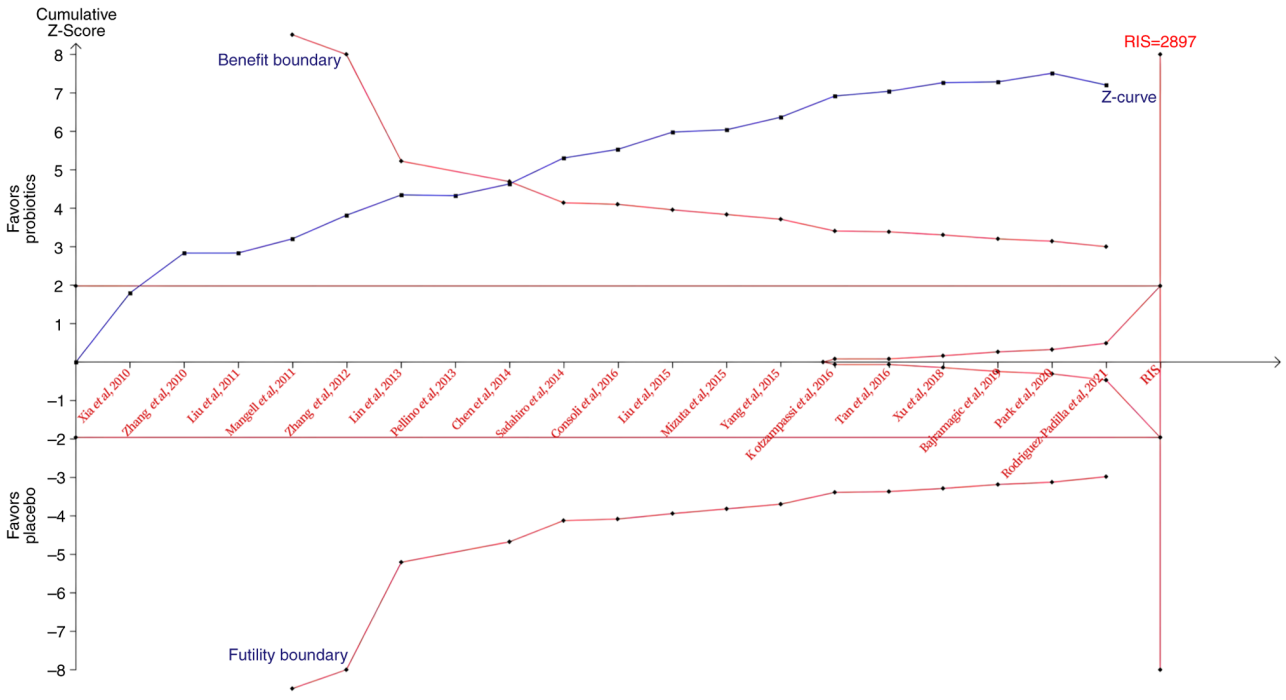



Figure 4. Trial sequential analysis results for probiotics for the incidence of postoperative infections. RIS, required information size.

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.

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