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EDITORIAL

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Cohort Study

Retrospective Study

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 16 Number 11 November 27, 2024

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META-ANALYSIS

Preventive effect of probiotics on infections following colorectal cancer surgery: An umbrella meta-analysis

Yue Han, Yong Wang, Min Guan

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Abstract

BACKGROUND

Postoperative infections remain a significant source of morbidity among patients undergoing colorectal cancer (CRC) surgery. While probiotics have been proposed as a potential strategy to mitigate the risk of these infections, contemporary meta-analyses have produced conflicting findings.

AIM

To synthesize the available evidence regarding the prophylactic efficacy of probiotics in preventing infections following CRC surgery.

METHODS

A comprehensive search of PubMed and Scopus was conducted to identify relevant meta-analyses published up to February 2024. To assess the efficacy of probiotics on outcomes, relative risks (RR) and their corresponding 95%CI were pooled using a random effects model.

RESULTS

This comprehensive umbrella meta-analysis integrated eleven meta-analyses encompassing 11518 participants who fulfilled the inclusion criteria. Probiotics administration resulted in a statistically significant reduction in the incidence of total infections (RR: 0.40, 95%CI: 0.31-0.51; moderate certainty), surgical site infections (RR: 0.56, 95%CI: 0.49-0.63; high certainty), pneumonia (RR: 0.38, 95%CI: 0.30-0.48; high certainty), urinary tract infections (RR: 0.44, 95%CI: 0.31-0.61; moderate certainty), bacteremia (RR: 0.41, 95%CI: 0.30-0.56; high certainty), and sepsis (RR: 0.35, 95%CI: 0.25-0.44; high certainty). However, probiotics did not significantly affect intra-abdominal, central line, or peritoneal infections.

CONCLUSION
Probiotics have demonstrated potential in mitigating postoperative infectious complications among patients undergoing CRC surgery.

Key Words: Probiotics; Colorectal cancer Surgery; Postoperative infections; Pneumonia; Urinary tract infections; Bacteremia; Sepsis; Meta-analysis

Core Tip: This meta-analysis of 11 studies involving 11518 colorectal cancer (CRC) patients found that probiotics significantly reduce postoperative infection rates, including surgical site infections, pneumonia, urinary tract infections, bacteremia, and sepsis. Probiotics were particularly effective in preventing these complications, demonstrating minimal efficacy against intra-abdominal, central line, and peritoneal infections. These findings support the integration of probiotics into post-CRC surgery prevention strategies.

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INTRODUCTION

Colorectal cancer (CRC) is a formidable global health burden, ranking as the third most prevalent cancer and the second leading cause of cancer-related mortality[1,2]. The escalating incidence of CRC in recent years underscores its status as a major public health concern[3]. Surgical resection remains the cornerstone of treatment for localized CRC[4]. Despite advancements in surgical techniques and perioperative care, post-operative infections continue to pose a significant challenge in patients with CRC[5]. Surgical site infections (SSIs), accounting for 30%-40% of all postoperative complications, constitute the most common infection following CRC surgery[6]. Other prevalent infections after CRC surgery include pneumonia, urinary tract infections (UTIs), and septicemia[7,8]. Postoperative infections in CRC surgery significantly contribute to increased morbidity, mortality, prolonged hospital stays, and escalating healthcare costs[9]. Such infections arise from a complex interplay of factors, including surgical stress, intestinal mucosal damage, local immune system dysfunction, intestinal flora imbalance, and bacterial translocation[10]. While intravenous antibiotics effectively prevent infections, the growing prevalence of antimicrobial resistance poses a significant challenge for future management[11]. Moreover, antibiotic therapy can exacerbate flora disruption, leading to antibiotic-induced diarrhea and delayed patient recovery[12]. Given these formidable challenges, there is an urgent imperative to develop novel strategies for preventing postoperative infections, particularly within the context of CRC surgery.

The gut microbiota is crucial in maintaining intestinal homeostasis and modulating immune responses[13]. Colorectal surgery, characterized by surgical trauma, can disrupt the intestinal flora, leading to systemic inflammation and an increased risk of infectious complications[14,15]. Recent studies have explored the potential of probiotics to mitigate post-operative infections in CRC patients. Probiotics, known for their beneficial effects on gut health and immune modulation, have demonstrated promise in reducing infection rates by restoring gut microbiota balance, enhancing gut mucosal barrier integrity, and strengthening host defense mechanisms[16,17]. However, the existing evidence is conflicting. While some studies have reported a reduction in sepsis, pneumonia, and SSIs[6,18], with probiotic supplementation, others, such as Ouyang *et al*[19] have not observed a beneficial effect on urinary tract infection prevention. These discrepancies may be attributed to differences in probiotic types and the timing of intervention (intervention before/after surgery). To address this uncertainty, this umbrella meta-analysis aims to systematically review and synthesize the available evidence from multiple meta-analyses on the efficacy of probiotics in preventing post-surgical infections in CRC patients.

MATERIALS AND METHODS

This umbrella meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[20].

Literature search

A comprehensive literature search was conducted using PubMed and Scopus electronic databases, with no language restrictions, up to February 12, 2024. To identify relevant studies, a search strategy combining Medical Subject Headings and text words was employed: (probiotic* OR prebiotic* OR synbiotic) AND (colorectal OR colon OR rectal OR rectum) AND (neoplasms OR cancer OR malignancy OR tumor OR neoplasm OR surgery) AND (meta-analysis). The citations of identified meta-analyses were reviewed to ensure no relevant studies were missed. The EndNote software facilitated the selection process. Titles and abstracts of all retrieved studies were screened, leading to the exclusion of irrelevant papers. Subsequently, full-text articles were carefully examined to verify their eligibility based on the established inclusion criteria. Any discrepancies encountered during the screening process were resolved through consensus among all investigators.

Eligibility criteria

To be eligible for inclusion, studies were required to meet the following criteria: (1) Be a meta-analysis of randomized controlled trials (RCTs); (2) Investigate the efficacy of probiotics, alone or in combination with prebiotics (synbiotics), in reducing the risk of infections among patients undergoing CRC surgery compared to placebo or standard care; (3) Report on outcomes as total infections, pneumonia, UTIs, SSIs, sepsis, bacteremia, central line infection, intra-abdominal infection, and peritoneal infection; and (4) Provide summary measures and a 95%CI for the results. There was no minimum number of primary studies required for inclusion in the umbrella review as a cut-off point. Studies were excluded if they did not include a quantitative meta-analysis, failed to report pooled effect sizes for the outcomes, investigated irrelevant interventions or outcomes, did not focus on CRC patients, or were animal studies. Two authors independently selected the studies, with disagreements resolved through consensus among all authors.

Data extraction

Two independent reviewers extracted data from each meta-analysis, with any discrepancies resolved through consensus. The data abstracted included the publication year, country of origin, first author, total sample size, number of included primary studies, type of supplementation (probiotics *vs* probiotics and synbiotics), outcomes assessed, methods to evaluate the risk of bias (RoB) in the primary studies, and pooled effect sizes [relative risk (RR) with 95%CI] for the impact of probiotics on outcome risk.

Quality assessment and strength of the evidence

The methodological quality of the included meta-analyses was assessed using the Assessment of Multiple Systematic Reviews-2 tool[21]. This instrument evaluates meta-analyses across 16 items, categorizing them as high, moderate, low, or critically low quality based on responses of 'Yes, Partial Yes, and No'. Additionally, the GRADE approach was employed to evaluate the certainty of evidence and the strength of recommendations for all outcomes[22]. Two reviewers independently assessed both GRADE and methodological quality. Any discrepancies were resolved through consultation with a third author.

Statistical analysis

All analyses were carried out with Stata software (version 14). The RRs and 95%CI were calculated as measures of effect and pooled across studies using a random-effects model. Before analysis, we converted the risk estimates from each meta-analysis to a logarithmic scale, and the corresponding SE. The I^2 statistic was used to assess heterogeneity; heterogeneity was defined as the presence of a P value less than 0.1 or an I^2 of 50% or greater. We visually examined small-study effects with funnel plots and used Egger's statistical test[23]. When there was significant evidence of publication bias, the trim-and-fill method[24] was used to adjust the pooled effect sizes for publication bias. Sensitivity analyses were performed by excluding individual studies and examining the remaining studies to determine the dependability of the results to single studies. A subgroup analysis was performed by supplementation type (multi-strain probiotics *vs* multi-strain probiotics and synbiotics), intervention time (preoperative *vs* pre- and postoperative), country (China *vs* other countries), and meta-analysis quality (moderate *vs* high) to assess potential sources of heterogeneity. A P value less than 0.05 was considered statistically significant.

RESULTS

Characteristics of studies

The systematic search identified 128 studies. After excluding 31 duplicates and 74 studies deemed irrelevant based on their titles and abstracts, 23 underwent a comprehensive full-text review. Twelve studies were excluded due to irrelevant intervention/outcome, non-CRC surgery patient populations, or their status as protocols or review studies without quantitative analysis. The study selection process is illustrated in Figure 1. This umbrella meta-analysis included 11 meta-analyses[3,6,19,25-32], encompassing 11518 participants. The included studies, published between 2013 and 2024, originated from China, Brazil, Germany, and Korea. Sample sizes ranged from 361 to 1975 patients. Five studies employed multi-strain probiotics as an intervention[3,19,27,28,30], while the remaining six utilized a combination of multi-strain probiotics and synbiotics. Seven investigations[3,25-27,29,31,32] investigated the preoperative effects of probiotics on outcomes, and assessed the preoperative effects of probiotics on outcomes, whereas four studies[6,19,28,30] examined the pre- and postoperative impacts. In terms of outcomes, effect sizes were reported for total infections in 6 studies[19,25,27-29,32], SSIs in 10[3,6,19,26-32], pneumonia in 8[6,19,26,27,29-32], UTIs in 5[19,26,27,30,32], bacteremia in 3 [26,28,32], sepsis in 5[6,25,27,29,32], intra-abdominal infection in 3[6,29,32], central line infection in 2[27,32], and peritoneal infection in 2[29,32]. The primary RCTs were evaluated for RoB using the Cochrane RoB tool[33], Jaded score [34], Joanna Briggs Institute's critical assessment tool[35], and the National Heart, Lung, and Blood Institute quality assessment tool[25]. Each meta-analysis incorporated between 9% and 100% of high-quality RCTs. de Andrade Calaça *et*

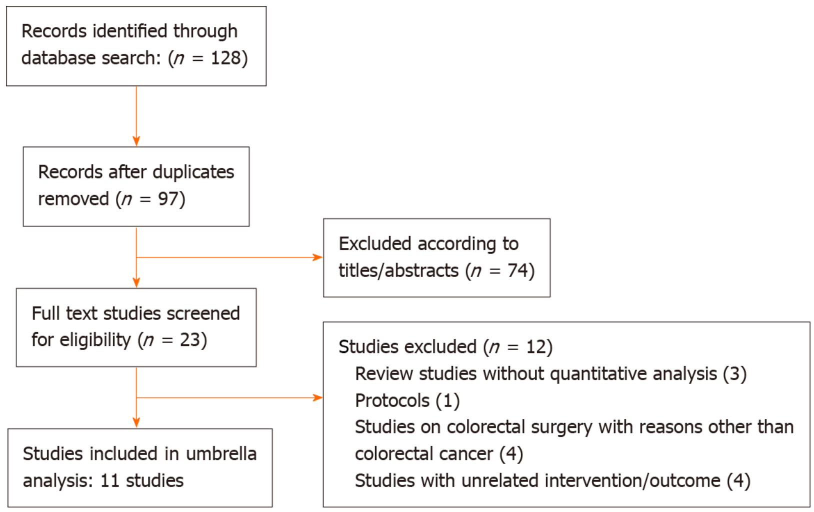


Figure 1 Flow diagram for the process of study selection.

al[28] and Persson *et al*[30] did not assess the RoB of the included RCTs. According to the AMSTAR-2 criteria, the included meta-analyses were deemed to be of high quality in six studies[6,25,26,29,31,32] and moderate in five[3,19,27,28,30] (Supplementary Table 1). Table 1 presents the characteristics of the studies included in the umbrella meta-analysis.

Findings from umbrella meta-analysis

A meta-analysis employing a random-effects model to aggregate multiple effect sizes revealed that probiotic intervention could significantly attenuate the risk of total infections (RR: 0.40, 95%CI: 0.31-0.51), SSIs (RR: 0.56, 95%CI: 0.49-0.63), pneumonia (RR: 0.38, 95%CI: 0.30-0.48), UTIs (RR: 0.44, 95%CI: 0.31-0.61), bacteremia (RR: 0.41, 95%CI: 0.30-0.56), and sepsis (RR: 0.35, 95%CI: 0.25-0.44; Figure 2). These substantial effects were consistently supported by subgroup analyses and were not influenced by supplementation type (multi-strain probiotics *vs* multi-strain probiotics and synbiotics), intervention timing (preoperative *vs* pre- and postoperative), geographic location (China *vs* other countries), or meta-analysis quality (moderate *vs* high) (Table 2). Probiotics did not exert a discernible effect on intra-abdominal, central line, or peritoneal infections (Figure 2). While total infections exhibited significant heterogeneity, other outcomes did not (Figure 2 and Table 2).

Sensitivity analysis and publication bias

The sensitivity analysis, which entailed excluding individual studies from the analysis followed by the recalculation of the pooled effect sizes using the residual studies, did not reveal any substantial alterations, suggesting the reliability of the findings. A significant publication bias was identified for UTIs (P = 0.009). However, there was no evidence of small study effects for other outcomes when evaluated using Egger's regression test (Figure 3 and Table 2). The adjusted pooled effect size for UTIs, as derived from the trim-and-fill method, yielded a similar estimate (RR: 0.45, 95%CI: 0.29-0.67).

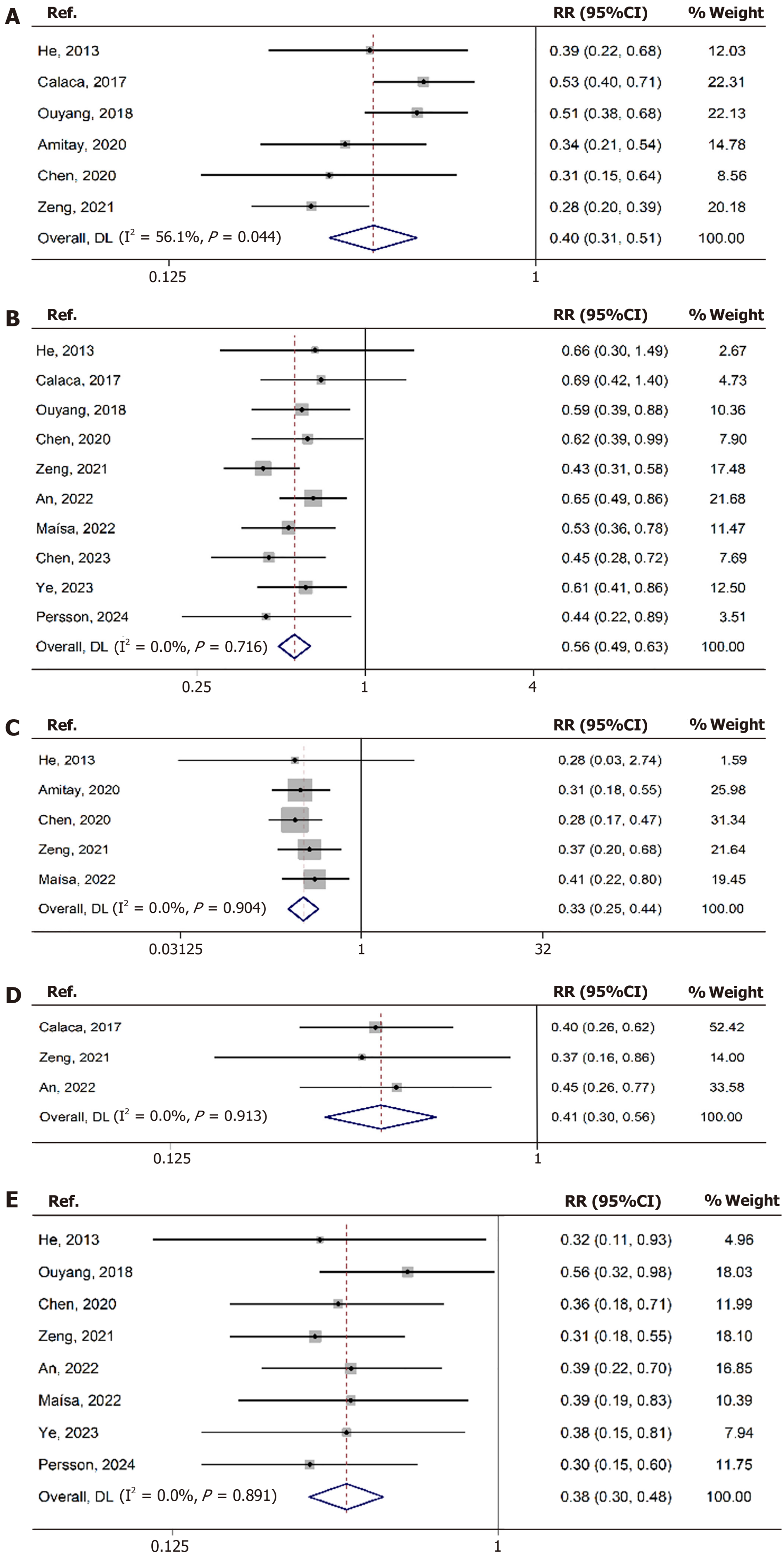
Strength of evidence

The GRADE criteria assessed the evidence quality of total infections, UTIs, central line infections, peritoneal infections, and intra-abdominal infections as moderate. SSIs, pneumonia, bacteremia, and sepsis were deemed to have high evidence quality (Table 3).

DISCUSSION

The primary objective of this umbrella meta-analysis was to ascertain the efficacy of probiotics in averting post-surgical infectious complications in patients undergoing CRC surgery. The empirical findings unequivocally demonstrate the exceptional efficacy of probiotics in preventing post-surgical infectious complications, including total infections, SSIs, pneumonia, UTIs, bacteremia, and sepsis.

Postoperative infectious complications represent a significant concern following CRC surgery, as they can prolong hospitalization, elevate healthcare expenditures, and potentially increase morbidity and mortality rates[36]. Susceptibility to these infections has been associated with gut barrier disruption, heightened intestinal permeability, gut microbiota imbalance, and compromised host immunity[37,38]. Surgical intervention that disrupts the gut microbiota can enhance susceptibility to infections, retard wound healing, and precipitate other adverse complications[39]. Several studies have postulated that probiotics can mitigate the risk of postoperative infections by ameliorating intestinal microbial flora and reducing intestinal permeability[17,19].


A
Ref.
RR (95%CI)
% Weight
He, 2013
0.39 (0.22, 0.68)
12.03
Calaca, 2017
0.53 (0.40, 0.71)
22.31
Ouyang, 2018
0.51 (0.38, 0.68)
22.13
Amitay, 2020
0.34 (0.21, 0.54)
14.78
Chen, 2020
0.31 (0.15, 0.64)
8.56
Zeng, 2021
0.28 (0.20, 0.39)
20.18
Overall, DL (I^2 = 56.1%, P = 0.044)
0.40 (0.31, 0.51)
100.00
0.125
1
B
Ref.
RR (95%CI)
% Weight
He, 2013
0.66 (0.30, 1.49)
2.67
Calaca, 2017
0.69 (0.42, 1.40)
4.73
Ouyang, 2018
0.59 (0.39, 0.88)
10.36
Chen, 2020
0.62 (0.39, 0.99)
7.90
Zeng, 2021
0.43 (0.31, 0.58)
17.48
An, 2022
0.65 (0.49, 0.86)
21.68
Maísa, 2022
0.53 (0.36, 0.78)
11.47
Chen, 2023
0.45 (0.28, 0.72)
7.69
Ye, 2023
0.61 (0.41, 0.86)
12.50
Persson, 2024
0.44 (0.22, 0.89)
3.51
Overall, DL (I^2 = 0.0%, P = 0.716)
0.56 (0.49, 0.63)
100.00
0.25
1
4
C
Ref.
RR (95%CI)
% Weight
He, 2013
0.28 (0.03, 2.74)
1.59
Amitay, 2020
0.31 (0.18, 0.55)
25.98
Chen, 2020
0.28 (0.17, 0.47)
31.34
Zeng, 2021
0.37 (0.20, 0.68)
21.64
Maisa, 2022
0.41 (0.22, 0.80)
19.45
Overall, DL (I^2 = 0.0%, P = 0.904)
0.33 (0.25, 0.44)
100.00
0.03125
1
32
D
Ref.
RR (95%CI)
% Weight
Calaca, 2017
0.40 (0.26, 0.62)
52.42
Zeng, 2021
0.37 (0.16, 0.86)
14.00
An, 2022
0.45 (0.26, 0.77)
33.58
Overall, DL (I^2 = 0.0%, P = 0.913)
0.41 (0.30, 0.56)
100.00
0.125
1
E
Ref.
RR (95%CI)
% Weight
He, 2013
0.32 (0.11, 0.93)
4.96
Ouyang, 2018
0.56 (0.32, 0.98)
18.03
Chen, 2020
0.36 (0.18, 0.71)
11.99
Zeng, 2021
0.31 (0.18, 0.55)
18.10
An, 2022
0.39 (0.22, 0.70)
16.85
Maísa, 2022
0.39 (0.19, 0.83)
10.39
Ye, 2023
0.38 (0.15, 0.81)
7.94
Persson, 2024
0.30 (0.15, 0.60)
11.75
Overall, DL (I^2 = 0.0%, P = 0.891)
0.38 (0.30, 0.48)
100.00
0.125
1

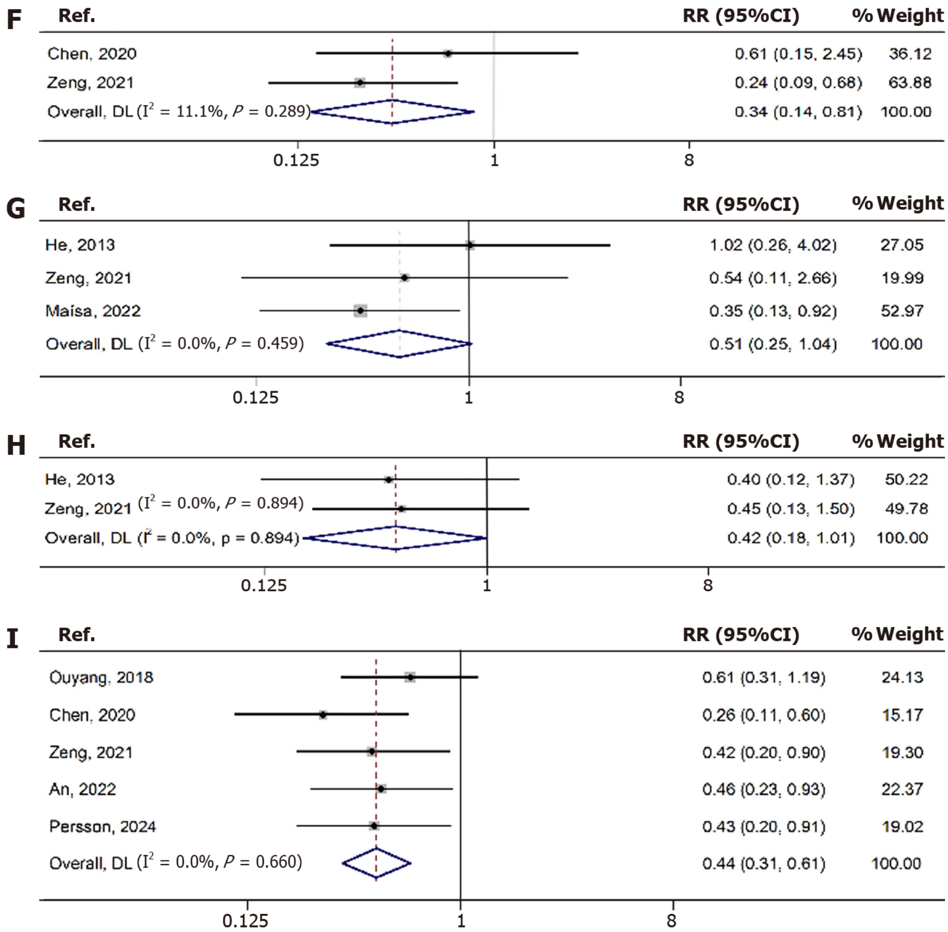


Figure 2 Pooled analysis for the effect of probiotics on infections after colorectal cancer surgery. A: Total infections; B: Surgical site infection; C: Sepsis; D: Bacteremia; E: Pneumonia, F: Central line infection; G: Intra-abdominal infection; H: Peritoneal infection; I: Urinary tract infection. RR: Relative risks.

Currently, there is no definitive consensus regarding the efficacy of probiotics in preventing postoperative infections following CRC surgery. Our umbrella meta-analysis revealed substantial evidence supporting the beneficial impact of probiotics on reducing the risk of infections after CRC surgery. The significant decrease in postoperative infections, as indicated by relative risks ranging from 0.34 to 0.56, transcends statistical significance and is clinically meaningful in terms of the magnitude of the effects. These findings can enhance patient outcomes, curtail antibiotic usage, diminish hospital readmissions, lower healthcare costs associated with treating infections, and improve the overall quality of care for patients undergoing CRC surgery. Furthermore, these findings may facilitate the development of targeted interventions and guidelines aimed at reducing postoperative infections and optimizing recovery outcomes for individuals undergoing surgery.

However, probiotics exhibited no significant effect on intra-abdominal, central line, or peritoneal infections. These observations underscore the need for further research to elucidate the optimal administration of probiotics in specific contexts, as well as potential combination therapies or tailored formulations. Future investigations should focus on refining probiotic protocols, identifying underlying mechanisms of action, and examining their broader implications for patient outcomes and healthcare costs.

Probiotics have demonstrated efficacy in mitigating post-surgical infections following CRC surgery through diverse mechanisms. These mechanisms encompass the preservation of gut microbiota equilibrium, augmentation of immune responses, diminution of pathogen adhesion, generation of antimicrobial substances, and fortification of intestinal barrier function[17,40-42]. Probiotics actively contribute to maintaining a balanced gut microbiota by stimulating the proliferation of beneficial bacteria while concurrently suppressing the growth of detrimental pathogens. This well-established microbiota plays a pivotal role in bolstering the immune system and safeguarding against infections[43]. Probiotics have been demonstrated in numerous studies to exert a significant influence on the immune response. By stimulating the production of anti-inflammatory cytokines and enhancing the functionality of immune cells, probiotics contribute to a more balanced immune milieu[44]. These beneficial microorganisms can effectively mitigate gut inflammation through mechanisms such as the inhibition of nuclear factor-κB activation and the augmentation of humoral immunity markers, including IgG, IgM, IgA, interleukin-2 (IL-2), and CD4+ T cells[45]. Moreover, probiotics play a pivotal role in regulating serum levels of IL-6 and C-reactive protein, alleviating stress, and diminishing the likelihood of postoperative infections [17]. The potentiated immune response facilitated by probiotics can significantly enhance the body's capacity to counter potential pathogens that may give rise to post-surgical infections. Additionally, probiotics exhibit a competitive advantage over pathogenic bacteria in vying for adhesion sites on the gut lining, thereby restricting their ability to

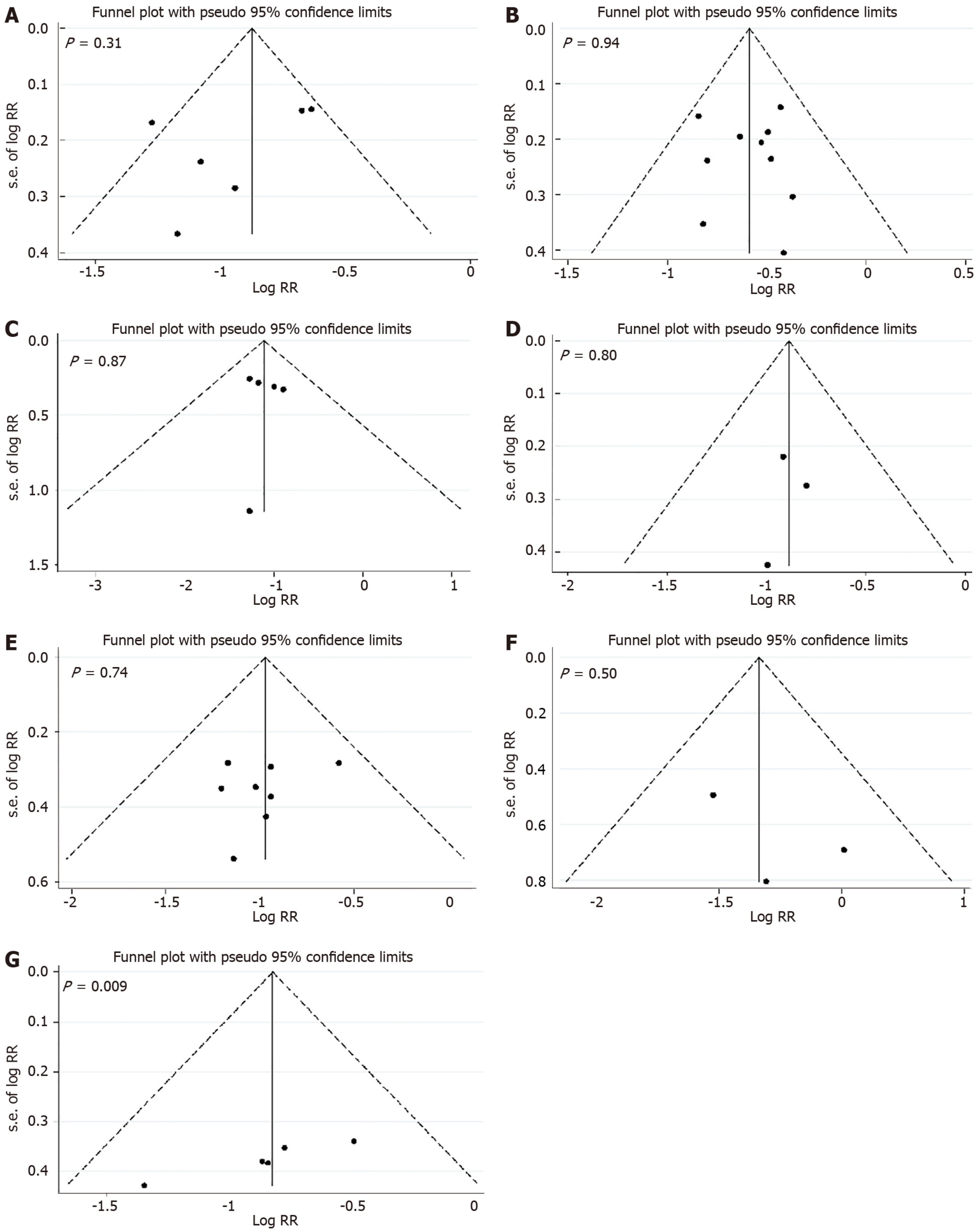


Figure 3 Funnel plots of publication bias for the effect of probiotics on infections after colorectal cancer surgery. A: Total infections; B: Surgical site infection; C: Sepsis; D: Bacteremia; E: Pneumonia, F: Intra-abdominal infection; G: Urinary tract infection. RR: Relative risks.

colonize and induce infections[46]. Certain probiotic strains synthesize antimicrobial compounds, including hydrogen peroxide, bacteriocins, and lactic acid, which can directly suppress the proliferation of pathogenic bacteria, thereby mitigating the likelihood of infection[42]. Moreover, probiotics contribute to reinforcing the intestinal epithelial barrier, preventing the translocation of harmful microorganisms from the gastrointestinal tract to other body regions[47], thereby diminishing the risk of systemic infections. Through modulating these biological processes, probiotics can effectively reduce the incidence of various postoperative infections.

Table 1 Characteristics of the included studies

Ref.	Country	Number of included studies	Sample size	Supplementation time	Type of supplementation	Risk of bias tool, No. of high quality/total studies	Percentage of high-quality studies (%)	Investigated outcomes	Quality
Zeng *et al* [32], 2021	China	19	1975	Preoperative	Multi-strain Probiotics and synbiotics	Cochrane, 19/19	100	Total infections, UTIs, bacteremia, sepsis, SSIs, pneumonia, central line infection, peritoneal infection, intra-abdominal infection	High
Amitay *et al*[25], 2020	Germany	11	NR	Preoperative	Multi-strain Probiotics and synbiotics	NHBLI tool, 1/11	9	Total infections, sepsis	High
Rueda-Robles *et al*[43], 2022	Brazil	13	1535	Pre- and postoperative	Multi-strain Probiotics and synbiotics	Joanna Briggs Institute's critical assessment tools, 2/13	15	Sepsis, SSIs, pneumonia, intra-abdominal infection	High
Ye *et al* [31], 2023	China	16	1798	Preoperative	Multi-strain Probiotics and synbiotics	Jadad, 16/16	100	SSIs, pneumonia	High
He *et al* [29], 2013	China	6	361	Preoperative	Multi-strain Probiotics and synbiotics	Jadad, 5/6	83	Total infections, sepsis, SSIs, pneumonia, peritoneal infection, abdominal infection	High
An *et al* [26], 2022	Korea	20	1763	Preoperative	Multi-strain Probiotics and synbiotics	Cochrane, 6/20	30	UTIs, bacteremia, SSIs, pneumonia	High
de Andrade Calaça *et al*[28], 2017	Brazil	7	821	Pre- and postoperative	Multi-strain Probiotics	NR	NR	Total infections, Bacteremia, SSIs	Moderate
Chen *et al* [27], 2020	China	6	803	Preoperative	Multi-strain Probiotics	Jadad, 6/6	100	Total infections, UTIs, sepsis, SSIs, pneumonia, central line infection	Moderate
Persson *et al*[30], 2024	Brazil	10	1276	Pre- and postoperative	Multi-strain Probiotics	NR	NR	UTIs, SSIs, pneumonia	Moderate
Ouyang *et al*[19], 2019	China	13	1186	Pre- and postoperative	Multi-strain Probiotics	Cochrane, 11/13	84	Total infections, UTIs, SSIs, pneumonia	Moderate
Chen *et al* [3], 2024	China	10	NR	Preoperative	Multi-strain Probiotics	Cochrane, 2/10	20	SSIs	Moderate

NR: Not reported; UTIs: Urinary tract infections; SSIs: Surgical site infection.

This meta-analysis represents, to our knowledge, the inaugural comprehensive assessment of probiotic efficacy in mitigating post-colorectal surgery infections. Distinguishing features of our study include substantial sample size, a thorough examination of infectious outcomes, and the inclusion of subgroup and sensitivity analyses to bolster result credibility. The moderate-to-high level of evidence, as determined by the GRADE method, for the evaluated outcomes establishes a robust framework for comprehending the impact of probiotic administration on postoperative infectious complications. This study empowers healthcare providers to make more evidence-based decisions regarding the management of patients undergoing colorectal surgery. By facilitating the rapid translation of scientific research into clinical practice, it represents a significant advancement in the field. Despite its strengths, certain limitations warrant

Table 2 Overall and stratified analyses for the impacts of probiotics on post-surgical infections in patients undergoing colorectal cancer surgery

		Subgroups	Studies	Relative risk (95%CI)	I^2 (%)	*P* value	Publication bias
Total infections		Overall	6	0.40 (0.31-0.51)	56.1	0.04	0.31
	Supplementation type	Multi-strain Probiotics	3	0.50 (0.41-0.61)	0.0	0.39	
		Multi-strain Probiotics and synbiotics	3	0.31 (0.25-0.40)	0.0	0.56	
	Intervention time	Preoperative	4	0.31 (0.25-0.40)	0.0	0.77	
		Pre- and postoperative	2	0.52 (0.42-0.64)	0.0	0.85	
	Country	China	4	0.37 (0.26-0.52)	59.6	0.06	
		Other countries	2	0.44 (0.29-0.68)	59.7	0.11	
	Quality of studies	High	3	0.31 (0.25-0.40)	0.0	0.56	
		Moderate	3	0.50 (0.41-0.61)	0.0	0.39	
Urinary tract infections		Overall	5	0.44 (0.31-0.61)	0.0	0.66	0.009
	Supplementation type	Multi-strain Probiotics	3	0.43 (0.27-0.69)	16.2	0.30	
		Multi-strain Probiotics and synbiotics	2	0.44 (0.26-0.74)	0.0	0.86	
	Intervention time	Preoperative	3	0.38 (0.25-0.59)	0.0	0.57	
		Pre- and postoperative	2	0.52 (0.32-0.86)	0.0	0.49	
	Country	China	3	0.43 (0.27-0.59)	16.4	0.30	
		Other countries	2	0.45 (0.27-0.75)	0.0	0.89	
	Quality of studies	High	2	0.44 (0.26-0.74)	0.0	0.86	
		Moderate	3	0.43 (0.27-0.69)	16.2	0.30	
Bacteremia		Overall	3	0.41 (0.30-0.56)	0.0	0.91	0.80
	Supplementation type	Multi-strain Probiotics	1	0.40 (0.26-0.62)	-	-	
		Multi-strain Probiotics and synbiotics	2	0.42 (0.27-0.67)	0.0	0.70	
	Intervention time	Preoperative	2	0.42 (0.27-0.67)	0.0	0.70	
		Pre- and postoperative	1	0.40 (0.26-0.62)	-	-	
	Country	China	1	0.37 (0.16-0.86)	-	-	
		Other countries		0.42 (0.30-0.59)	0.0	0.74	
	Quality of studies	High	2	0.42 (0.27-0.67)	0.0	0.70	
		Moderate	1	0.40 (0.26-0.62)	-	-	
Sepsis		Overall	5	0.35 (0.25-0.44)	0.0	0.90	0.87
	Supplementation type	Multi-strain Probiotics	1	0.28 (0.17-0.47)	-	-	
		Multi-strain Probiotics and synbiotics	4	0.35 (0.25-0.50)	0.0	0.92	
	Intervention time	Preoperative	4	0.31 (0.23-0.43)	0.0	0.92	
		Pre- and postoperative	1	0.41 (0.22-0.78)	-	-	
	Country	China	3	0.31 (0.21-0.46)	0.0	0.78	
		Other countries	2	0.35 (0.23-0.53)	0.0	0.52	
	Quality of studies	High	4	0.35 (0.25-0.50)	0.0	0.92	

		Moderate	1	0.28 (0.17-0.47)	-	-	
Surgical site infection		Overall	10	0.56 (0.49-0.63)	0.0	0.71	0.94
	Supplementation type	Multi-strain Probiotics	5	0.56 (0.45-0.70)	0.0	0.70	
		Multi-strain Probiotics and synbiotics	5	0.56 (0.47-0.66)	5.8	0.37	
	Intervention time	Preoperative	6	0.55 (0.47-0.65)	3.2	0.39	
		Pre- and postoperative	4	0.56 (0.44-0.71)	0.0	0.78	
	Country	China	6	0.53 (0.44-0.63)	0.0	0.59	
		Other countries	4	0.60 (0.49-0.73)	0.0	0.64	
	Quality of studies	High	5	0.56 (0.47-0.66)	5.8	0.37	
		Moderate	5	0.56 (0.45-0.70)	0.0	0.73	
Pneumonia		Overall	8	0.38 (0.30-0.48)	0.0	0.89	0.74
	Supplementation type	Multi-strain Probiotics	3	0.61 (0.55-0.67)	5.1	0.34	
		Multi-strain Probiotics and synbiotics	5	0.36 (0.26-0.49)	0.0	0.97	
	Intervention time	Preoperative	5	0.35 (0.26-0.48)	0.0	0.98	
		Pre- and postoperative	3	0.42 (0.29-0.62)	0.0	0.37	
	Country	China	5	0.39 (0.29-0.59)	0.0	0.65	
		Other countries	3	0.36 (0.25-0.53)	0.0	0.82	
	Quality of studies	High	5	0.36 (0.26-0.49)	0.0	0.97	
		Moderate	3	0.41 (0.28-0.60)	5.1	0.34	
Central line infection		Overall	2	0.34 (0.14-0.81)	11.1	0.28	-
Peritoneal infection		Overall	2	0.42 (0.18-1.01)	0.0	0.89	-
Intra-abdominal infection		Overall	3	0.51 (0.25-1.04)	0.0	0.45	0.50
	Supplementation type	Multi-strain Probiotics and synbiotics	3	0.51 (0.25-1.04)	0.0	0.45	
	Intervention time	Preoperative	2	0.78 (0.28-2.02)	0.0	0.55	
		Pre- and postoperative	1	0.35 (0.13-0.97)	-	-	
	Country	China	2	0.78 (0.28-2.02)	0.0	0.55	
		Other countries	1	0.35 (0.13-0.97)	-	-	
	Quality of studies	High	3	0.51 (0.25-1.04)	0.0	0.45	

consideration. Although heterogeneity was minimal in most analyses, a notable degree of variability was observed among studies investigating total infections. This heterogeneity was not attributable to differences in supplementation type, intervention time, study quality, publication year, sample size, number of primary RCTs, or the proportion of trials with low ROB. However, geographical variations emerged as a potential source of the observed heterogeneity. A random-effects model was employed to mitigate the influence of heterogeneity on the pooled estimates. Among the examined outcomes, publication bias was most pronounced for UTIs. However, a trim-and-fill analysis indicated that the impact of publication bias on the combined estimate was minimal, suggesting the robustness of our findings. The included studies did not explore the effects of specific bacterial types, dosage, or follow-up duration, thereby limiting our capacity to conduct subgroup analyses based on these factors and identify the most efficacious interventions.

CONCLUSION

In conclusion, the present umbrella meta-analysis provides compelling evidence supporting the efficacy of probiotics in preventing SSIs, pneumonia, UTIs, bacteremia, and sepsis following CRC surgery. These findings underscore the potential for probiotics to enhance surgical recovery outcomes. However, further research is imperative to elucidate the optimal treatment regimen, including the most efficacious probiotic strains, appropriate dosages, and duration of

Table 3 Strength of evidence according to the GRADE

Outcome	No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative risk (95%CI)	Quality	Importance
Total infections	6 studies	Meta-analysis of RCTs	No serious	Serious[2]	No serious	No serious	None	0.40 (0.31-0.51)	Moderate (+)(+)(+)	Critical
Urinary tract infections	5 studies	Meta-analysis of RCTs	Serious[1]	No serious	No serious	No serious	None	0.44 (0.31-0.61)	Moderate (+)(+)(+)	Important
Bacteremia	3 studies	Meta-analysis of RCTs	No serious	No serious	No serious	No serious	None	0.41 (0.30-0.56)	High (+)(+)(+)(+)	Important
Sepsis	5 studies	Meta-analysis of RCTs	No serious	No serious	No serious	No serious	None	0.35 (0.25-0.44)	High (+)(+)(+)(+)	Critical
Surgical site infection	10 studies	Meta-analysis of RCTs	No serious	No serious	No serious	No serious	None	0.56 (0.49-0.63)	High (+)(+)(+)(+)	Critical
Pneumonia	8 studies	Meta-analysis of RCTs	No serious	No serious	No serious	No serious	None	0.38 (0.30-0.48)	High (+)(+)(+)(+)	Critical
Central line infection	2 studies	Meta-analysis of RCTs	No serious	No serious	No serious	Serious[3]	None	0.34 (0.14-0.81)	Moderate (+)(+)(+)	Critical
Peritoneal infection	2 studies	Meta-analysis of RCTs	No serious	No serious	No serious	Serious[3]	None	0.42 (0.18-1.01)	Moderate (+)(+)(+)	Critical
Intra-abdominal infection	3 studies	Meta-analysis of RCTs	No serious	No serious	No serious	Serious[3]	None	0.51 (0.25-1.04)	Moderate (+)(+)(+)	Critical

[1]Significant publication bias.
[2]Significant heterogeneity.
[3]CI include null effect or include appreciable harm or benefit.
RR: Relative risk; RCTs: Randomized clinical trials.

therapy.

FOOTNOTES

Author contributions: Han Y was responsible for conceptualization, methodology, investigation, writing-original draft, writing-review and editing, visualization; Wang Y was responsible for methodology, investigation, resources, software, formal analysis, data curation, writing original draft, visualization; Guan M was responsible for supervision, methodology, conceptualization, project administration, investigation, writing-review and editing. All authors have read and approved the final manuscript.

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