International Journal of Surgery 65 (2019) 61–69

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Review

The significance of probiotics in preventing radiotherapy-induced diarrhea in patients with cervical cancer: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Probiotics
Diarrhea
Cervical cancer

ABSTRACT

Aims: A systematic review and meta-analysis was designed to evaluate the efficacy and safety of probiotics for prevention of radiotherapy-induced diarrhea (RID) in patients with cervical cancer. Previous studies failed to give a comprehensive analysis of the efficacy and safety of probiotics in this point.

Methods: We searched the Cochrane Library, PubMed, EMBASE and Web of Science up to June 4, 2018. We also hand searched some studies included in previous reviews. Our primary outcome aims to compare the incidence of all Common Toxicity Criteria (CTC) grades of RID and adverse events (AEs) in both probiotics groups and placebo groups. Relative risk (RR) with its 95% confidence interval (CI) was used to compare the efficacy of probiotics in prevention of RID, and the pooled RRs were estimated using a fixed- or random-effect model; heterogeneity was assessed with Cochran's Q and Higgins I^2 test. Two reviewers assessed trial quality and extracted data independently. The analysis and bias for each of included studies were performed and assessed using Review Manager 5.2.

Results: Nine randomized, placebo-controlled studies (N = 1508 participants) were included for assessing the efficacy of probiotics. Compared with placebo groups, participants in probiotic groups experienced much lower incidence of RID with RR of 0.61 (95% CI 0.46–0.81; $P = 0.0007$). In addition, significant results were also observed in CTC grade ≥2 and grade ≥3 RID, with the pooled RRs of 0.52 (95% CI 0.30–0.98; $P = 0.02$) and 0.32 (95% CI 0.12–0.82; $P = 0.02$) respectively. Eight studies, included 1410 participants (726 consuming probiotics, 657 consuming placebo, 27 lost to follow-up), were used for the analysis of safety of probiotics. Of the 8 studies, 4 studies had no AEs caused by probiotics, while another 4 studies reported varying degrees of AEs during their treatment.

Conclusions: Probiotics may have a beneficial effect in prevention of RID generally, especially for Grade ≥2 or 3 diarrhea. Probiotics may be safe and rarely cause severe AEs during treatment.

1. Introduction

Probiotics were initially defined as live microbial feed supplements which beneficially affected the host improving its intestinal microbial balance in 1989 by Fuller R [1]. Recently, it has been reported that probiotics may have many benefits in preventing radiotherapy or chemotherapy induced gastrointestinal (GI) disease, including diarrhea during many therapies for tumors.

In particular, radiotherapy induced diarrhea (RID) is more and more common nowadays, with more abdominal and pelvic cancers treated by radiotherapy. It was reported that nearly 17,000 patients per year received radiotherapy in the UK [2]. Further, across the developed countries, an estimated 150,000 to 300,000 people were treated annually [3]. It was demonstrated that RID may worsen patients' quality of life, which could lead to interruptions or discontinuation of their treatment [4]. One of the possible mechanisms of RID may be that the malabsorption of lactose and bile acids, the changes of intestinal flora and intestinal motility may lead to impaired secretion, absorption and immune function of the digestive tract [5]. Radiation can give rise to changes in bacterial flora, vascular permeability of the mucosal cells and intestinal motility [6]. Furthermore, radiotherapy may change the composition of the native intestinal microflora, which is significant for metabolism of various intestinal enzymes and regulation of intestinal angiogenesis as well as immune functions that maintain the integrity of gut barrier [7]. Gut microbiota influences human health through an impact on the gut defense barrier, immune function, nutrient utilization

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https://doi.org/10.1016/j.ijsu.2019.03.015
Received 9 December 2018; Received in revised form 1 February 2019; Accepted 22 March 2019
Available online 27 March 2019
1743-9191/

and potentially by direct signaling with the gastrointestinal epithelium [8,9].

Up to now, several clinical trials have shown the efficiency of probiotics in preventing RID for patients with cervical cancer [10–20]. However, there exists some inconsistency in their dosages, bacterial strains and duration of therapy. Additionally, some studies failed to show positive curative effect and improvement of the quality of patients [13,14]. Besides, the safety of probiotics in preventing RID has not been demonstrated yet, because some adverse events (AEs), such as infection, septicemia, lactose intolerance, stomach pain and bloating, were observed in several studies [16,19,21,22].

Previous systematic reviews and meta-analyses showed that probiotics could reduce the incidence of diarrhea or bowel disease resulting from acute infections, antibiotic, chemotherapy or radiotherapy [23,24]. But few studies comprehensively analyzed and evaluated the efficacy and safety of probiotics in preventing RID for patients with cervical cancer. Thus, we conduct the present systematic review including eleven studies with low risk of bias to clear whether probiotics are effective in reducing incidence of RID. Nine randomized, placebo-controlled studies (N = 1508 participants) are included to assess the efficacy of probiotics. Eight studies, included 1410 participants (726 consuming probiotics, 657 consuming placebo, 27 lost to follow-up), are used to analyze the safety of probiotics.

2. Methods

2.1. Criteria for considering studies for this review

We included RCTs that compared the efficacy and safety of probiotics in preventing RID in cervical cancer patients who received radiotherapy and experienced RID. Studies will be excluded if: (1) they were trials about animals or non-human studies; (2) Patients having other primary tumors or received other treatment such as chemotherapy or surgical resection; (3) studies were abstracts, letters, editorials, expert opinions, reviews, case reports; (4) studies without sufficient data or did not meet our including criteria were excluded.

2.2. Types of outcome measures

2.2.1. The primary outcomes

(1) Incidence of radiotherapy-induced diarrhea in both probiotics groups and placebo groups;
(2) Efficacy of probiotics in decreasing use of loperamide.

2.2.2. Secondary outcomes

Incidence of the adverse events (AEs) in both probiotics groups and placebo groups.

2.3. Search strategy

We searched the Cochrane Library, PubMed, EMBASE and Web of Science up to June 4, 2018. We also manually searched the citation lists of included studies and previous systematic reviews identified to identify further relevant trials.

We searched the databases with English, including references of some literature we read.

2.4. Selection of studies

Two assessors independently screened the titles and abstracts of each studies searched through the databases. Once potential studies which may meet our including criteria were found, their full texts were obtained for further evaluation.

2.5. Data collection

Data for analysis were extracted by the second reviewer. The extracted contents included study demographics, published years, trial design, probiotic regimens outcomes, diarrhea grades (according to the National Cancer Institute Common Toxicity Criteria, now called the Common Terminology Criteria for Adverse Events (CTC) [25]), using a standardized form. Data that displayed as percentages were converted into number of people. In addition, some grades of diarrhea were merged and split for analysis. Furthermore, we collected the incidence of abdominal pain and the number of patients using loperamide as an anti-diarrheal medication respectively.

The quality of the included studies was scrutinized using the Cochrane Collaboration's “Risk of bias” tool and assessed according to the Cochrane Collaboration Reviewers' Handbook and strictly abiding by the standards of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) [26,27] and Assessing the Methodological Quality of Systematic Reviews (AMSTAR) guidelines. Data collected were input into RevMan 5.2 software for analysis [28].

2.6. Statistical analysis

The data of comparable outcome between probiotics groups and placebo groups were combined-analyzed, using the standard statistical procedures provided in RevMan 5.2 [28]. All variables in both treatment groups were measured with risk ratio (RR) with its 95% confidence intervals (CIs). The heterogeneity between studies was evaluated by the chi-square-based Q statistical test [29], with P_h value and I^2 statistic, ranging from 0% to 100%, to quantify the effect of heterogeneity. $P_h \leq 0.10$ was deemed to represent significant heterogeneity [30], and pooled MDs or RRs was estimated using a random-effect model (the DerSimonian and Laird method [31]). On the contrary, if statistical study heterogeneity was not observed ($P_h > 0.10$), a fixed-effect model (the Mantel–Haenszel method [32]) was used. The effects of outcome measures were considered to be statistically significant if pooled RRs with 95% CI did not overlap with 1. In addition, we also performed subgroup analysis for the pooled results of the efficacy of probiotics versus placebo in prevention of RID for patients with cervical cancer according to different CTC grades.

3. Results

3.1. Included studies and study characteristics

We excluded 36 full articles after thorough evaluation. In our excluding studies, the study of Scartoni D 2015 was excluded because its objects included patients with diagnosis of endometrial, cervical, anal canal, colorectal and prostate cancer. And there are no sub-results about cervical cancer [35]. Nine randomized, placebo-controlled studies (N = 1508 participants) were included for assessing efficacy. Among them, two studies graded diarrhea according to toxicity criteria of the World Health Organization [12,13]. Four studies graded diarrhea according to the Common Toxicity Criteria of the National Cancer Institute [10,11,14,15]. Diarrhea was not graded and was only reported with the overall incidence in three studies [16,19,20].

Eight studies, included 1410 participants (726 consuming probiotics, 657 consuming placebo, 27 lost to follow-up), were used for the analysis of safety of probiotics. Of the 8 studies, 4 studies reported no Adverse Events (AEs) caused by probiotics [11–14], while another 4 studies reported varying degrees AEs during their treatment [16,19,21,22].

The search process and strategy were displayed according to a flow diagram (Fig. 1). Further characters of the eligible studies were presented in Table 1 and Table S1. Eight studies were excluded for review articles. Eight studies were excluded for not about cervical cancer. In addition, 20 studies were excluded for wrong aims and interventions.

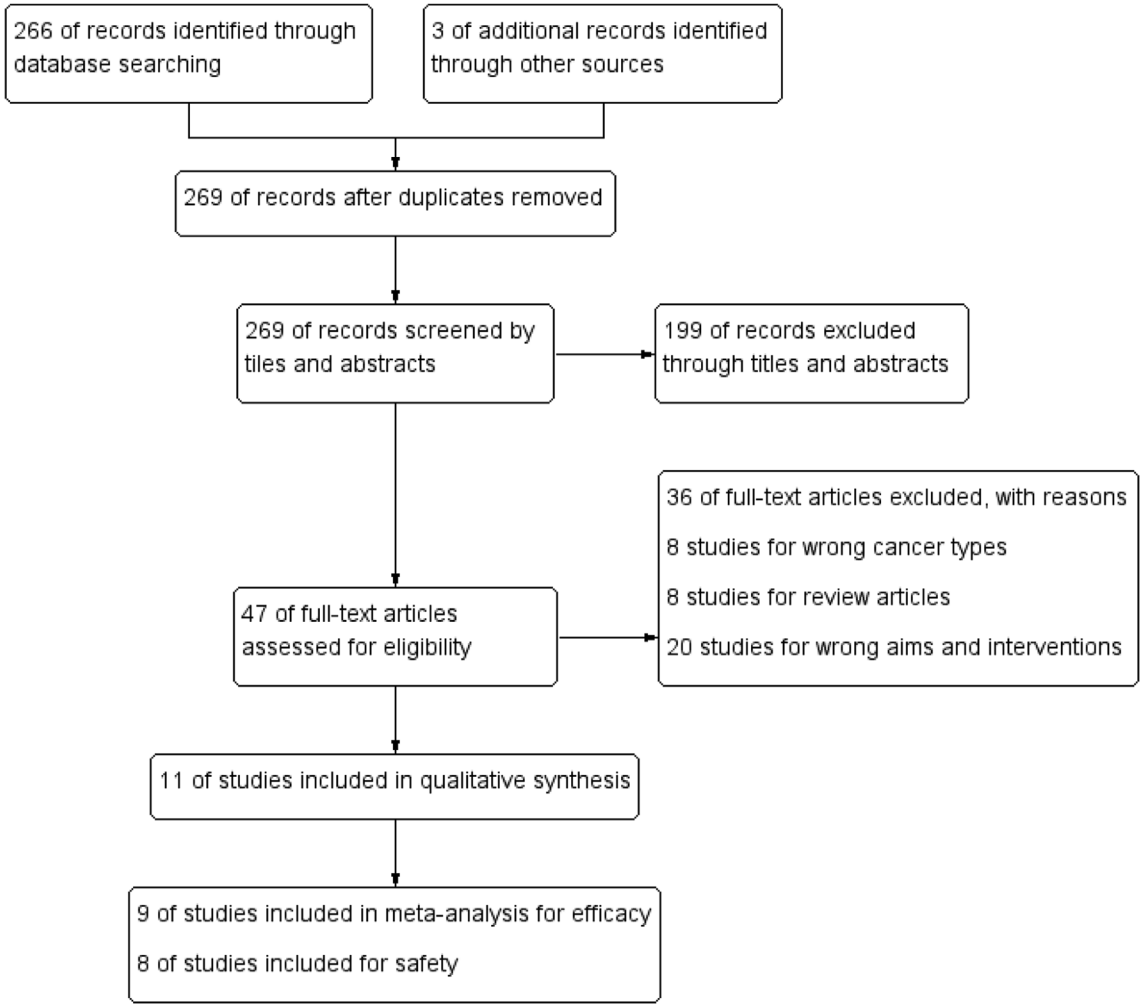

Fig. 1. Flow diagram of the search process and strategy for the efficacy and safety of probiotics for prevention of radiotherapy-induced diarrhea in patients with cervical cancer.

3.2. Quality assessment

In order to further identify the risk of bias of our including studies, we generated risk of bias graphs. The risk of bias item for each included study is displayed in Fig. 2 and the risk of bias for each RCT is presented as percentages across all included studies in Fig. 3. The risk of bias graphs indicated generally good methodological quality. As Fig. 3 showing, low risk of bias was found in mainly in selection bias and reporting bias. High risk of bias was mainly about attrition bias and intention-to-treat analysis. Unclear risk of bias was mainly observed in detection bias and other bias.

"Systematic reviews of adverse effects: framework for a structured approach" reported by Loke YK et al., 2007 was used for the quality assessment of studies for the safety analysis. It detected that the definition of AEs of many studies were not clear and reporting bias were evidently, which made the measuring of AEs a puzzle.

3.3. Efficacy of probiotics

3.3.1. Efficacy of probiotics in preventing RID

As Fig. 4 displaying, compared probiotics groups with placebo groups of incidence of RID in patients with cervical cancer, almost half reduction was found in overall incidence of RID in probiotics groups, with pooled RR of 0.61 (95% CI 0.46–0.81; $P = 0.0007$), which indicated that probiotics was effective in preventing RID of cervical cancer patients. The pooled analysis was estimated using random-effect model because significant heterogeneity ($P_h = 0.003$ and $I^2 = 66\%$) between studies was found.

3.3.2. Efficacy of probiotics in preventing grade ≥ 2 RID

We also analyzed the efficacy of probiotics in preventing CTC grade ≥ 2 diarrhea. As shown in Fig. 5, significant reduction of incidence of grade ≥2 RID was observed, with pooled RR being 0.52 (95% CI 0.30–0.89; $P = 0.02$). The result indicated that the use of probiotics reduced nearly half of the incidence of RID for patients with cervical cancer. Considering the significant heterogeneity ($P_h = 0.10$ and $I^2 = 57\%$), a random-effect model was used.

3.3.3. Efficacy of probiotics in preventing grade ≥ 3 RID

In order to explore the efficacy of probiotics futher in higher grade of diarrhea, we identified and compared the incidence of grade ≥ 3 RID in patients with cervical cancer. As shown in Fig. 6, significant reduction of incidence of grade ≥3 RID was observed, with pooled RR being 0.32 (95% CI 0.12–0.82; $P = 0.02$). The result indicated that more than half of reduction in the incidence of RID for patients with cervical cancer was found. Considering the significant heterogeneity ($P_h = 0.0002$ and $I^2 = 82\%$), a random-effect model was used.

3.3.4. Efficacy of probiotics in decreasing use of loperamide

Additionally, to further explore the safety of probiotics, we pooled analyzed the number of patients used loperamide as an anti-diarrheal medication and incidence of abdominal pain in both groups. As Fig. 7,

Table 1
Characteristics of included studies for analysis of efficacy.

Study	Country	Design	Participants	Interventions and Comparisons	Outcomes
Demers M et al., 2014[$]	Canada	Randomized parallel-group, placebo-controlled trial	Patients with rectal, cervical, endometrial or prostatic cancer were treated between 2006 and 2010 (n = 246).	Standard and High dose probiotics (*Lactobacillus acidophilus* and *Bifidobacterium longum*) vs. placebo	Time of appearance and grade of Diarrhea; other digestive symptoms.
Chitapanarux I et al., 2010*	Thailand	Prospective, randomized, double-blind, placebo-controlled study	Patients undergoing pelv- ic radiotherapy concurrent with weekly cisplatin (n = 63); FIGO stage IIB and IIIB squamous cell carcinoma of cervix.	Placebo and probiotics (*Lactobacillus acidophilus* plus *Bifidobacterium bifidum*) (n = 32) (infloran) vs. Placebo (n = 31)	Incidence of diarrhea, anti-diarrhea drug used, stool, WCC in stools, red blood cells in stools, median overall time, median weight change.
Castro MG et al., 2009*	USA	Randomized, double-blind, placebo-controlled trials	Radiation-induced bowel damage patients with gynaecologic cancer (n = 40).	Probiotics (*Lactobacillus casei* Shirota e o *Bifidobacterium breve*) (n = 20) vs. Placebo (n = 20).	Daily stool consistency (Bristol scale); Incidence of diarrhea, defined by a CTC of 2 or greater, or the need for loperamide.
Giralt J et al., 2008*	Spain	Double-blind, placebo-controlled randomized clinical trial in two parallel groups	Female patients with a diagnosis of endometrial adenocarcinoma or advanced cervical squamous cell carcinoma (n = 85)	Probiotics (*Lactobacillus casei DN-114,001*, *Streptococcus thermophilus* and *Lactobacillus delbrueckii*, subsp. *Bulgaricus*) vs. Placebo	Incidence of diarrhea; Incidence of loperamide use; Mean time to diarrhea symptoms; Stool consistency; Median time before loose stools.
NCT01706393. 2012	South Korea	Double-blind, parallel-arm RCT	26 patients receiving pelvic/abdominal RT	Arm 1: Probiotics - 1 tablet twice a day for 6 weeks (including during 5 weeks of RT) Arm 2: Identical placebo	Primary: Change in intestinal microbiome; Secondary: Diarrhea (according to CTCAE) and GI symptoms (GSRS).
NCT02351089. 2015	Sweden	Double-blind, parallel-arm RCT	200 women with gynaecological cancer undergoing primary or postoperative RT	Arm A: Probiotic capsule Arm B: Placebo	Primary: Change in incidence of loose/watery stools (baseline to 10 weeks) Secondary: Not stated
Delia P et al., 2007[$]	Italy	Double-blind, randomized, parallel-group, placebo-controlled trial	Patients who underwent adjuvant post-operative radiation therapy after surgery for sigmoid, rectal, or cervical cancer (n = 490).	Probiotics VSL#3 (*Lacto- bacillus* subsp. *Bulgaricus*, *Bidobacterium*, *Streptococcus salivarius* subsp. *thermophilus*) vs. Placebo.	Incidence of diarrhea; daily bowel movements; mean time to the use of loperamide.
Okawa T et al., 1993[△]	Japan	Randomized, parallel-group, controlled trial	Patients with FIGO Stage IIIB Squamous cell carcinoma of the uterine cervix (n = 213).	Probiotics LC9018 (Yakult, prepared from *Lactobacillus casei*) (n = 102) vs. Placebo (n = 111).	Incidence of diarrhea; incidence of abdominal pain.
Salminen E et al., 1988[△]	Finland	Randomized parallel group study (with no treatment group)	Patients with diagnosis of cervix or uterus carcinoma (age: 40–75 years) (n = 24).	Probiotics (*Lactobacillus acidophilus bacteria*) (n = 11) vs. Placebo (dietary counseling) (n = 10).	Incidence of diarrhea, flatulence and loss of appetite.
Mansouri-Tehrani HS et al., 2016[△]	Iran	3-arm randomized placebo-controlled trial	Adults undergoing pelvic RT (Gender: 58.2% male, Age: 20–85 years (mean 62 years, SD = 14.8 years)) (n = 67).	CT/RT received by 26/67 participants with rates across groups as follows: 11.9% (Probiotic group); 13.4% (Probiotic + honey group); 13.4% (Placebo group)	GI toxicity: Diarrhea (CTCAE v2.0); Other review outcomes:Medication for symptom control; Other study outcomes: Stool frequency and consistency (Bristol scale); Duration of follow-up: During RT only.
Linn YH et al., 2018*	Myanmar	Randomized Double-Blind Placebo-Controlled Study	Patients receiving external beam pelvic radiotherapy with or without concurrent chemotherapy were randomized into probiotic or placebo groups (n = 54).	Probiotics (*Lactobacillus acidophilusLA-5 plus Bifidobacteriumanimalis* subsp. *lactisBB-12*) (n = 26) vs. Placebo (identically appearing capsules containing starch) (n = 28).	Incidence of mild-to-moderate and severe diarrhea; the use of loperamide; the difference in grade 2 abdominal pain and episodes of abdominal pain in days.

*Diarrhea was graded according to the Common Toxicity Criteria of the National Cancer Institute.
[$] Diarrhea was graded according to toxicity criteria of the World Health Organization (similar to the CTC of the NCI).
[△]Diarrhea was not graded and was only reported with the overall incidence.
The National Cancer Institute Common Toxicity Criteria; NCI CTC version 2.0 (grade 0 = none; grade 1 = increase of < 4 stools/day over pre-treatment; grade 2 = increase of 4–6 stools/day, or nocturnal stools; grade 3 = increase of ≥7 stools/day or incontinence or need for parenteral support for dehydration; grade 4 = physiologic consequences requiring intensive care, or hemodynamic collapse).

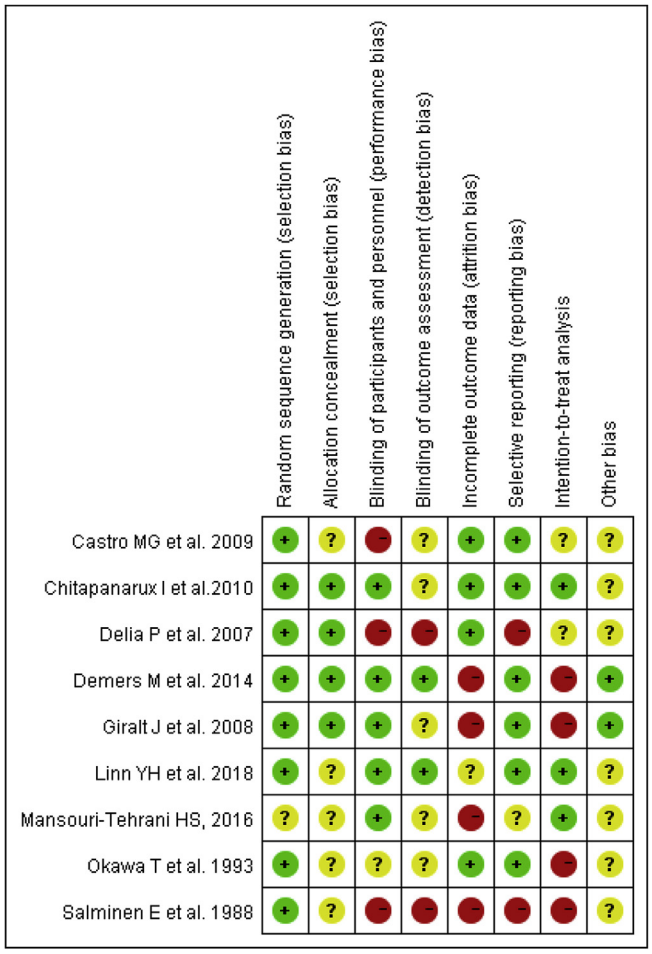

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

the number of patients used loperamide was more than half reduction in probiotics groups, with pooled RR of 0.43 (95% CI 0.29–0.64; $P < 0.0001$). No difference was found in the incidence of abdominal pain, with pooled RR of 0.45 (95% CI 0.13–1.61; $P = 0.22$) (Fig. 8).

3.3.5. *The pooled results of subgroup analysis for the incidence of different grade diarrhea*

In addition, we also performed subgroup analysis for the pooled results of the efficacy of probiotics versus placebo in prevention of RID for patients with cervical cancer according to different CTC grades. As Table 2 showing, compared probiotics groups with control groups in the incidence of different grade diarrhea, significant results were observed in grade 1, grade 4, grade ≥2 and grade ≥3, with the pooled RRs of 1.63 (95% CI 1.17–2.27; $P = 0.004$), 0.25 (95% CI 0.06–0.97; $P = 0.04$), 0.52 (95% CI 0.30–0.89; $P = 0.02$) and 0.32 (95% CI 0.12–0.82; $P = 0.02$). However, we noted that the result of grade 1 was contrary with others. No significant result was found in other grade diarrhea.

3.4. *Safety of probiotics*

Eight studies were included to analyze the safety of probiotics. As Table S1 showing, of the eight studies, four studies reported no Adverse Events (AEs) caused by probiotics [11–14], while another four studies reported varying degrees AEs during their treatments [16,19,21,22]. The exact number of patients suffering AEs was not clear, for some studies only gave the incidence of AEs without stating study group or control group. In these studies, a total of 132 experienced various AEs they defined. In addition, the incidence of AEs was 35.8% (59 in 165) in probiotics group and 39.3% (53 in 135) in placebo group respectively.

Okawa T et al. reported one death during radiation therapy. In addition, 9 patients receiving probiotics and 1 patients receiving placebo experienced fever respectively; the incidence of Anorexia were 27 of 102 in probiotics group and 42 of 111 in control group [19]. In the study of Demers M et al., no septicemia was recorded although a few cases of neutropenia occurred during treatment, but the incidence of neutropenia was not given [13]. Urbancsek H reported that severe AEs were not observed in his study, but three patients reported adverse events in both two groups. In the Antibiophilus group, three patients reported mild to moderate gastrointestinal problems while in the placebo group, two patients reported moderate to severe gastrointestinal events and one patient observed a mild labial oedema [22]. In the study by Henriksson, one patient displayed a worse reaction due to lactose intolerance. Mansouri-Tehrani HS reported that 3 probiotics users reported stomach pain and bloating, and 45 patients complained of bloating (19 patients of the probiotic group, 16 patients of the probiotic plus honey group and 10 patients in the placebo group). In short, based on the literature there is no statistically significant association of probiotics with any adverse effects in patients receiving radiation for cervix cancer.

3.5. *Publication bias*

Funnel plot was conducted for assessing the publication bias of included literature and we could roughly assess the publication bias by seeing whether the shape was of any obvious asymmetry. The funnel plot showed no clear evidence of publication bias with regard to the effect on overall incidence of RID (Fig. 9).

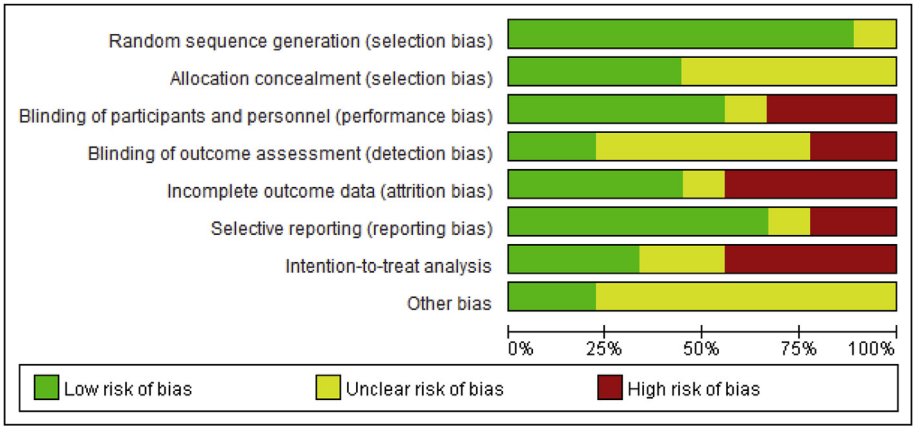

Fig. 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

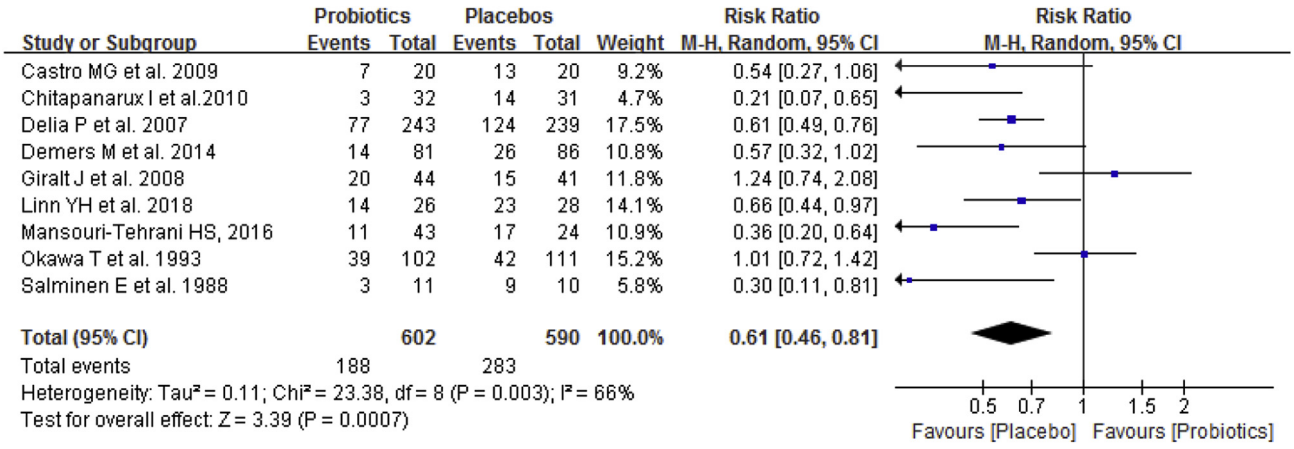

Fig. 4. Forest plot comparing probiotics with placebo with respect to incidence of radiotherapy-induced diarrhea in patients with cervical cancer.

4. Discussion

In recent years, the diarrhea-preventing effect of probiotics aroused wide interest because of its safety and cost effectiveness. RID is troublesome and has long-term consequences, which makes prevention worthwhile. The probiotics may delay the onset of diarrhea for about 3 days compared to placebo. In one RCT from Linn YH 2008, it was reported that diarrhea occurred after a mean dose of 29 Gy in the probiotic group [15]. Probiotics could reduce all grades of abdominal pain and can significantly reduce the episode of abdominal pain in days. The use of probiotics may increase the tolerance of the intestine to the higher doses of radiation and decrease the severity of radiation-induced enteritis [15].

Up to now, the exact underlying mechanisms of the effect of probiotics on preventing RID are not yet well studied. Some proposed mechanisms may explain this effect. One of the possible mechanisms may be recovering or repairing of gastrointestinal micro-ecological environment dysbiosis [33]. According to Chase D et al. [34], the core human microbiome is variable, depending on amyriad of factors that can impact the microbiome composition include cancer, chemotherapy, and radiation treatment, all of which can contribute to gastrointestinal and vaginal symptoms in cancer patients (Fig. S1). These factors that impact the gut and vaginal microbiomes (GI) can result in toxicity during cancer and cancer-related treatment. Cancer treatment, environmental factors, and pre-existingmedical conditions can alter the GI microbiota and cause GI symptoms like nausea, vomiting, diarrhea, constipation, bloating, and abdominal pain. The vaginal microbiome of a healthy female is dominated by Firmicutes, specifically Lactobacilli spp. Perturbations of the vaginal microbiota can contribute to vaginal symptoms including pain, sexual dysfunction, and urinary symptoms (Fig. S2). The relationship between probiotic, pathogenic, and commensal microbiota in the gut and vagina is much complex. At both mucosal sites, probiotic bacteria have beneficial functions including lowering the pH locally, bolstering mucosal immunity by interacting with IgA and altering antimicrobial peptide (AMP) secretion, blocking pathogen growth in the mucus layer, and blocking pathogen adhesion to epithelial cells. In addition, probiotic bacteriamay serve a beneficial role by enhancing commensal colonization. In both the gut and vagina, these beneficial functions help to enhance epithelial barrier function (Fig. S3). It was demonstrated that probiotics could lower the intestinal pH thereby setting the barrier to the potential pathogens. They may also cause down-modulation of the severity of intestinal inflammation by triggering and regulating the function of immune cells [13]. Other mechanisms are down-modulation of apoptosis which is regarded as the main factor responsible for the radiation-induced injury of the intestinal epithelium, up-regulation of the innate immune response in the gut which gives protection against intestinal colonization by invasive pathogens [5]. Probiotics also could stimulate lactase production, which helps lactose digestion because lactase may be reduced or loss due to the damage to the intestinal villi [5].

Previous studies and systematic reviews showed that probiotics could reduce the incidence of diarrhea or bowel disease resulting from acute infections, antibiotic, chemotherapy or radiotherapy [23,24]. But few studies comprehensively analyzed and evaluated the efficacy and safety of probiotics in preventing RID for patients with cervical cancer. Since bloating may be a side effect of probiotics use, Mansouri-Tehrani HS et al. showed that patients taking probiotics suffered from bloating more than the control group during the treatment [16]. However, the severity of the symptom was not enough to discontinue the use of probiotics. In the similar studies that have investigated effects of probiotics on diarrhea, bloating has not evaluated.

In current systematic review, we identified 11 RCTs to evaluate the efficacy and safety of probiotics in preventing RID in patients with cervical cancer. Our analysis results showed that probiotics could reduce the incidence of RID regarding to RR of 0.61 (95% CI 0.46–0.81; $P = 0.0007$). Significant efficacy of probiotics were also observed in CTC grade ≥2 and grade ≥3 RID respectively. In addition, significant results were also observed in grade 1, grade 4. However, we noted that

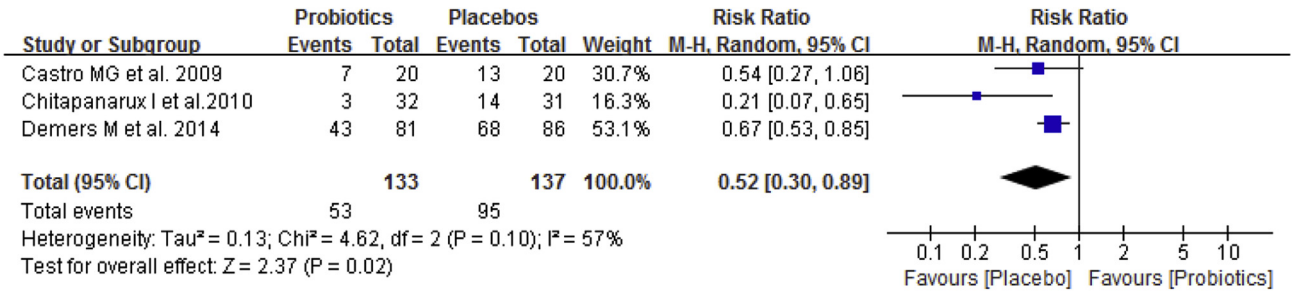

Fig. 5. Forest plot comparing probiotics with placebo with respect to incidence of CTC grade ≥2 radiotherapy-induced diarrhea in patients with cervical cancer.

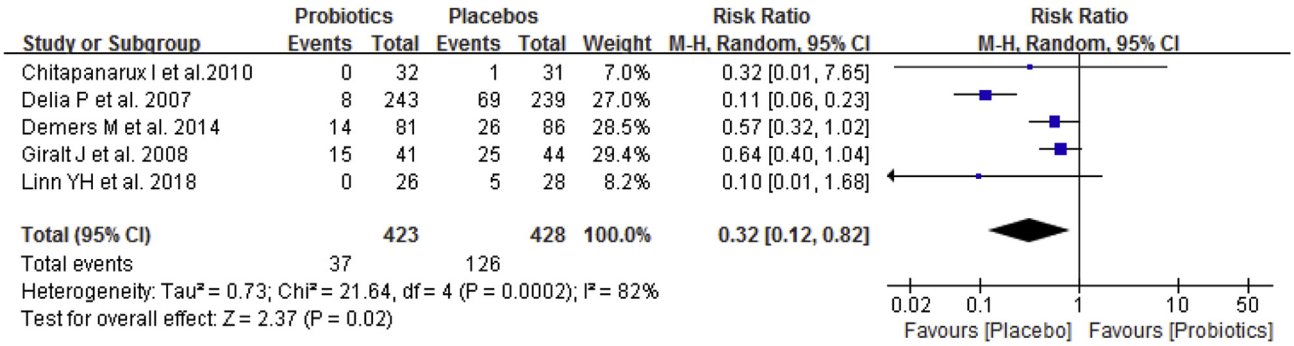

Fig. 6. Forest plot comparing probiotics with placebo with respect to incidence of CTC grade ≥3 radiotherapy-induced diarrhea in patients with cervical cancer.

in diarrhea of grade 1, the incidence of diarrhea in probiotics group was higher than placebo group, which was contrary with other results. Though no significance was observed in many subgroups we conducted as Table 2, we could roughly come to the conclusion that probiotics seems more effective or only effective in higher grade of diarrhea, for the significant results were found in subgroups of grade ≥2, ≥ 3 and 4, not in other subgroups of lower grades. Additionally, our results showed that the number of patients used loperamide as an anti-diarrheal medication was much less in probiotics group. The number of patients used loperamide was more than half reduction in probiotics groups, with pooled RR of 0.43 (95% CI 0.29–0.64; $P < 0.0001$). There was no difference in the incidence of abdominal pain in both groups. For the safety of probiotics in preventing RID of cervical cancer patients, though there was no enough data for pooled analysis, based on the literature there is no statistically significant association of probiotics with any adverse effects in patients receiving radiation for cervix cancer. Thus we may feel relieved for the safety of probiotics. However, further well designed studies were needed to explorer the actual safety of probiotics in clinics. As one widely accepted four levels of clinical treatment evidence in the scientific and health care community, this analysis has an evidence of level 1 (defined as randomized controlled trials–includes quasi-randomized processes such as alternate allocation).

There were also other outcomes in included studies, such as stool consistency and mean daily number of bowel movements. However, because of much too inconsistency and poor homogeneity, these outcomes were not been assessed in this meta-analysis.

There were several limitations for the present meta-analysis. One of main limitations was the inconsistency of intervention programmes and duration of intervention. The treatment duration ranged from 3 weeks to 10 weeks [13,15]. In addition, many studies failed to report their follow-up time or duration. This limitation led to our failure of subgroup analysis to further explore the efficacy and safety of probiotics in short-term and long-term. Besides, in order to detailed and systematically assess and analyze the efficacy of probiotics for radiotherapy-induced diarrhea and support credible evidence, in this meta-analysis, we only strictly select RCTs that reported incidence of diarrhea according to CTC. Thirdly, though RCTs were included in our analysis, the sample size of many studies was small. This may lead to any bias in these studies. Fourthly, probiotics include many strains and different probiotic strains may have different efficacy and safety in treatment. We did not conduct subgroup analysis according to different probiotic strains, which may be one important limitations of our work. Finally, the therapy effects may also be influenced by other multiple factors, such as age of participants, clinical stages, if complicated other diseases that influence the efficacy and safety, treatment duration and compliance of patients, which should also be taken into consideration. Considering these limitations above, further studies with large sample size shuld be designed to compare and analyze the efficacy and safety of different probiotic strains in different follow-up time.

5. Conclusion

In conclusion, our analysis found that supplement of probiotics could decrease the incidence of overall grade of RID, especially the incidence of CTC Grade ≥2 and Grade ≥3 diarrhea induced by radiotherapy. Additionally, probiotics could decrease the use of anti-diarrheal medication (loperamide) for RID patients. Probiotics may be a promising therapeutic alternative for cervical cancer patients suffering radiotherapy-induced diarrhea.

Declarations

(1) Ethics approval and consent to participate: Not applicable.
(2) Consent for publication: Not applicable. Our manuscript contains none of individual person's data.
(3) Availability of data and materials: Data and materials of this analysis were extracted from the original researches which were referenced in this article.
(4) Competing interests: The authors declare no relevant conflict of interest.
(5) Funding: There is no funding for this work.
(6) Authors' contributions: The authors on this paper all participated in study design. All authors read, critiqued and approved the manuscript revisions as well as the final version of the manuscript. Also, all authors participated in a session to discuss the results and

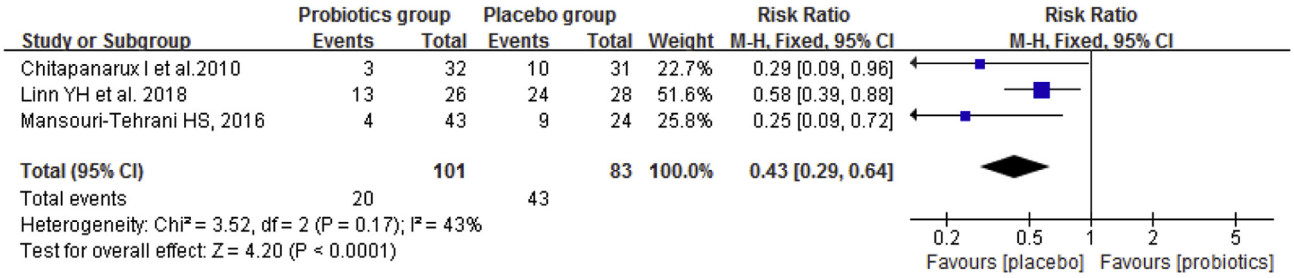

Fig. 7. Forest plot of comparing probiotics with placebo with respect to number of patients used loperamide as an anti-diarrheal medication.

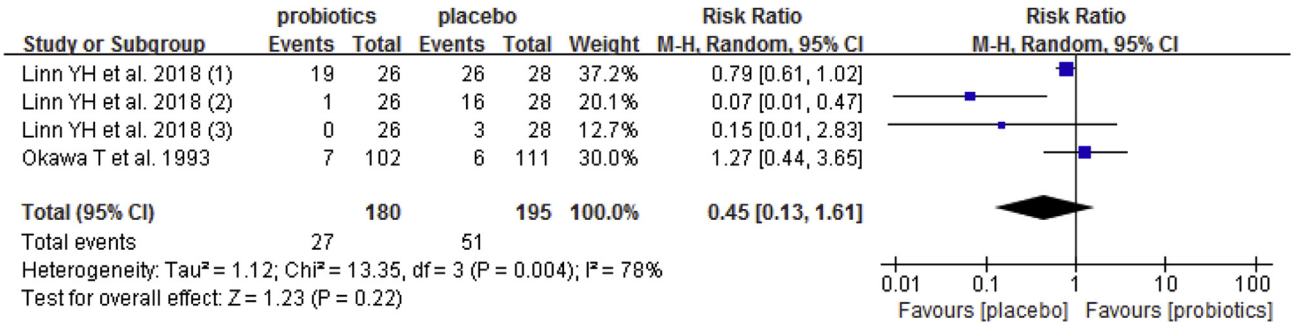

Fig. 8. Forest plot comparing probiotics with placebo with respect to incidence of abdominal pain.

consider strategies for analysis and interpretation of the data before the final data analysis was performed and the manuscript written. W YP and W XY mainly contributed to the study design, data analysis and quality assessment. W YP mainly contributed to the literature search. W XY contributed to the manuscript writing. All authors have the appropriate permissions and rights to the reported data.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data statement

The material of this article is original research. All data in this manuscript is available and transparent for readers.

Ethical Approval

Ethical Approval is not applicable.

Conflicts of interest

The authors declare no relevant conflict of interest.

Sources of funding

There is no funding for this work.

Author contribution

The authors on this paper all participated in study design. All authors read, critiqued and approved the manuscript revisions as well as the final version of the manuscript. Also, all authors participated in a session to discuss the results and consider strategies for analysis and interpretation of the data before the final data analysis was performed and the manuscript written. All authors have the appropriate permissions and rights to the reported data.

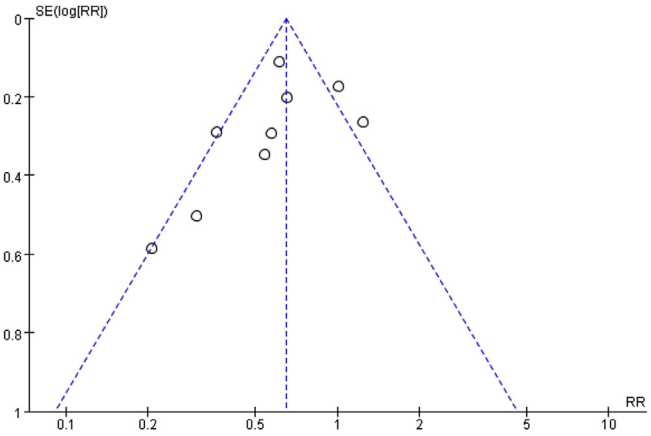

Fig. 9. Funnel plot for assessing the publication bias of included literature.

Research registration number

reviewregistry641.

Guarantor

Xinyan Wang and Qiu Guijing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.03.015.

Table 2
The pooled results of subgroup analysis for the incidence of different grade diarrhea.

Groups/Subgroups	Pooled results			Heterogeneity		
	RR	95% CI	*P* value	I^2	P_h value	Analytical effect model
Diarrhea CTC grade 0	2.84	0.82, 9.79	0.10	63%	0.07	Random-effect model
Diarrhea CTC grade 1	1.63	1.17, 2.27	0.004*	0%	0.91	Fixed-effect model
Diarrhea CTC grade 2	0.44	0.15, 1.27	0.13	71%	0.06	Random-effect model
Diarrhea CTC grade 3	0.71	0.37, 1.38	0.31	0%	0.61	Fixed-effect model
Diarrhea CTC grade 4	0.25	0.06, 0.97	0.04*	0%	0.86	Fixed-effect model
Diarrhea CTC grade≤2	0.90	0.71, 1.14	0.39	82%	0.0002	Random-effect model
Diarrhea CTC grade≥1	0.57	0.13, 2.48	0.45	99%	< 0.00001	Random-effect model
Diarrhea CTC grade≥2	0.52	0.30, 0.89	0.02*	57%	0.10	Random-effect model
Diarrhea CTC grade≥3	0.32	0.12, 0.82	0.02*	82%	0.0002	Random-effect model

CTC, Common Toxicity Criteria; RR, risk ratio; CI, confidence intervals; UUIE, urinary urge incontinence episodes.

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