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ORIGINAL ARTICLE

Probiotics for preventing postoperative infection in colorectal cancer patients: a systematic review and meta-analysis

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Abstract

Purpose Postoperative infection has seriously affected the prognosis of cancer patients, while probiotics have been increasingly used to prevent postoperative infection in clinical practice. This study aimed to evaluate the preventive effect of probiotics on infection after colorectal cancer (CRC) surgery.

Methods Related clinical trial reports were collected from Pubmed, Embase, Cochrane Library as well as China National Knowledge Infrastructure (CNKI) databases. These reports were then strictly screened, and information as well as data were extracted. Finally, the enrolled studies were evaluated by systematic review and meta-analysis using STATA v11 and Revman v5.2.

Results Probiotics administration contributed to the reduction of overall infection rate after colorectal surgery, with a pooled odds ratio (OR) of 0.51 (95% CI: 0.38–0.68, $P = 0.00$). Meanwhile, the incidence of incision infection (pooled OR = 0.59, 95% CI 0.39–0.88, $P = 0.01$) and pneumonia (pooled OR = 0.56, 95% CI 0.32–0.98, $P = 0.04$) as well as the first flatus time (SMDs = − 0.70, 95% CI − 1.13–− 0.27, $P = 0.002$) were also reduced by probiotics. In addition, urinary tract infection, anastomotic leakage, and duration of postoperative pyrexia were also analyzed, which displayed no statistical differences compared with those of control.

Conclusion Probiotics have potential efficacy on preventing postoperative infection and related complications in cancer patients undergoing colorectal surgery.

Keywords Meta-analysis · Probiotics · Colorectal surgery · Postoperative infection

Introduction

Postoperative infection remains a clinically relevant problem, which may lead to higher recurrence rate, medical costs, and fatality rate [1, 2]. Often caused by the overgrowth of intestinal pathogens, postoperative infection could be inhibited by restoring the beneficial commensal microbiota [3]. What's more, increasing evidences have shown that the curative effect for cancer and other diseases can be improved by manipulating microbiota [4]. Probiotics refer to viable microorganisms that promote or support the balance of autochthonous microbial population in gastrointestinal tract [5], and their clinical values, especially their preventive effects on postoperative infection, have also been well examined [6, 7].

Colorectal cancer (CRC) is the third most common cancer and the fourth leading cause of cancer-related death worldwide [8]. In recent years, probiotics have been increasingly applied in the rehabilitation and prevention of CRC [9, 10], including the prevention of postoperative infection. It is verified that probiotics show excellent preventive effect on postoperative surgical site infection (SSI) in CRC patients [11–13]. Nonetheless, opposite or insignificant results are also

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reported in several studies [14–16], especially in those regarding complications such as postoperative pneumonia, urinary tract infection, and anastomotic leakage [11, 14, 17].

Therefore, it is necessary to conduct a systematic review and meta-analysis to get a better understanding of the preventive effect of probiotics on postoperative infection in CRC patients. In this study, trials concerning CRC patients undergoing colorectal resection with probiotic preparation were collected, and the preventive efficacy of probiotics on postoperative infection was evaluated.

Material and methods

This meta-analysis was conducted in strict accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 Checklist (http://www.prisma-statement.org/statement.htm) (Table S1).

Retrieval strategy and study inclusion and exclusion criteria

Pubmed, Embase, Cochrane Library, and CNKI were systematically retrieved from their inception to September 2017 using all combinations of "probiotics" or "intestinal flora" with "cancer," "neoplasm," "carcinoma," or "malignant" as keywords. Studies conforming to the following criteria were included: (i) probiotics were used for postoperative infection prevention, (ii) patients undergoing CRC surgery were studied, and (iii) the individual effect of probiotics on postoperative infection was investigated. Moreover, studies were excluded according to the following criteria: (i) reviews, comments, conference abstracts, letters, or non-clinical studies; (ii) probiotics were used in combination with prebiotics or as synbiotics; and (iii) researches lack of key data that odds ratio (ORs) or standard mean difference (SMD) could not be calculated. For multiple reports on the same trial, the one with more details was selected for analysis.

Research information, including titles, abstracts, and full texts, was extracted from the eligible reports independently by Xiaojing Ouyang and Qingfeng Li. One of them subsequently checked these screened articles for the second time. Any disagreement was solved through discussion or consultation with Mengjing Shi. References of the selected articles were checked to identify additional eligible studies. If necessary, we send e-mails to corresponding authors to get essential information and data for analysis.

Quality assessment

All the included studies were assessed according to the Cochrane Collaboration's tool for assessing risk of bias [18]. Studies containing the following information were considered to be of high quality: (i) adequate sequence generation, (ii) enough information of allocation concealment, (iii) enough information of blinding method, (iv) clear description about the intervention strategy of probiotics, (v) effective evaluation of postoperative effect and clear records, and (vi) without other possible factors leading to bias. Meanwhile, studies without mentioning the information above were excluded.

Data collection and conversion

Standardized forms were used to collect research information, including the following details: (i) publication information, surname of first author, and publication year; (ii) study design, especially the randomized, controlled, and blind design; (iii) patient characteristics, such as gender, cancer type, and surgical option; (iv) intervention strategy of probiotics in clinical practice and intervention period; (v) ORs and their 95% confidence intervals (CI) for related dichotomous data, or the means with standard deviations (SD) for continuous data. Notably, if there was no available ORs in original articles, ORs and their 95% CIs were calculated using subject's numbers or percentage in each group.

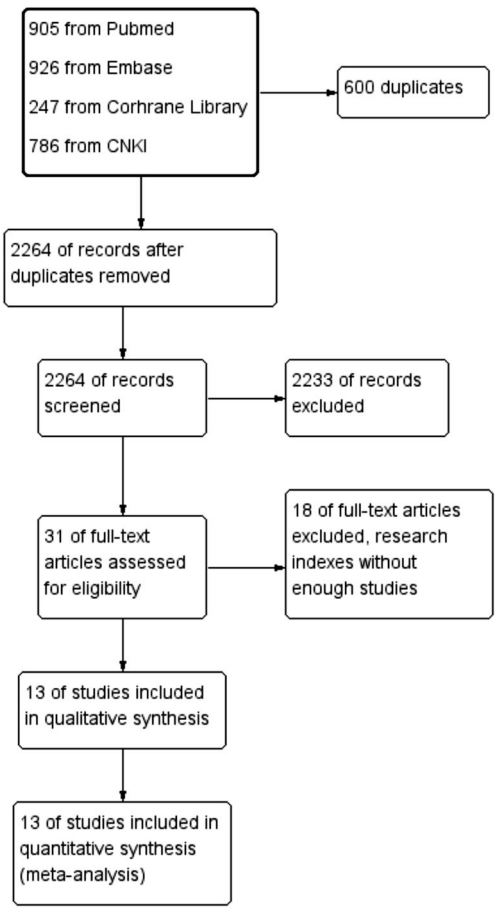

Fig. 1 The flowchart showed the selection of studies for meta-analysis

Table 1 Characteristics of included studies

Author	Year	Cancer type	Research design	Groups	Surgical options	Probiotics preparation	Dosage and regimen	Time for Intervention
Yu	2008	CRC	q-RCT	$N = 25$ (IG); $N = 25$ (Con)	CRR	Combined *Bifidobacterium* and *Lactobacillus* and *S. thermophilus* Tab (Golden Bifid®)	*B. longum* $\geq 4 \times 10^7$ CFU/day; *L. bulgaricus* $\geq 4 \times 10^6$ CFU/-day; *S. thermophilus* $\geq 4 \times 10^6$ CF-U/day; b.i.d., oral	− 7 to − 1 day, total 7 days
Xia	2010	CRC	q-RCT	$N = 30$ (IG); $N = 30$ (Con)	Elective CRR	*Lactobacillus acidophilus* LA11 (ProLac®), powder	$6–10 \times 10^8$ CFU/day; q.d., oral	at least 5 to − 1 day, total ≥ 5 days
Mangell	2012	CC	RCT, DB	$N = 32$ (IG); $N = 32$ (Con)	Elective CRR	*Lactobacillus plantarum* 299v (Probi®), with drink	1×10^{11} CFU/day; q.d., oral	− 8 to 0 days, and + 1 to + 5days, total 14 days
Zhang	2012	CRC	RCT, DB	$N = 30$ (IG); $N = 30$ (Con)	Elective CRR	Combined *B. longum*, *L. acidophilus*, and *E. faecalis* (Bifico®), Cap.	9×10^8 CFU/d; t.i.d., oral	− 5 to − 3days, total 3 days
Ding	2013	CRC	RCT	$N = 30$ (IG); $N = 30$ (Con)	CRR (laparoscopic)	Combined *Bifidobacterium* and *Lactobacillus* and *S. thermophilus* Tab (Golden Bifid®)	*B. longum* $\geq 6 \times 10^7$ CFU/day; *L. bulgaricus* $\geq 6 \times 10^6$ CFU/-day; *S. thermophilus* $\geq 6 \times 10^6$ CF-U/day; t.i.d., oral	− 3 to − 1 day, total 3 days
Chen	2014	CRC	RCT	$N = 35$ (IG); $N = 35$ (Con)	Elective CRR	Combined *Clostridium Butyricum* and *Bifidobacterium* Cap. (ChangLeKang®)	*C. butyricum* $\geq 3.7 \times 10^7$ CF-U/day; *Bifidobacterium* $\geq 3.7 \times 10^6$ C-FU/day; t.i.d., oral	− 5 to + 7 days, total 13 days
Sandahiro	2014	CC	RCT	$N = 100$ (IG); $N = 95$ (Con)	Elective colon cancer surgeries	Viable *Bifidobacterium bifidum* (Biofermin®), Tab	*B. bifidum* $\geq 1 \times 10^9$ CFU/day t.i.d., oral	− 8 to −2 days and + 5 to + 15 days, total 17 days
Aisu	2015	CRC	Controlled trial	$N = 75$ (IG); $N = 81$ (Con)	Elective CRR	Enterococcus faecalis T110, *Clostridium butyricum* TO-A, and *Bacillus mesentericus* TO-A (BIO-THREE®), Tab	*E. faecalis* T110:12 mg; *C. butyricum* TO-A:60 mg; *B. mesentericus* TO-A:60 mg; q.d., oral	(− 15~− 3) days to 0 days, and restarted form starting drinking water
Kotzampassi	2015	CRC	RCT, DB	$N = 84$ (IG); $N = 80$ (Con)	Elective colonic resection (open procedure)	Combination of *L. acidophilus* LA, 5, *L. plantarum*, *B. lactis* BB,12, and *Saccharomyces boulardii* (LactoLevure®)	*L. acidophilus* LA-5: 3.5×10^9 CFU/day ; *L. plantarum*: 1.0×10^9 CFU/day; *B. lactis* BB, 12: 3.5×10^9 CFU/day; *S. boulardii*: 3.0×10^9 CFU/day; b.i.d., oral or through nasogastric tube	− 1 day to + 14 days, total 16 days
Liu	2015	CRC (liver metastases)	RCT, DB	$N = 66$ (IG); $N = 68$ (Con)	CRR and liver metastases resection	*Lactobacillus plantarum*, *Lactobacillus acidophilus*, and *Bifidobacterium longum* (acid-resistant coating), Cap.	*L. plantarum* $\geq 2 \times 10^{11}$ CFU/-day; *L. acidophilus*, $11 \geq 1.4 \times 10^{11}$ CFU/day; *B. longum*, $88 \geq 1 \times 10^{11}$ CFU/day	− 6 to − 1day, and + 1 to + 10 days, total 16 days

Table 1 (continued)

Author	Year	Cancer type	Research design	Groups	Surgical options	Probiotics preparation	Dosage and regimen	Time for Intervention
Consoli	2015	CC	RCT	$N = 15$ (IG); $N = 18$ (Con)	Elective colon resection	Lyophilized *Saccharomyces boulardii* (BIOFLOR®), Cap.	5×10^7 CFU/day; q.d., oral	at least − 7 to − 1 day, total ≥ 7 days
Yang	2016	CRC	RCT, DB	$N = 30$ (IG); $N = 30$ (Con)	Confined CRR	*B. longum*, *L. acidophilus*, and *E. faecalis* (Bifico®), Cap.	*B. longum* $\geq 6 \times 10^7$ CFU/day, *L. acidophilus* $\geq 6 \times 10^7$ CFU/day, *E. faecalis* $\geq 6 \times 10^7$ CFU/day; t.i.d., oral or by gastric gavage	− 5 to + 7 days, total 13 days
Li	2016	CRC	RCT	$N = 40$ (IG); $N = 40$ (Con)	CRR	Combined *Bifidobacterium* and *Lactobacillus* and *S. thermophilus* (Golden Bifid®), Tab.	*B. longum* $\geq 6 \times 10^7$ CFU/day; *L. bulgaricus* $\geq 6 \times 10^6$ CFU/day; *S. thermophilus* $\geq 6 \times 10^6$ CFU/day; t.i.d., oral	− 5 to − 1 day, and + 1 to + 7 days, total 12 days

RCT randomized controlled trial, *q-RCT* quasi-randomized control trial, *DB* double-blind, *CRC* colorectal cancer, *CC* colon cancer, *IG* intervention group, *Con* control group, *CRR* colorectal radical resection, *Cap* capsules, *Tab* tablets

Statistical analysis

All statistical analyses were performed using STATA v11 software. In addition, the pooled ORs and SMDs were calculated to estimate the effect of probiotics interventions. Test of heterogeneity for each outcome was carried out using Cochran's Q test and Higgins I-squared statistic. P value (Q test) < 0.05 and/or $I^2 > 50\%$ indicated substantial heterogeneity, and a random effect model (Der Simonian and Laird method) was applied accordingly. In contrast, a fixed effect model (inverse variance method) was employed in the presence of mild or low heterogeneity ($P \geq 0.05$ and/or $I^2 < 50\%$). The 95% CI of a pooled effect measure overlapping 1 for ORs or 0 for SMD (Z-test, $P < 0.05$) indicated statistical insignificance. Publication bias was evaluated by Begg's bias indicator test using the funnel plot.

Results

We retrieved a total of 2864 articles, including 905 from Pubmed, 926 from Embase, 247 from Cochrane Library and 786 from CNKI. Six hundred duplicates were excluded from the initial articles and 26 relevant full texts were obtained after examining the publication types, titles, as well as abstracts. Finally, 13 studies were enrolled into our meta-analysis after checking research details according to our criteria [11–17, 19–24]. Later, all the references in the 13 studies were checked in case of missing eligible records, but no additional record was found. Figure 1 showed the flow diagram of this study.

Study characteristics

The primary information extracted from enrolled articles was summarized in Table 1. Data were extracted from 1186 participants, including 592 probiotics-treated patients and 594 controls. Twelve of the eligible articles were randomized controlled trials (RCTs) in design, whereas the other one was controlled clinical trials (CCTs). Quality assessment results of included studies were summarized in the risk of bias graph (Fig. 2).

Three of the included studies focused on colon cancer patients, while the remaining ten on CRC patients. Resection surgeries (either laparoscopic or open procedure) were performed in all studies, and the intervention start time ranged from at least 8 days to 1 day before operation, while the end time varied from 3 days preoperatively to 15 days postoperatively. In addition, three studies used single-strain probiotics, two used probiotics combined with two live microorganisms, and eight used triple or more strains of viable probiotics. Moreover, both capsules and tablets were adopted as dosage forms in five studies respectively, while three studies used powder forms. All probiotics were taken orally, except in

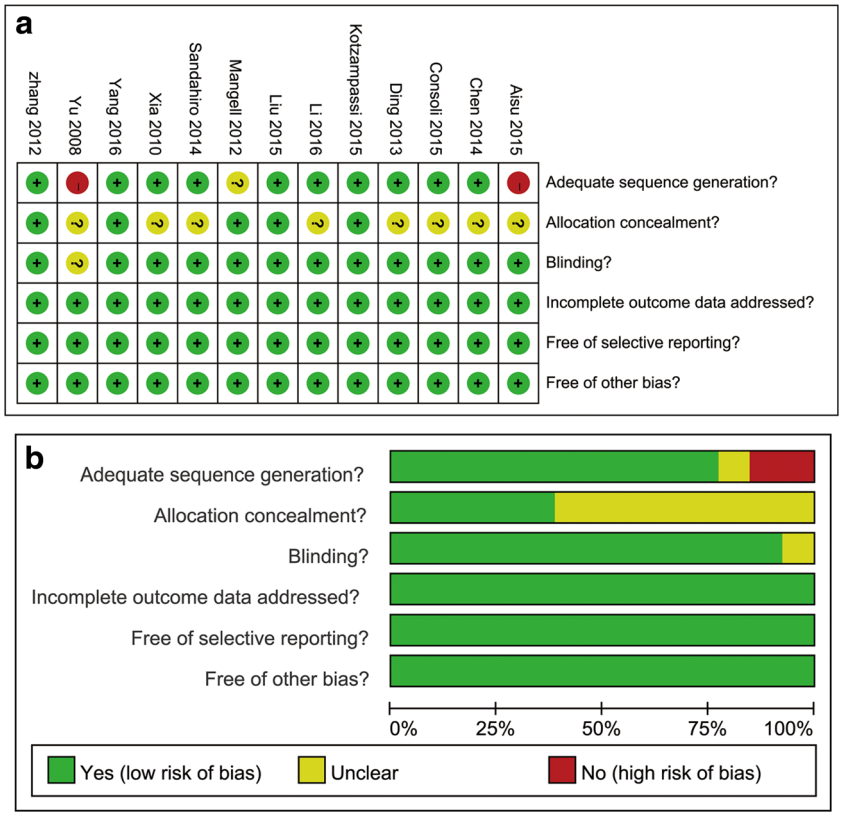

Fig. 2 Risk of bias summary and graph. **a** Risk of bias summary. **b** Risk of bias graph

some rare cases nasogastric tube was used for a short time. As to complications, nine researches evaluated the preventive effect of probiotics on incision infection, eight on anastomotic leakage, eight on urinary tract infection, and nine on pneumonia (Table 2). What's more, 5 studies evaluated the effect of probiotics on the first intestinal exhaust time and 4 on the duration of postoperative pyrexia (Table 3).

Meta-analysis results

Since no heterogeneity was observed among studies about the preventive effect of probiotics on overall postoperative infection rate ($P = 0.60$, $I^2 < 0.01\%$), we calculated the pooled OR and its 95% CI using a fixed effect model. Probiotics intervention could remarkably reduce overall postoperative infection rate, and the pooled OR was 0.51 (95% CI: 0.38–0.68, $P < 0.01$) (Fig. 3). Low heterogeneity was also observed in incision infection rate analysis ($P = 0.50$, $I^2 < 0.01\%$) and anastomotic leakage rate analysis ($P = 0.79$, $I^2 < 0.01\%$). Therefore, a fixed effect model was used to calculate the pooled ORs, which were 0.59 (95% CI: 0.39–0.88, $P = 0.01$) and 0.72 (95%CI: 0.35–1.47, $P = 0.37$) respectively, revealing that probiotics treatment would prevent postoperative incision infection but not anastomotic leakage (Fig. 4).

No heterogeneity was observed in the preventive effect analysis of probiotics on postoperative pneumonia and urinary tract infection (($P = 0.89$, $I^2 < 0.01\%$) and ($P = 0.77$, $I^2 < 0.01\%$), respectively). Thus, a fixed effect model was used to calculate their pooled ORs and 95% CIs. As a result, postoperative pneumonia (OR = 0.56, 95% CI: 0.32–0.98, $P = 0.04$) and urinary tract infection (OR = 0.61, 95% CI: 0.32–1.19, $P = 0.15$) could be prevented by probiotics intervention. However, the preventive effect of probiotics on urinary tract infection was not statistically significant (Fig. 4).

Substantial heterogeneity was found in the five studies evaluating the effect of probiotics on first intestinal exhaust time and four on the duration of postoperative pyrexia ($P = 0.003$, $I^2 = 75.1\%$; $P < 0.01$, $I^2 = 91.2\%$). Consequently, a random effect model was used to calculate the pooled SMDs. Compared with control group, probiotics intervention could shorter the first intestinal exhaust time and duration of pyrexia after surgery, for the pooled SMDs were − 0.70 (95% CI: − 1.13–− 0.27, $P = 0.002$) and − 0.68 (95% CI: − 1.49–0.12, $P = 0.096$), respectively. Nevertheless, the preventive effect of probiotics on duration of postoperative pyrexia was not statistically significant (Fig. 5).

Finally, the publication bias of included studies was assessed using funnel plots and Begg's tests. As shown in Fig. 6, the funnel plots were mainly symmetric. Besides, the P values of Begg's test in overall infection, incision infection and pneumonia analysis were 0.161, 0.835, and 0.754 respectively. Therefore, there was no obvious publication bias in our meta-analysis.

Table 2 Summary table of ORs and their 95% CI

Author	Year	Cancer type	OR	LL	UL	Recorded outcome
Yu	2008	Colorectal cancer	0.33	0.057	1.899	OI
			0.158	0.017	1.472	II
			0.967	0.058	16.192	UTI
			0.458	0.039	5.414	PP
Xia	2010	Colorectal cancer	0.651	0.155	2.45	OI
			1	0.13	7.605	AL
Mangell	2012	Colon cancer	0.619	0.157	2.444	OI
			1	0.06	16.713	II
			0.312	0.031	3.17	UTI
			1	0.06	16.713	PP
Zhang	2012	Colorectal cancer	0.222	0.054	0.914	OI
			2.071	0.178	24.148	AL
			0.224	0.024	2.136	PP
Ding	2013	Colorectal cancer	0.31	0.03	3.168	OI
			1	0.06	16.713	AL
Chen	2014	Colorectal cancer	0.848	0.276	2.612	OI
			0.75	0.262	2.151	II
			0.821	0.24	2.814	UTI
			0.837	0.26	2.699	PP
Sandahiro	2014	Colon cancer	0.934	0.487	1.793	OI
			1.007	0.485	2.094	II
			0.75	0.195	2.881	AL
Aisu	2015	Colorectal cancer	0.579	0.272	1.232	OI
			0.29	0.101	0.837	II
			0.527	0.094	2.967	AL
			1.095	0.067	17.815	UTI
			1.095	0.067	17.815	PP
Consoli	2015	Colon cancer	0.242	0.041	1.412	OI
			1.214	0.069	21.217	UTI
Kotzampassi	2015	Colorectal cancer	0.33	0.15	0.76	OI
			0.31	0.11	0.83	II
			0.13	0.01	0.99	AL
			0.62	0.17	2.27	UTI
			0.19	0.04	0.92	PP
Liu	2015	Colorectal cancer (liver metastases)	0.519	0.255	1.055	OI
			0.75	0.245	2.293	II
			0.101	0.012	0.82	UTI
			0.75	0.245	2.293	PP
Li	2016	Colorectal cancer	0.181	0.036	0.901	OI
			0.475	0.041	5.456	II
			0.487	0.042	5.599	AL
			0.475	0.041	5.456	PP
Yang	2016	Colorectal cancer	0.328	0.113	0.949	OI
			1	0.06	16.713	II
			2.071	0.178	24.148	AL
			1	0.13	7.605	UTI
			0.556	0.12	2.569	PP

OI overall infection, *II* incision infection, *AL* anastomotic leakage, *UTI* urinary tract infection, *PP* postoperative pneumonia, *LL* lower limit, *Ul* upper limit

Discussion

According to the Food and Agriculture Organization (FAO)/World Health Organization (WHO), probiotics are live microorganisms that confer a health benefit to the host when administered in adequate amounts [25]. Usually, probiotics are supplemented from the diet, which could help to maintain health and have the advantages of low cost and easy production. Notably, probiotics have become a possible and promising therapeutic approach in various clinical conditions, including infantile diarrhea [26], antibiotic-associated diarrhea [27], helicobacter pylori infection [28], inflammatory bowel disease [29], cancer [30], and surgical infection [31]. Lactobacillus, Bifidobacterium, Streptococcus, and Enterococcus are the most frequently used probiotics [32].

Postoperative infectious complications [33], including surgical site infection (SSI), urinary tract infection, septicemia, and pneumonia, always result in a prolonged duration of

Table 3 Summary table of the shorten effect of probiotics on duration of postoperative pyrexia and first flatus time

Author	Year	Cancer type	Probiotics group			Control group			Clinical index
			N	Mean (day)	SD	*N*	Mean (day)	SD	
Xia	2010	CRC	30	4.28	0.59	30	6.17	1.03	DOPP
Chen	2014	CRCr	35	4.5	1	35	4.6	1.2	DOPP
			35	2.5	1.7	35	4.5	2	FFT
Liu	2015	CRC	66	6.02	1.68	68	6.98	2.22	DOPP
Yang	2016	CRC	30	4.77	1.79	30	4.8	2.34	DOPP
			30	3.27	0.58	30	3.63	0.67	FFT
Yu	2008	CRC	25	3.02	1.11	24	3	0.78	FFT
Ding	2013	CRC (liver metastases)	30	2.7	0.54	30	3.5	0.6	FFT
Aisu	2015	CRC	75	2	1.1	81	2.8	2	FFT

DOPP duration of postoperative pyrexia, *FFT* first flatus time, *SD* standard deviation

postoperative pyrexia, extended hospital stays, and higher costs. In some severe cases, even cancer therapy will be interrupted giving rise to frequent recurrence and high mortality [34, 35]. It is believed that gut barrier disruption, intestinal permeability elevation, gut microbial imbalance, and host immunologic compromise are all factors that accounted for postoperative infectious complications [36]. What's worse, dysbacteriosis is prone to the colonization of drug-resistant bacteria, which may lead to refractory infection, such as Clostridium difficile infection. Plenty of studies have indicated that probiotics are able to lower the rates of postoperative infectious complications by enhancing intestinal microbial populations and reducing intestinal permeability [37].

In vitro studies suggest that probiotics will improve barrier function following *E. coli* infection or proinflammatory cytokines incubation, which directly interfere with pathogen adhesion and invasion [38]. In addition, probiotics will also enhance natural killer cell activity, induce cytokine secretion, and thereby contribute to dendritic cell maturation [39]. Furthermore, some probiotics play a significant role in regulating intestinal inflammatory response by inhibiting nuclear factor-κ B activation [40]. Besides, probiotics administration will also improve the levels of humoral immunity factors IL-2, IgA, IgM, and IgG, as well as CD4+ T cells [41]. In addition, by regulating serum IL-6 and C-reactive protein (CRP), probiotics attenuate stress response and consequently result in a reduced postoperative infection risk [15].

In this study, articles concerning probiotics treatment in CRC patients were systematically retrieved from online databases, and were strictly screened according to our inclusion/exclusion criteria. Research quality was then evaluated by our study group, and related information as well as data were

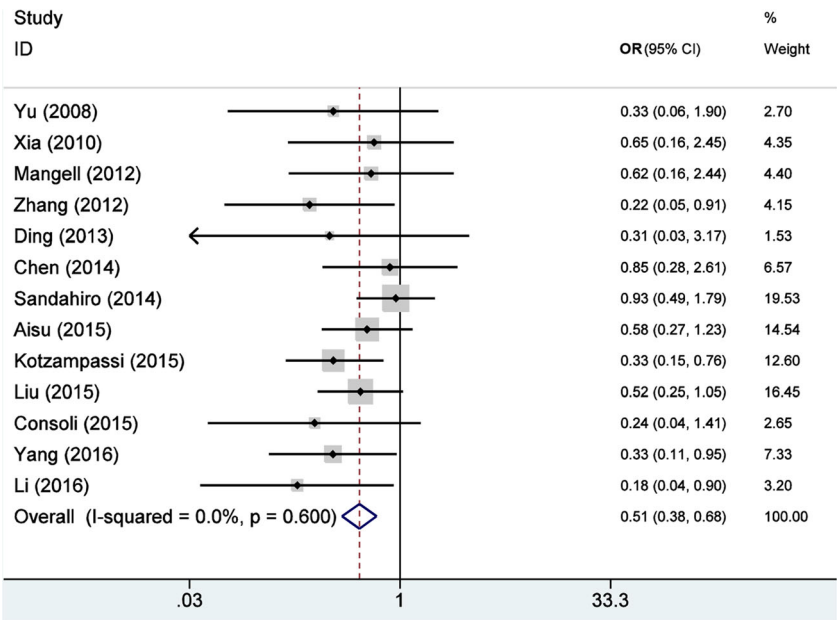

Fig. 3 Forrest plots of studies evaluating the preventive effect of probiotics on postoperative overall infection. Data from 13 records were pooled to calculate a pooled OR. The fixed effects analysis model showed the pooled OR for overall infection is 0.51 with 95% CI 0.38–0.68

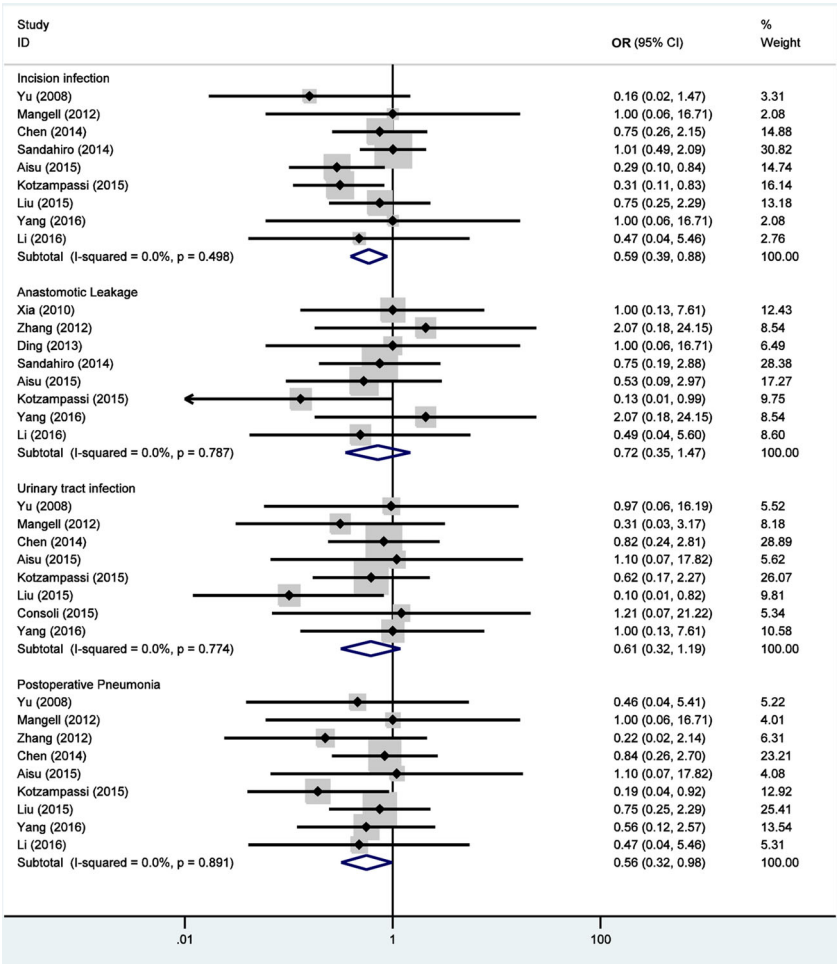

Fig. 4 Forrest plots of studies evaluating the preventive effect of probiotics on postoperative infection. As to incision infection, nine records were pooled and the fixed effects analysis model showed pooled OR 0.59 with 95% CI 0.39 to 0.88. As to anastomotic leakage, eight records were pooled and the fixed effects analysis model showed pooled OR 0.72 with 95% CI 0.35–1.47. As to urinary tract infection, eight records were pooled and the fixed effects analysis model showed pooled OR 0.61 with 95% CI 0.32–1.19. As to postoperative pneumonia, nine records were pooled and the fixed effects analysis model showed pooled OR 0.52 with 95% CI 0.32–0.98

extracted and analyzed. Our analysis results indicated that probiotics played a significant role in preventing infection after CRC surgery, including overall infection, incision infection, and pneumonia, which was a conclusion similar with the previous meta-analysis [42–45]. Besides, probiotics intervention could shorten the duration of postoperative

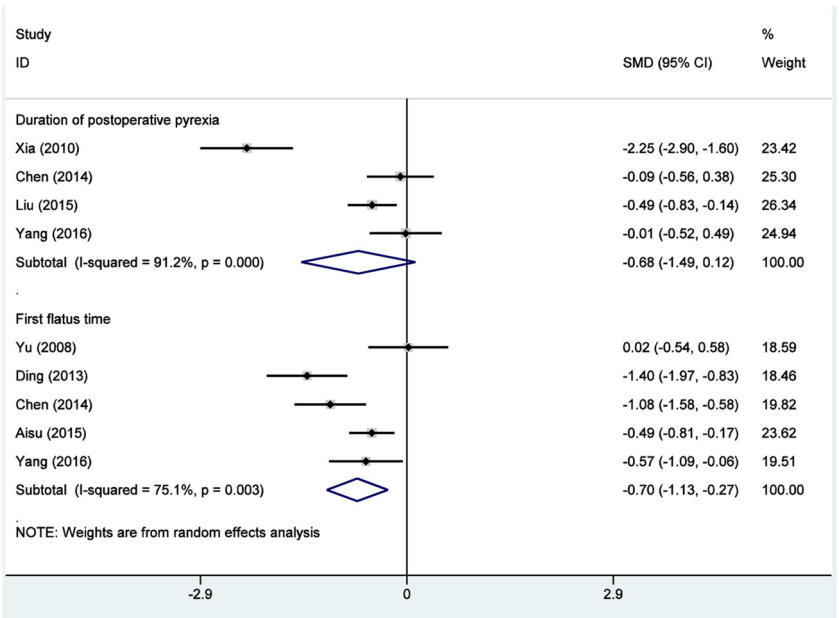

Fig. 5 Forrest plots of studies evaluating the preventive effect of probiotics on postoperative infection-related indexes. As to duration of postoperative pyrexia, data from four records were pooled to calculate a pooled effect. The random effects analysis model showed the pooled SMD is − 0.68 with 95% CI − 1.49–0.12. As to first flatus time, five records were pooled and the random effects analysis model showed the pooled SMD is − 0.70 with 95% CI − 1.13–− 0.27

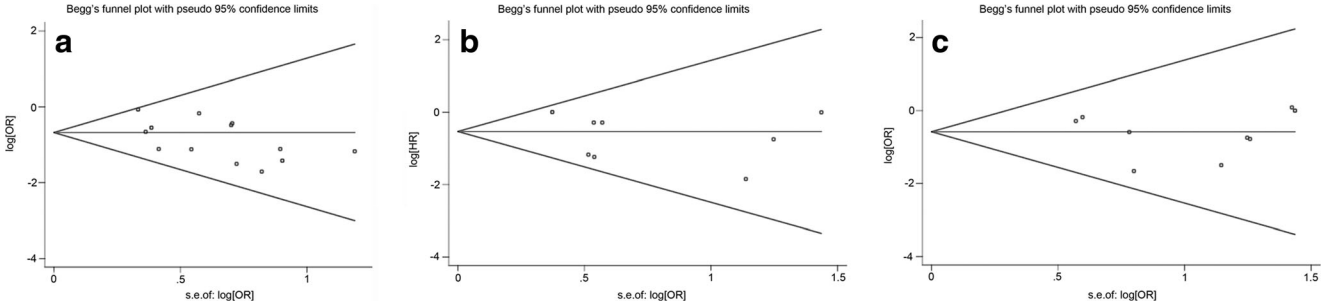

Fig. 6 Funnel plots of studies included in the three meta-analysis **a** overall infection, **b** incision infection, and **c** pneumonia

pyrexia and the first intestinal exhaust time, though the effect on the latter was not statistically significant. Our analysis also showed insignificant preventive effect of probiotics on anastomotic leakage and urinary tract infection, which was a different conclusion from the former work, collection of more, and updated researches may lead to the main differences. What's more, our meta-analysis only focused on the individual role of probiotics (prebiotics or synbiotics was not analyzed) on postoperative infection of colorectal cancer patients, which might also be a source of differences. Taken together, our results suggested that probiotics would prevent infection-related complications after radical colorectal resection, which might be beneficial to health-related quality of life [34, 46].

Attention should also be paid to conclusion interpretation. Firstly, all studies collected in this meta-analysis were English or Chinese in language, which might lead to the loss of valuable studies in other languages. Secondly, only the individual effect of probiotics was analyzed, and the situation that probiotics were used in combination with prebiotics or as synbiotics was not taken into consideration, which was a way to ensure analysis quality though incomplete understanding was inevitable. Thirdly, we abandoned some valuable data mentioned only in few studies for more credibility, including concentrations of serum antibody and inflammatory factors as well as microflora composition, which might reduce the comprehensiveness of our results. Fourthly, the probiotics strain, dose and dosage form in collected studies were not consistent, and probiotics treatment was combined with other pretreatment modes in some studies, which might induce certain confounding factors.

Undoubtedly, safety is a nonnegligible issue in clinical application of probiotics. Cancer patients are always immunocompromised, and probiotics intervention may lead to unpredictable adverse effects (AEs). No study enrolled in our meta-analysis has evaluated probiotics application safety in preventing postoperative infection. Additionally, four of included researches give a short description that no probiotics related AEs are observed. Wang et al. conducted a meta-analysis involving 11 studies to evaluate the efficacy and safety of probiotics for preventing chemoradiotherapy-induced diarrhea in patients with abdominal and pelvic cancer. Seven of these studies presented no probiotics related AEs, whereas four reported different AEs [47]. Generally, the safety of certain probiotics has been confirmed, but systematic studies assuring the safety of probiotics in immunocompromised people are lacking.

Conclusions

In conclusion, our systematic review and meta-analysis shows that probiotics can prevent infection after CRC surgeries, which is beneficial to surgical recovery. Nevertheless, multicenter trials with large sample size, especially those focusing on different medicine combination and safety issues, are still needed.

Author contributions Xiaojing Ouyang and Jian Wang conceived the study and planning. Xiaojing Ouyang, Qingfeng Li, Mengjing Shi, Dongsheng Niu, and Wenjing Song performed the literature search, studies selection, and data collection. Qinggong Nian and Xiangda Li performed statistical analyses and prepared figures and tables. Xiaojing Ouyang, Jian Wang, and Zhonghui Ding drafted the initial manuscript. Xianyin Ai and Zhonghui Ding gave methodological support and modify the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no interest conflict.

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