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Efficacy and safety of probiotics in eradicating *Helicobacter pylori*

A network meta-analysis

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Abstract

Background: Due to decreasing eradication rate and increasing side effects, probiotics have gradually become an important supplement to standard eradication regimens for *Helicobacter pylori*.

Objective: To evaluate the effectiveness and safety of probiotics in facilitating the eradication of *H pylori* and to explore the best timing and duration of probiotic supplementation, use of eradication regimens, strains, locations, and common side effects.

Methods: Eligible studies were retrieved from the PubMed, EMBASE, Cochrane Library, Web of Science, and CNKI databases, and we applied the Stata 12.0 software for the standard meta-analysis and network meta-analysis.

Results: Forty eligible studies with 8924 patients were included in the analysis. We used a random-effects model (I^2 = 52.1% and I^2 = 81.4%) to analyze the eradication rate and the incidence of total side effects by intention to treat (ITT). Compared with the control group, a higher eradication rate (relative risk [RR] 1.140, 95% confidence interval (CI) 1.101–1.180, $P < .001$) and lower incidence of total side effects (RR 0.470, 95% CI 0.391–0.565, $P < .001$) were observed in the probiotic group. In the subgroup analysis, we evaluated the surface under the cumulative ranking curve scores for the before + same (75.2%), >2 weeks (92.6%), probiotic + quadruple regimen (99.9%), *Lactobacillus* (73.6%), multiple strains (72.1%), China (98.5%) groups. The rankings of common side effects are shown in Table 6. SUCRA scores for diarrhea (39.7%), abdominal pain (43.9%), nausea (78.8%), taste disturbance (99.6%), vomiting (7.1%), and constipation (30.9%) were reported. The consistency of all comparison groups was good.

Conclusions: Probiotics improved the eradication rate and reduced side effects when added to the treatments designed to eradicate *H pylori*. The use of probiotics before the eradication treatment and throughout the eradication treatment, and also the use of probiotics for more than 2 weeks, exerted better eradication effects. Probiotics combined with the bismuth quadruple regimen was the best combination. *Lactobacillus* and multiple strains were better choices of probiotic strains. The eradication effect observed in China was better than the effect observed in other countries.

Abbreviations: CI, confidence interval IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; ITT, intention to treat; RR, relative risk; SUCRA = surface under the cumulative ranking curve.

Keywords: eradication, *Helicobacter pylori*, network meta-analysis, probiotics, side effect

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1. Introduction

Helicobacter pylori has been extensively studied by scientists worldwide since its isolation and cultivation by J. RobinWarren and Barry J. Marshall in 1983.[1] The infection rate of *H pylori* is nearly 50% across the global and 41.5% to 72.3% in China.[2] At present, *H pylori* is recognized as the main cause of many digestive diseases, including chronic active gastritis, gastroduodenal ulcers, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer.[3,4] It is urgent to find the satisfied eradication regimens. In the past few years, the recommended eradication regimens include clarithromycin triple regimen, bismuth quadruple regimen, concomitant regimen, and sequential regimen.[5] Because of highly resistant to antibiotics, the quadruple regimen containing bismuth was recommended to increase the sensibility.[6] However, the side effects during treatment, such as antibiotic-associated diarrhea, nausea, or vomiting, may reduce patients' compliance.[5,7] Therefore, high resistance and poor compliance have hindered the satisfactory eradication effects of standard regimens.[8]

As an adjuvant of eradication treatment, probiotics have been recommended in some current guidelines, such as *Lactobacilli*, *fecal bacteria*, *Bifidobacterium*, *Saccharomyces*, and *Bacillus licheniformis*.[4,5,9] On one hand, probiotics help to competitive inhibit the colonization of *H pylori* and produce bacteriostatic substances.[7] On the contrary, probiotics have a positive effect on reducing the side effects of treatment, such as antibiotic-associated diarrhea.[10–14] However, other studies hold the opposite views on the efficiency and safety of probiotics in assisting with the eradication.[15–17] Although some previous studies was focused on the probitic addition, the timing and duration of probiotic addition remain unclear.[18–21] Therefore, we performed a meta-analysis of the most recent and most favorable evidence to evaluate the efficacy and safety, and explore the optimal timing and duration of probiotics in assisting with the eradication of *H pylori*.

2. Methods

2.1. Search strategy

The literature search was performed up to July, 2018. Reviewers systematically searched PubMed, EMBASE, Cochrane Library, Web of Science, and CNKI databases using the following terms: (probiotic OR probiotics OR yeast OR yeasts OR yogurt OR *Lactobacillus* OR *Bifidobacterium* OR *Saccharomyces*) AND (*Helicobacter pylori* OR *H. pylori*).

2.2. Inclusion criteria and exclusion criteria

Inclusion criteria were the following: randomized controlled trial; patients' aged ≥18 years, receiving the first anti-*H pylori* treatment; confirmation of eradication results by histology or *H pylori* fecal antigen tests performed at least 4 weeks after the end of eradication; the use of at least 2 groups, including the control group (placebo or no other intervention) and the experimental group (*H pylori* standard eradication regimen plus probiotics) (*H pylori* standard eradication regimen refers to standard triple regimen, sequential regimen, standard quadruple regimen); the probiotic strains were *Lactobacilli, Bifidobacterium, Saccharomyces*, or a mixture of the 3; and the eradication rates were available.

Exclusion criteria were the following: an uncertain eradication rate; the use of an agent other than probiotics as an auxiliary treatment for *H pylori* infection in the intervention group; studies for which the complete text was not available; studies that were not published in Chinese or English; repeated studies; inappropriate randomization method; no description of withdrawals and dropout rates; intention to treat (ITT) was not used when withdrawals and dropouts occurred; and the original data were incorrect.

2.3. Study quality assessment

Two researchers independently screened the studies and evaluated the quality of the included studies. Disagreements were resolved by a third researcher. Quality was mainly assessed using the Jadad scale,[22,23] based on the following three criteria: randomization, double blinding, and description of withdrawals and dropout. The maximum number of points was 5: a low-quality study scored ≤2 and a high-quality study scored >2.[22,23]

2.4. Data extraction

The data were extracted using a self-made form, and the extracted contents are listed below. Patients meeting at least 1 of the following criteria were defined as *H pylori*-positive patients: 13C-urea breath test (UBT), rapid urea test (RUT), *H pylori* antibody, histopathology, or stool antigen test. The primary outcome of this meta-analysis was the successful eradication of *H pylori*, which was confirmed by 13C-UBT or other generally accepted methods 4 weeks after the end of treatment. Secondary outcomes were side effects during *H pylori* eradication. The data extracted and assessed in the meta-analysis were: author and publication year; number of patients in the study (experimental group/control group); type and duration of the first *H pylori* eradication treatment (triple or quadruple); number of probiotic strains and probiotic species; timing and duration of addition; and an ITT analysis of the *H pylori* eradication rate and incidence of side effects (nausea, vomiting, abdominal pain, constipation, diarrhea, taste disturbance, and total side effects).

2.5. Statistical analysis

2.5.1. Standard meta-analysis. For direct comparisons, we used the metan command in Stata 12.0 for the standard meta-analysis. The eradication rate and the incidence of total side effects were analyzed using two-category data. Relative risk (RR), an effector, and 95% confidence intervals (95% CIs) were calculated. The heterogeneity between the results of the study was examined using the Q test (test level is $\alpha = 0.1$), and the magnitude of heterogeneity was judged by combining the findings with the I^2 test.[24] If heterogeneity between studies was not observed ($P > .10$ or $I^2 \leq 50\%$), the fixed-effect model was used for analysis; if heterogeneity existed ($P \leq .10$ or $I^2 > 50\%$), the heterogeneity source was analyzed. If significant clinical heterogeneity was not observed, a random-effects model was used for the analysis.

2.6. Network meta-analysis

We used the mvmeta command in Stata 12.0 to perform the network meta-analysis of subgroups and common side effects.[25] First, we constructed a network of evidence for the comparison of treatments.[26] Inconsistency factors (IFs) and 95% CIs were used to evaluate the consistency of each closed loop. The 95% CI lower limit was equal to 0, which was considered consistent. Otherwise, the closed loop was considered obviously inconsistent.[27] In the present study, the outcome index was used as the count data. Therefore, the RR was used to combine the effect sizes, and the interval estimation was performed with 95% CIs, where the upper limit of the 95% CI was less than 1 or the lower limit was greater than 1, which indicated a statistically significant difference; otherwise the difference was not statistically significant. The PrBest and surface under the cumulative ranking curve (SUCRA) functions were used to rank the results of the network meta-analysis.[28] The SUCRA score was 100%. In the subgroup analysis, a greater SUCRA score indicated a better treatment effect. PrBest indicated the probability that the treatment would be the best treatment. In the side effect analysis, a greater SUCRA score indicated more common side effects. PrBest was the probability that this side effect became the most common side effect.

For data displaying significant clinical heterogeneity, a subgroup analysis or sensitivity analysis was conducted, and

only a descriptive analysis was performed, if necessary. Publication bias was assessed using a funnel plot and an Egger linear regression analysis.

This study aimed to compare the incidence of the *H pylori* eradication rate and side effects between the probiotic group and the control group, and conducted the following subgroup analyses: probiotic addition timing: compared before (used before the eradication treatment), same (started and ended at the same time as the eradication treatment), after (used when the eradication treatment ended), before + same (used before the eradication treatment and ending with the eradication treatment), and same + after (starting at the same time as the eradication treatment and continuing when the eradication treatment was complete); probiotic duration: ≤2 weeks and >2 weeks; different eradication regimens: triple regimen, bismuth quadruple regimen, probiotic + triple regimen and probiotic + bismuth quadruple regimen; different probiotic species compared with multiple strains; eradication treatments used in China and other countries; and the occurrence of common side effects (including nausea, vomiting, abdominal pain, constipation, diarrhea, and taste disturbance).

2.7. Ethical statement

All analyses were based on previous published studies; thus no ethical approval and patient consent were required.

3. Results

3.1. Study identification and selection

We retrieved 905 studies, but excluded 530 nonclinical studies. Two hundred fifty-four replicated studies were excluded after a primary screen. Of the 121 studies obtained after screening,

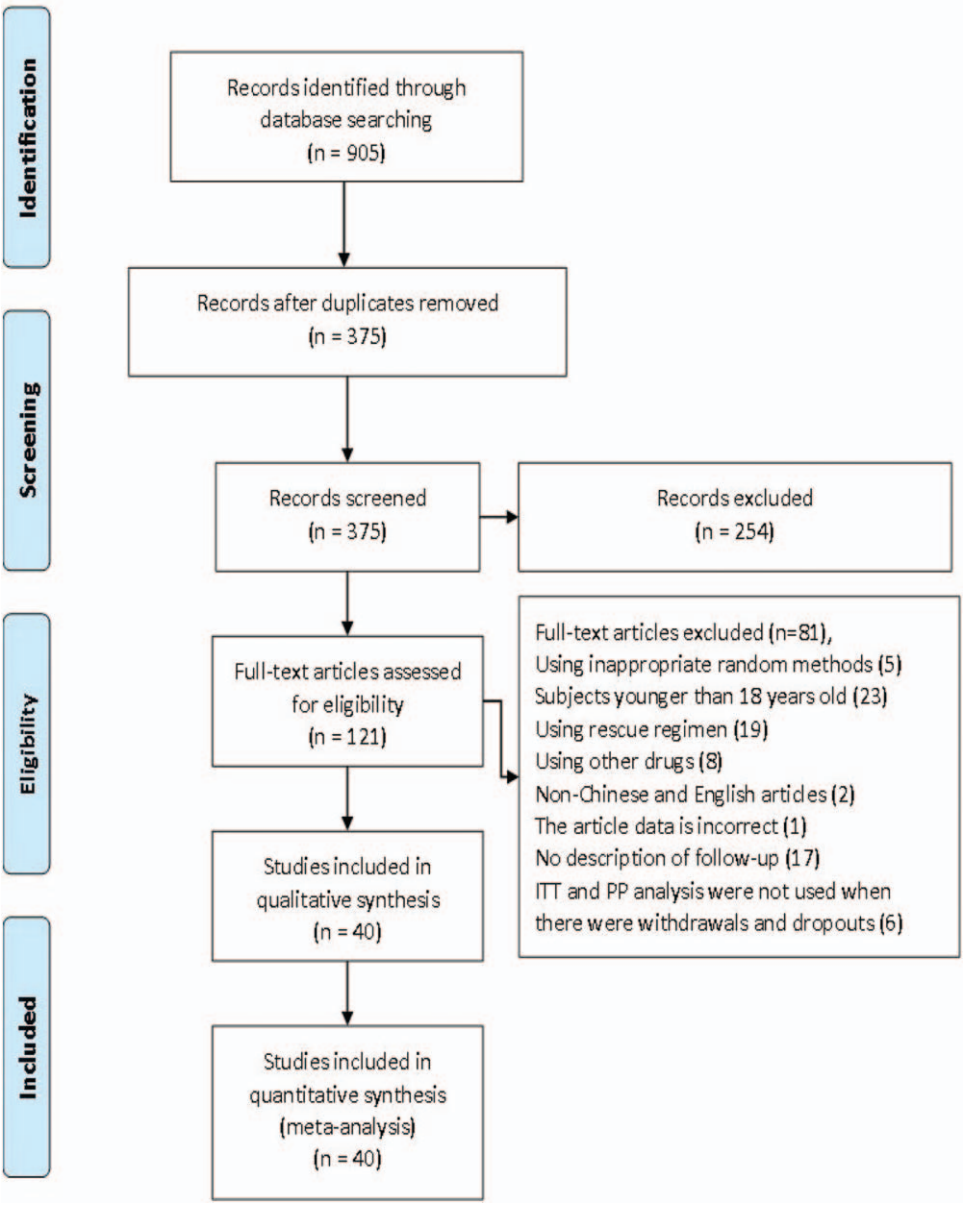

Figure 1. Flow diagram of the trials identified and selected.

81 studies did not meet the inclusion criteria (5 studies used inappropriate randomization methods, patients in 23 studies were younger than 18 years, 19 studies used rescue regimens, 8 studies used other drugs, 2 studies were not published in Chinese or English, 1 study listed incorrect data, and 17 studies did not describe withdrawals and dropouts. When withdrawals and dropouts occurred, 6 studies did not use the ITT analysis. Finally, 40 randomized controlled trials were eligible, including 16 Chinese studies and 24 English studies[29–68] (Fig. 1).

3.2. Study characteristics and quality

Forty randomized controlled trials with 8924 patients were analyzed in our study. Among these patients, 4903 were in the probiotic group and 4021 in the control group. We summarized the baseline characteristics of the included studies (Table 1).

3.3. Standard meta-analysis

3.3.1. H pylori eradication. The *H pylori* eradication rate was obtained from 40 randomized controlled trials. The eradication rates of the probiotic group and the control group obtained from the ITT analysis were 81.5% and 71.6%, respectively. Greater heterogeneity between studies ($P < .001$, $I^2 = 52.1\%$) necessitated the use of the random-effects model for meta-analysis, which showed that the difference between the probiotic group and the control group was statistically significant (RR 1.140, 95% CI 1.101–1.180, $P < .001$) (Fig. 2).

Table 1

Characteristics of the included studies.

First author (y)	Location	Total cases (exp/cont.)	Eradication regimen	Regimen duration (d)	Number of probiotic strain (species)	Time of probiotic	Duration of probiotic (d)	Jadad score
Zhu, 2015[29]	China	162 (112/50)	Triple	10	Single (S), Multiple	S	10	3
Zhang, 2015[30]	China	246 (198/48)	Quadruple	10	Multiple	B or A	14	3
Tian, 2015[31]	China	240 (120/120)	Triple, quadruple	10	Single (S)	S	10	3
Chen, 2015[32]	China	188 (94/94)	Quadruple	14	Multiple	SA	28	3
Ma, 2015[33]	China	132 (66/66)	Triple	7	Single (L)	S	7	3
Sun, 2014[34]	China	270 (180/90)	Triple	14	Single (B), Multiple	S	14	1
He, 2014[35]	China	210 (105/105)	Triple	10	Single (S)	SA	14	1
Emara, 2014[36]	Egypt	70 (35/35)	Triple	14	Single (L)	SA	28	5
Zhao, 2013[37]	China	100 (50/50)	Triple	7	Multiple	S	7	3
Zhang, 2013[38]	China	350 (117/233)	Triple	7	Multiple	SA	14	2
Shavakhi, 2013[39]	Iran	180 (90/90)	Quadruple	14	Multiple	S	14	5
Qian, 2012[40]	China	210 (105/105)	Quadruple	10	Multiple	S	10	2
Du, 2012[41]	China	234 (155/79)	Triple	7	Multiple	BS or A	21 or 14	2
Deguchi, 2012[42]	Japan	229 (115/114)	Triple	7	Single (L)	BS	28	2
Ozdil, 2011[43]	Turkey	285 (98/187)	Triple	14	Single (S)	S	14	1
Medeiros, 2011[44]	Portugal	62 (31/31)	Triple	8	Single (L)	S	8	2
Yasar, 2010[45]	Turkey	76 (38/38)	Triple	14	Single (B)	S	14	1
Wen, 2010[46]	China	200 (96/104)	Triple	7	Multiple	S	7	2
Song, 2010[47]	Korea	991 (660/331)	Triple	7	Single (S)	SA	28	3
Kim, 2008[48]	Korea	347 (168/179)	Triple	7	Multiple	BS	28	3
de Bortoli, 2007[49]	Italy	206 (105/101)	Triple	7	Single (L)	S	7	2
Cindoruk, 2007[50]	Turkey	124 (62/62)	Triple	14	Multiple	S	14	5
Myllyluoma, 2005[51]	Finland	47 (23/24)	Triple	7	Multiple	SA	28	5
Sheu, 2002[52]	Taiwan	160 (80/80)	Triple	7	Multiple	SA	35	2
Armuzzi, 2001[53]	Italy	120 (60/60)	Triple	7	Single (L)	SA	14	3
Armuzzi, 2001[54]	Italy	60 (30/30)	Triple	7	Single (L)	SA	14	5
Jiang, 2018[55]	China	222 (111/111)	Quadruple	14	Single (B)	S	14	5
Zhu, 2017[56]	China	360 (240/120)	Quadruple	10	Multiple	SA	14 or 28	3
Sun, 2017[57]	China	120 (60/60)	Triple	14	Multiple	S	14	1
Peng, 2017[58]	China	280 (224/56)	Triple	14	Multiple	B or S or SA	14 or 28	2
Peng, 2017[59]	China	342 (110/232)	Triple	14	Multiple	S	14	2
Zhu, 2017[60]	China	240 (160/80)	Quadruple	10	Single (S)	SA	14 or 28	3
Chotivitayatarakorn, 2017[61]	Thailand	108 (54/54)	Triple	7 or 14	Single (S)	S	7 or 14	5
Shun, 2016[62]	China	143 (94/49)	Triple	10	Multiple	S or SA	10 or 20	2
Shafaghi, 2016[63]	Iran	76 (38/38)	Quadruple	14	Multiple	BS	17	5
Grgov, 2016[64]	Serbia	167 (90/77)	Triple	7	Multiple	SA	28	1
Tongtawee, 2015[65]	Thailand	300 (200/100)	Triple	7	Multiple	B	7	2
Tongtawee, 2015[66]	Thailand	200 (100/100)	Triple	7	Multiple	B	7	2
Hauser, 2015[67]	Croatia	804 (398/406)	Triple	14	Multiple	S	14	3
Chitapanarux, 2015[68]	Thailand	63 (31/32)	Triple	7	Single (B)	SA	28	5

Number of probiotic strains: single, the study contains only 1 probiotic; multiple, the study contains at least 2 probiotics.

Probiotic strain: L = *Lactobacillus*; B = *Bifidobacterium*; S = *Saccharomyces*.

Time of probiotic: S = "same," that is, start at the same time as eradication regimen and end at the same time. B = "before," that is, used before the eradication regimen. A = "after," that is, used when the eradication regimen has ended.

BS = "before + same," that is, used before the eradication regimen and continuing until the end of the eradication regimen. SA = "same + after," that is, beginning with the eradication regimen and continuing when the eradication regimen has ended.

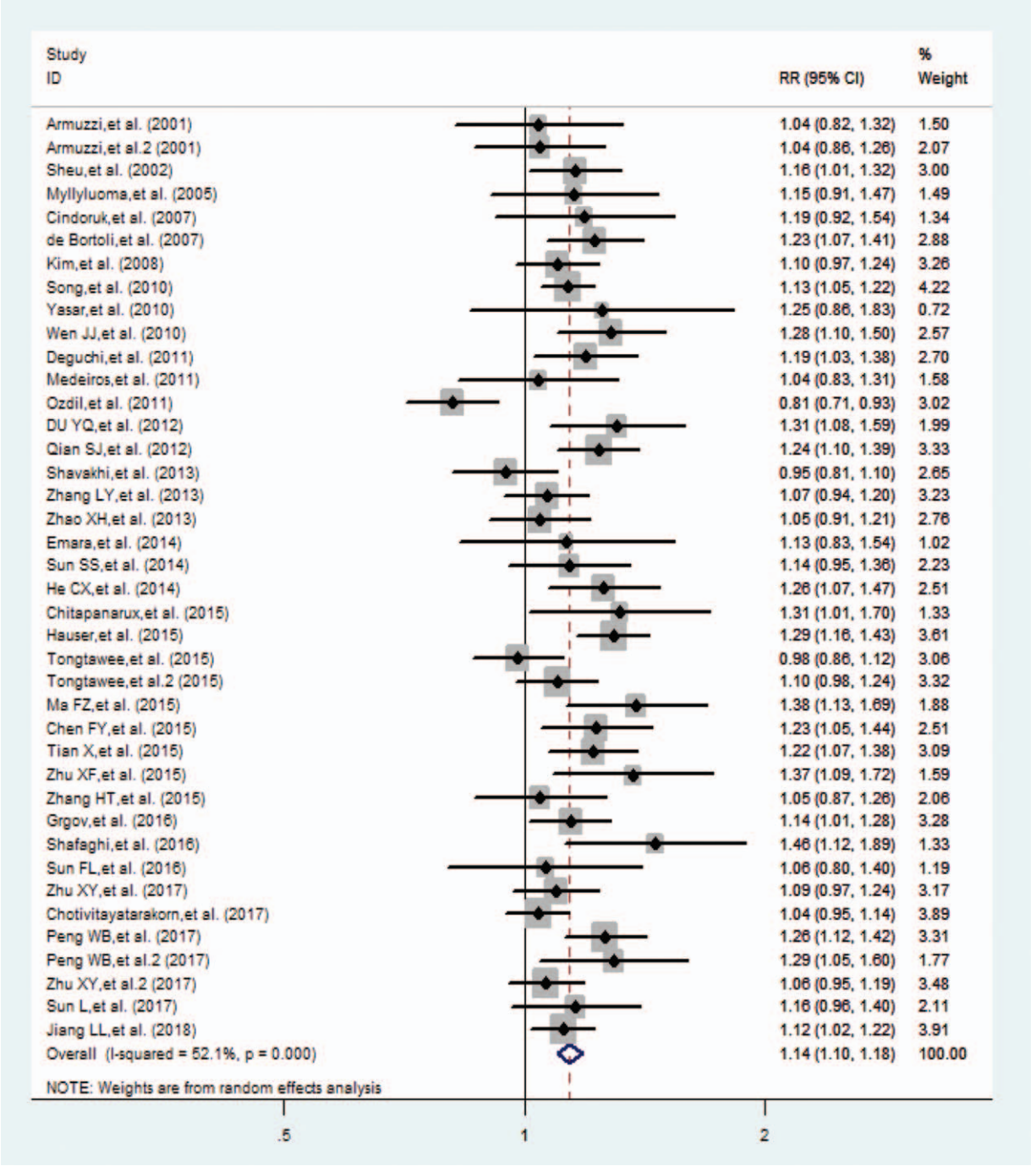

Figure 2. Forest plot comparing the eradication rate of probiotic addition by intention-to-treat analysis. CI = confidence interval, RR = relative risk.

3.4. Total side effects

Total side effects were described by 31 studies. The incidence of total side effects in the probiotic group obtained from the ITT analysis was 18.9%. The incidence of total side effects in the control group was 39.0%. The heterogeneity was greater ($P < .001$, $I^2 = 81.4\%$), and the result was obtained with the random-effects model was (RR 0.470, 95% CI 0.391–0.565, $P < .001$) (Fig. 3).

On the basis of the results from the standard meta-analysis, the incidence of diarrhea, abdominal pain, nausea, taste disturbance, vomiting, and constipation was significantly decreased in the probiotic group compared with the control group. Using a fixed-effect model, the following results were obtained: diarrhea (RR 0.392, 95% CI 0.329–0.468, $P < .001$), abdominal pain (RR 0.750, 95% CI 0.583–0.965, $P = .025$), nausea (RR 0.585, 95% CI 0.487–0.702, $P < .001$), vomiting (RR 0.590, 95% CI 0.409–0.851, $P = .005$), and constipation (RR 0.613, 95% CI 0.453–0.829, $P < .001$). The taste disturbance was analyzed using a random-effects model (RR 0.713, 95% CI 0.573–0.887, $P = .002$) (Table 2).

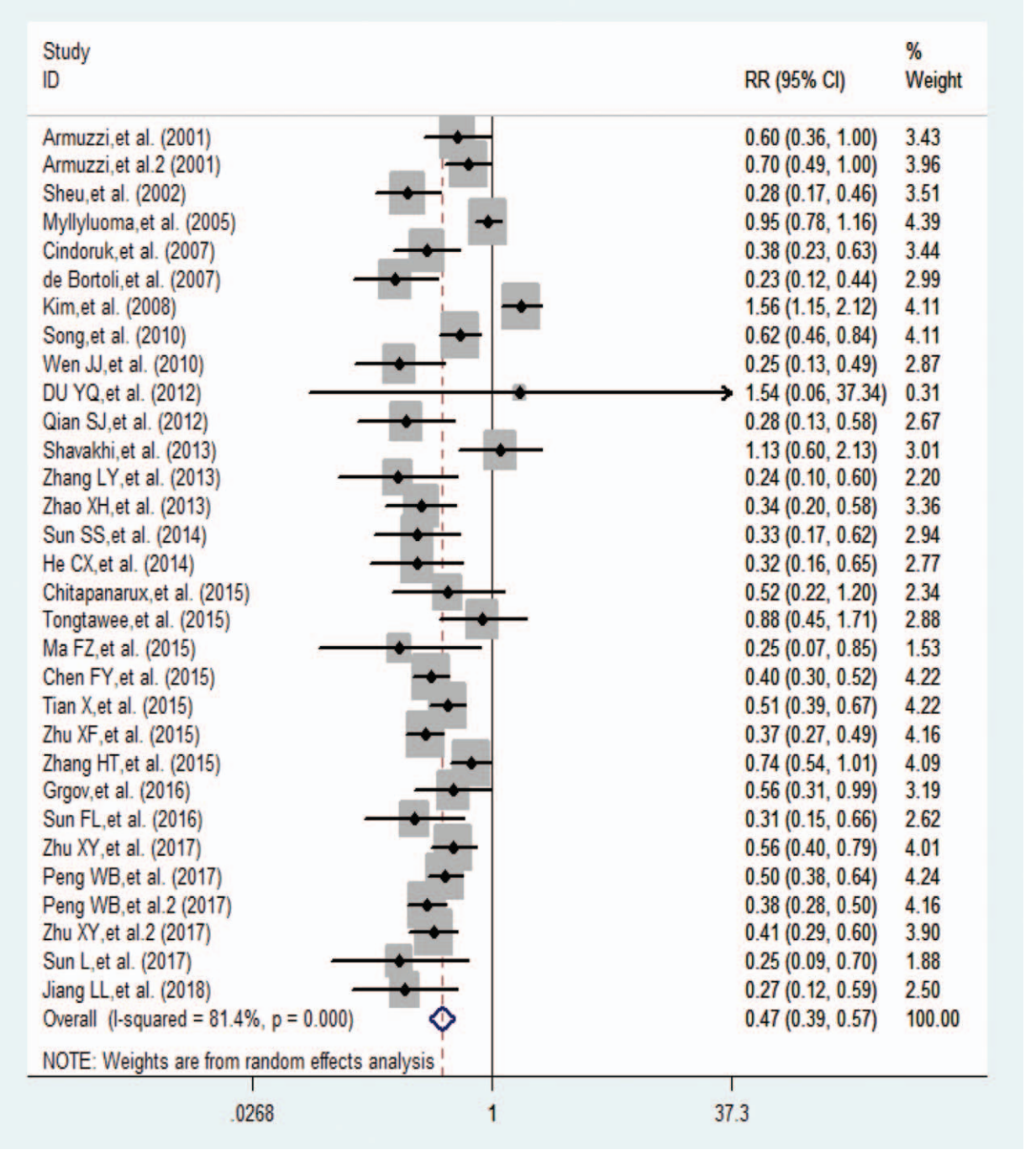

Figure 3. Forest plot comparing the total side effects of probiotic addition by intention-to-treat analysis. CI = confidence interval, RR = relative risk.

Table 2

Standard meta-analysis of side effects.

Side effects	Objects	Relative risk (95% CI)	*P*	Heterogeneity (I^2)
Diarrhea	27	0.392 (0.329, 0.468)	<.001	0.0%
Abdominal pain	16	0.750 (0.583, 0.965)	.025	0.0%
Nausea	22	0.585 (0.487, 0.702)	<.001	21.9%
Taste disturbance	23	0.713 (0.573, 0.887)	.002	60.0%
Vomiting	12	0.590 (0.409, 0.851)	.005	0.0%
Constipation	14	0.613 (0.453, 0.829)	.001	32.2%

CI = confidence interval.

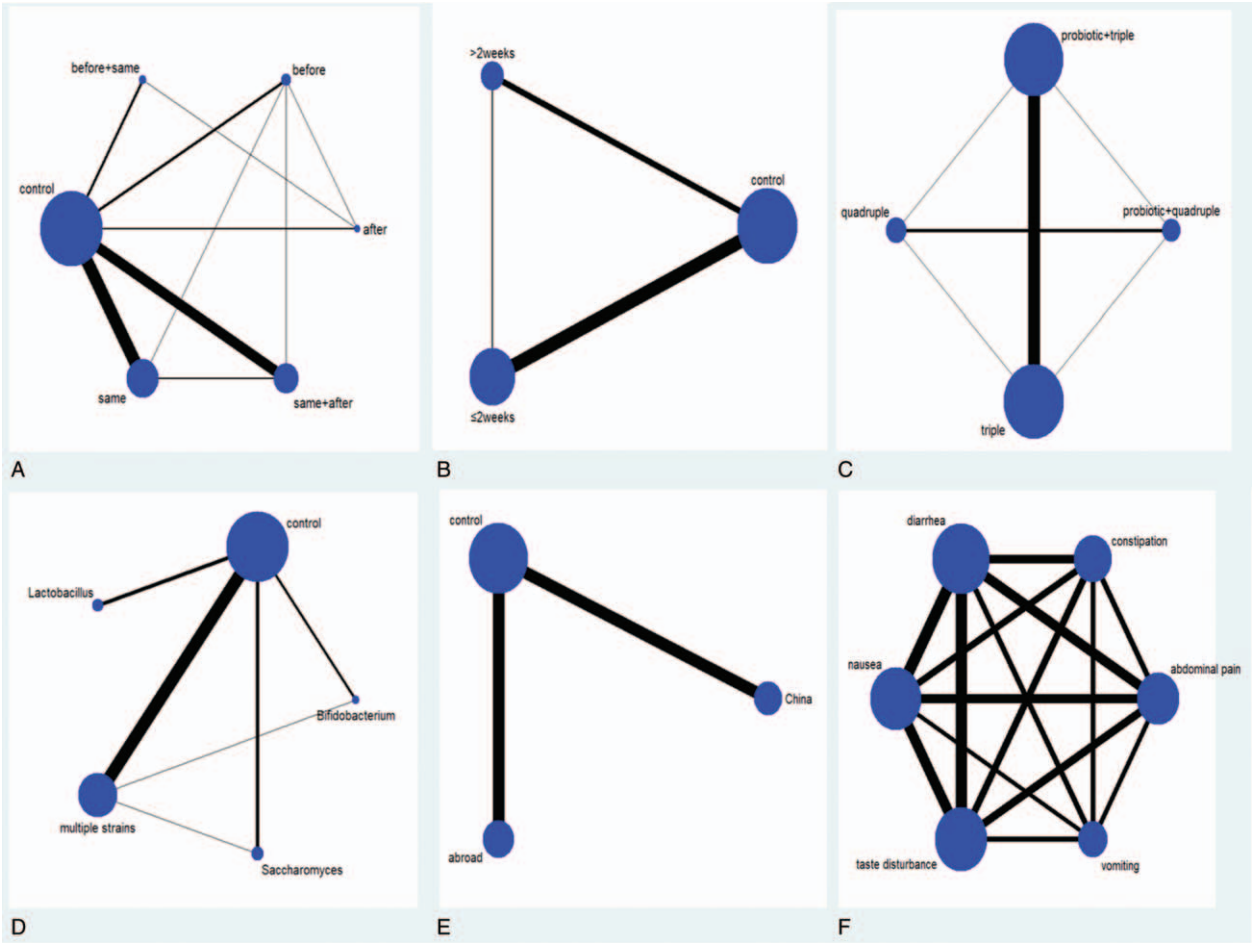

Figure 4. Network plot of subgroup and common side effects. (A) Probiotic addition time; (B) duration of probiotic addition; (C) eradication regimens; (D) species of probiotics; (E) location; (F) common side effects.

3.5. Network meta-analysis

3.5.1. Network evidence. The options tested in the network were: probiotic addition time: before, same, after, before + same, and same + after; duration of probiotic addition: ≤2 weeks and >2 weeks; eradication regimens: triple regimen, quadruple regimen, probiotic + triple regimen, and probiotic + quadruple regimen; species of probiotics: *Lactobacillus*, *Saccharomyces*, *Bifidobacterium*, and multiple strains, location: China and abroad; and common side effects: diarrhea, abdominal pain, nausea, taste disturbance, vomiting, and constipation. Network plots for various treatment methods and common side effects were constructed (Fig. 4).

3.6. Statistical analysis

3.6.1. H pylori eradication. In the probiotic addition timing subgroup, the before + same (RR 2.09, 95% CI 1.22–3.58), same (RR 1.88, 95% CI 1.47–2.41), and same + after (RR 1.96, 95% CI 1.46–2.63) groups all yielded statistically significant differences from the control group. In the duration of probiotic addition subgroup.≤2 weeks (RR 1.78, 95% CI 1.48–2.16) and >2 weeks (RR 2.11, 95% CI 1.60–2.78) both produced statistically significant differences compared with the control group. When we compared the quadruple regimen in the eradication regimens subgroup with the probiotic + triple regimen (RR 0.53, 95% CI 0.24–1.16), a statistically significant difference was not observed between the 2 subgroups. Statistically significant differences between the other eradication regimens were observed. Compared with the control group, *Lactobacillus* (RR 1.99, 95% CI 1.25–3.16), *Saccharomyces* (RR 1.62, 95% CI 1.08–2.44), and multiple strains (RR 1.96, 95% CI 1.57–2.45) exhibited statistically significant differences in the analysis of the probiotic species. Regarding different locations, China (RR 2.18, 95% CI 1.73–2.75) and other countries (RR 1.60, 95% CI 1.26–2.03) were statistically significantly different from the control group. The results of the network meta-analysis are presented in Table 3.

3.7. Common side effects

For the analysis of common side effects, nausea versus diarrhea (RR 1.68, 95% CI 1.07–2.65), taste disturbance versus diarrhea (RR 2.78, 95% CI 1.78–4.34), taste disturbance versus abdominal pain (RR 2.66, 95% CI 1.61–4.42), taste disturbance versus nausea (RR 1.65, 95% CI 1.05–2.59), vomiting versus nausea (RR 0.38, 95% CI 0.19–0.75), and constipation versus nausea (RR 0.53, 95% CI 0.29–0.98), vomiting versus taste disturbance (RR 0.23, 95% CI 0.12–0.46), and constipation versus taste disturbance (RR 0.32, 95% CI 0.18–0.59) produced statistically significant differences. The results of the network meta-analysis of side effects are shown in Table 4.

Table 3

Network meta-analysis results of subgroup eradication rate.

Subgroup	Comparison between groups		Relative risk (95% CI)
Probiotic addition time	Before	Control	1.65 (0.98–2.78)
	Before + same	Control	2.09 (1.22–3.58)
		Before	1.27 (0.61–2.64)
	Same	Control	1.88 (1.47–2.41)
		Before	1.14 (0.65–2.01)
		Before + same	0.90 (0.50–1.63)
	Same + after	Control	1.96 (1.46–2.63)
		Before	1.19 (0.66–2.15)
		Before + same	0.94 (0.51–1.73)
		Same	1.04 (0.72–1.51)
	After	Control	1.38 (0.69–2.74)
		Before	0.83 (0.39–1.79)
		Before + same	0.66 (0.30–1.46)
		Same	0.73 (0.35–1.51)
		Same + after	0.70 (0.33–1.48)
Duration of probiotic addition	≤2 wks	Control	1.78 (1.48–2.16)
	>2 wks	Control	2.11 (1.60–2.78)
		≤2 wks	1.18 (0.87–1.62)
Eradication regimens	Triple regimen	NA	NA
	Quadruple regimen	Triple regimen	3.50 (1.63–7.54)
	Probiotic + triple regimen	Triple regimen	1.87 (1.54–2.26)
		Quadruple regimen	0.53 (0.24–1.16)
	Probiotic + quadruple regimen	Triple regimen	6.08 (2.89–12.79)
		Quadruple regimen	1.74 (1.17–2.57)
		Probiotic + triple regimen	3.26 (1.53–6.93)
Species of probiotics	*Lactobacillus*	Control	1.99 (1.25–3.16)
	Saccharomyces	Control	1.62 (1.08–2.44)
		Lactobacillus	0.82 (0.44–1.52)
	Bifidobacterium	Control	1.78 (0.99–3.20)
		Lactobacillus	0.90 (0.42–1.90)
		Saccharomyces	1.10 (0.54–2.24)
	Multiple strains	Control	1.96 (1.57–2.45)
		Lactobacillus	0.99 (0.59–1.66)
		Saccharomyces	1.21 (0.76–1.92)
		Bifidobacterium	1.10 (0.60–2.03)
Location	China	Control	2.18 (1.73–2.75)
	Abroad	Control	1.60 (1.26–2.03)
		China	0.73 (0.53–1.02)

CI = confidence interval.

Table 4

Network meta-analysis results of side effects.

Side effects	Comparison between groups	Relative risk (95% CI)
Diarrhea	NA	NA
Abdominal pain	Diarrhea	1.04 (0.63–1.73)
Nausea	Diarrhea	1.68 (1.07–2.65)
	Abdominal pain	1.61 (0.97–2.68)
Taste disturbance	Diarrhea	2.78 (1.78–4.34)
	Abdominal pain	2.66 (1.61–4.42)
	Nausea	1.65 (1.05–2.59)
Vomiting	Diarrhea	0.64 (0.33–1.25)
	Abdominal pain	0.62 (0.31–1.23)
	Nausea	0.38 (0.19–0.75)
	Taste disturbance	0.23 (0.12–0.46)
Constipation	Diarrhea	0.89 (0.49–1.63)
	Abdominal pain	0.85 (0.45–1.62)
	Nausea	0.53 (0.29–0.98)
	Taste disturbance	0.32 (0.18–0.59)
	Vomiting	1.39 (0.66–2.93)

CI = confidence interval.

3.8. Inconsistency analysis

In the location subgroup, no closed loop was formed, and no inconsistency analysis was performed. In the subgroups, closed loops were formed. The IFs for each subgroup were: probiotic addition timing (IF 0.04–0.18), duration of probiotic addition (IF 0.05), eradication regimens (IF 0.04–0.18), and species of probiotics (IF 0.06–0.17). The IFs for common side effects ranged between 0.00 and 0.90. The lower limit of the 95% CI for the subgroups and common side effects were 0, indicating that the closed loop consistency was better (Fig. 5).

3.9. Ranking probability

The rankings of the various treatment modalities in the subgroups are shown in Table 5. The SUCRA scores for the probiotic subgroups were: before (49.6%), same (65.2%), after (33.6%), before + same (75.2%), and same + after (71.9%); duration of probiotic addition: ≤2 weeks (57.4%) and >2 weeks (92.6%); eradication regimens: triple regimen (0.0%), quadruple regimen (65.1%), probiotic + triple regimen (35.0%), and probiotic + quadruple regimen (99.9%); species of probiotics:

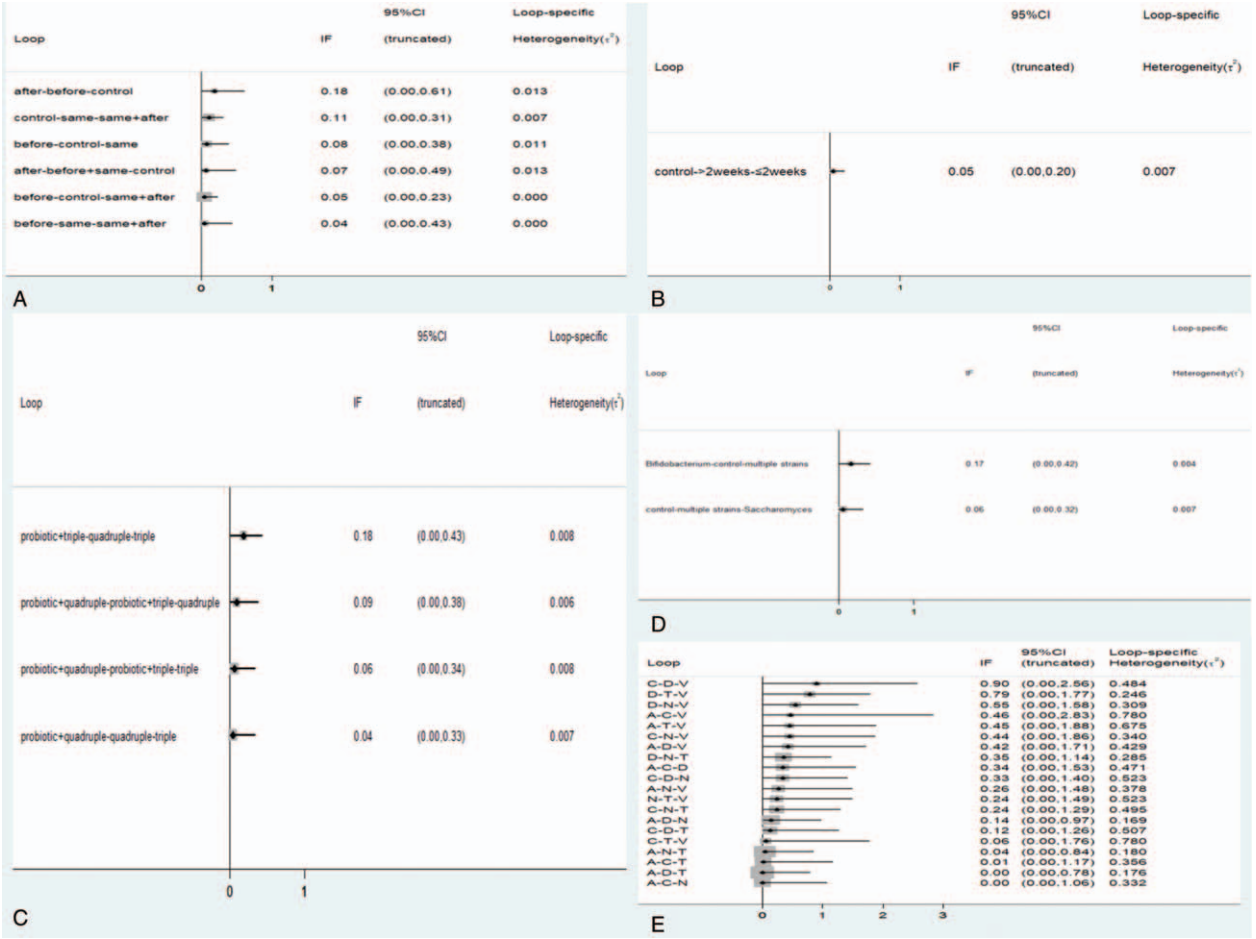

Figure 5. Inconsistency plot of subgroup and common side effects. (A) Probiotic addition time; (B) duration of probiotic addition; (C) eradication regimens; (D) species of probiotics; (E) common side effects. A = abdominal pain, C = constipation, D = diarrhea, N = nausea, T = taste disturbance, V = vomiting.

Lactobacillus (73.6%), *Saccharomyces* (43.9%), *Bifidobacterium* (59.4%), and multiple strains (72.1%); location: China (98.5%) and abroad (51.5%). The rankings of common side effects are shown in Table 6. The SUCRA scores for diarrhea (39.7%), abdominal pain (43.9%), nausea (78.8%), taste disturbance (99.6%), vomiting (7.1%), and constipation (30.9%) were calculated. The SUCRA ranking plots were constructed according to the SUCRA curve (Fig. 6).

Table 5

Ranking according to subgroup analysis of SUCRA curves.

Subgroup		SUCRA	PrBest	Mean rank
Probiotic addition time	Before	49.6	10.8	3.5
	After + same	75.2	42.2	2.2
	Same	65.2	15.0	2.7
	Same + after	71.9	25.9	2.4
	After	33.6	6.1	4.3
Duration of probiotic addition	≤2 wks	57.4	14.9	1.9
	>2 wks	92.6	85.1	1.1
Eradication regimens	Triple regimen	0.0	0.0	4.0
	Quadruple regimen	65.1	0.2	2.0
	Probiotic + triple regimen	35.0	0.1	3.0
	Probiotic + quadruple regimen	99.9	99.7	1.0
Species of probiotics	*Lactobacillus*	73.6	41.8	2.1
	Saccharomyces	43.9	7.3	3.2
	Bifidobacterium	59.4	24.6	2.6
	Multiple strains	72.1	26.3	2.1
Location	China	98.5	96.9	1.0
	Abroad	51.5	3.1	2.0

SUCRA = surface under the cumulative ranking curve.

Table 6

Ranking according to the common side effects of the SUCRA curve.

Side effects	SUCRA	PrBest	Mean rank
Diarrhea	39.7	0.0.	4.0
Abdominal pain	43.9	0.0	3.8
Nausea	78.8	0.0	2.1
Taste disturbance	99.6	98.2	1.0
Vomiting	7.1	0.0	5.6
Constipation	30.9	0.0	4.5

SUCRA = surface under the cumulative ranking curve.

3.10. Publication bias

The funnel plot obtained by an intentional analysis of the eradication rates of the 40 studies included was asymmetric. However, after the Egger test, no publication bias was detected (Fig. 7).

3.11. Sensitivity analysis

A sensitivity analysis was applied because the included studies were heterogeneous. When performing a sensitivity analysis according to ITT, the 95% CIs of each study overlapped, and thus the difference was not significant. When the most different study was removed,[43] the CI and RR did not change significantly. Therefore, the results of the meta-analysis were reliable.

3.12. Heterogeneity

When we conducted a meta-analysis of the total side effects, the heterogeneity was greater. Therefore, we used a meta-regression analysis to assess heterogeneity. The probiotic addition duration, study language, and study quality were the main sources of heterogeneity.

4. Discussion

This study investigated the efficacy and safety of probiotics in the eradication of *H pylori*. Our study indicated that probiotics improved the eradication rate and reduced the incidence of side effects when administered with treatments of eradicating *H pylori*, especially combined with the bismuth quadruple regimen. Better eradication effects were exerted when using probiotics before and throughout the eradication treatment or using probiotics for more than 2 weeks. Also, the eradication effect of Chinese was better than other countries.

In the past years, the decreasing eradication rate and increasing side effects made it urgent to find the optimized eradicative

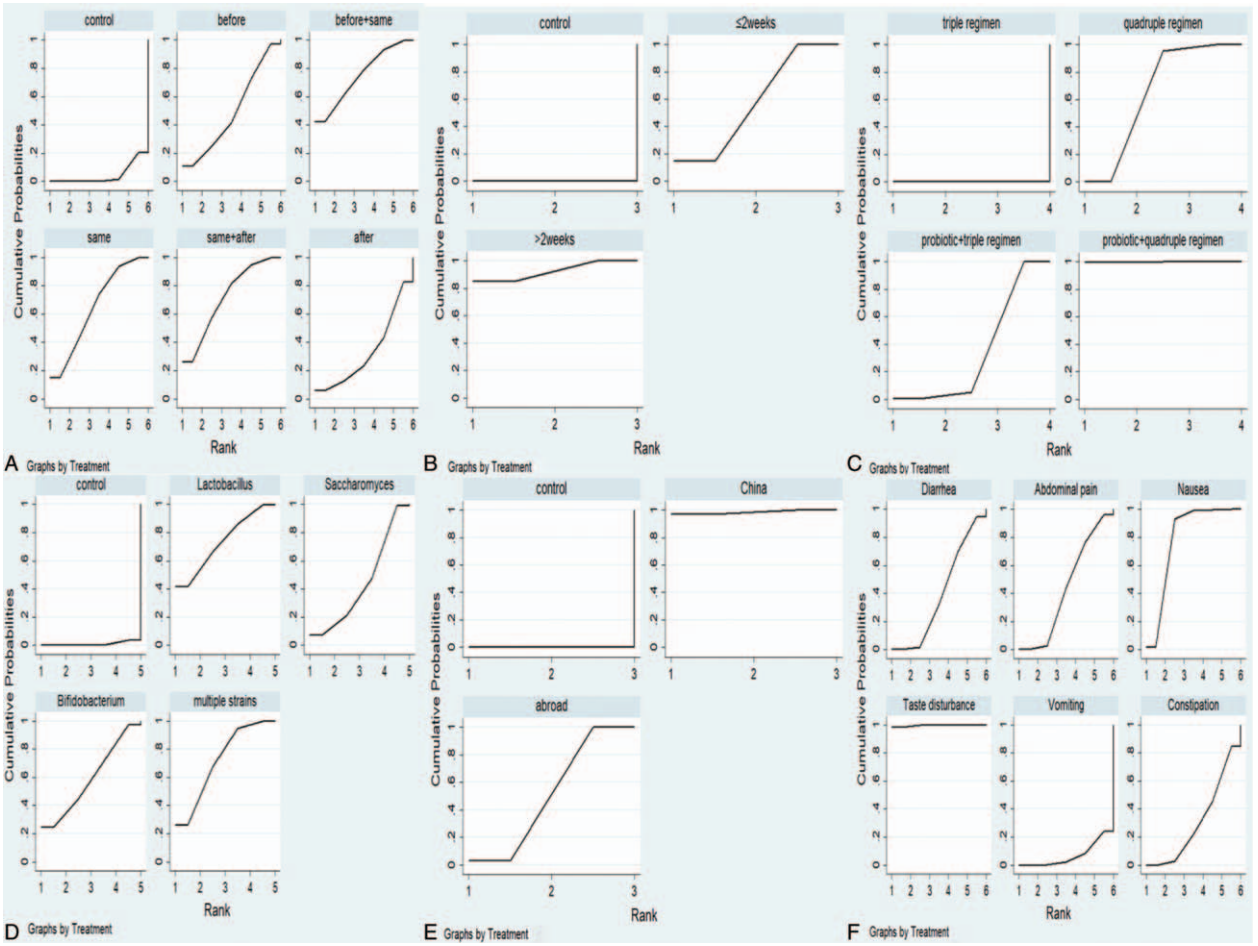

Figure 6. SUCRA plot of subgroup and common side effects. (A) Probiotic addition time; (B) duration of probiotic addition; (C) eradication regimens; (D) species of probiotics; (E) location; (F) common side effects. SUCRA = surface under the cumulative ranking curve.

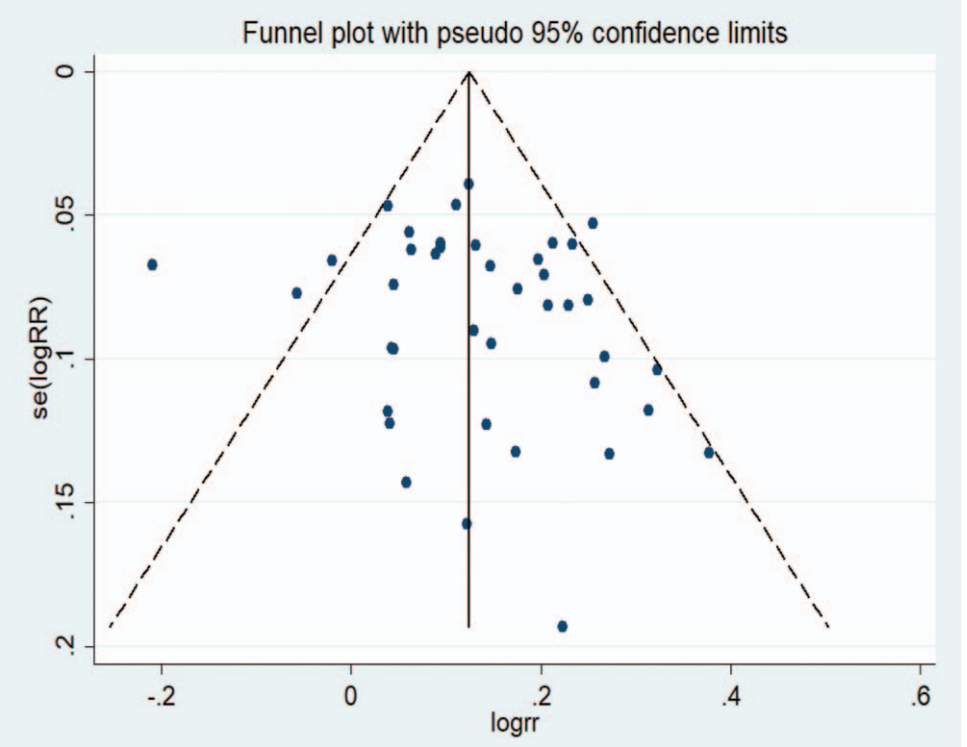

Figure 7. Funnel plot of the included studies for eradication rate.

regimens of *H pylori*.[6–8] Probiotics have been receiving more and more attention as an adjuvant of eradication treatment. Probiotics, initially proposed by Lilly and Sttillwel in 1965, were defined as factors derived from microorganisms that stimulate the proliferation of other beneficial bacteria.[69] It have been used on the treatment of variety diseases, including IBD, irritable bowel syndrome, and diarrhea.[70] Bhatia et al firstly shown that *H pylori* growth was inhibited by *Lactobacillus acidophilus* in vitro.[71–73] Also, the mechanism might be related to the reduction in urease activity mediated by short-chain fatty acids produced by probiotics, an enhancement of the acidic environment of the stomach, damages of the cell wall of *H pylori* strains, and inhibition of the colonization of *H pylori* in the gastric mucosa.[74–74,49,75] What is more, probiotics had a positive effect on inhibiting the inflammatory response which mediated by interleukin (IL)-8 after an *H pylori* infection.[76,77] Meanwhile, probiotics helped to alleviate antibiotic-related gastrointestinal reactions and improved drug compliance.[78]

Combined probiotics with the bismuth quadruple regimen exerted the best eradication effect in our study. Because the eradication rate of combined probiotics and standard triple regimen was inferior to that in the bismuth quadruple regimen, probiotics were not able to replace bismuth. The results were the same as those reported by Chinese scholars.[79,80] On the basis of the strong antibacterial effect of bismuth quadruple regimen, adding probiotics could increase the eradication rate. However, internists should have noticed that bismuth has an inhibitory effect on probiotics. To avoid this effect, bismuth and probiotics should be taken at different times.

Lactobacillus and multiple strains exerted better eradication effects. Previous analyses also supported this result.[18,81] This might be related to the species specificity of the probiotics.[82] The metabolites of *Lactobacillus* exert a strong antibacterial effect, potentially increasing humoral and cellular immunity. Moreover, the use of multiple strains included the characteristics of other probiotics. However, *Saccharomyces* needed to cooperate with other probiotics to more substantially improve the eradication effect. In China, the multiple probiotic strains and bismuth quadruple regimen were used widely. Therefore, the eradication effect of Chinese was better than other countries.

Our study indicated that using the probiotics before and throughout the eradication treatment achieved a higher eradication rate. Also, the optimal duration of probiotics was more than 2 weeks. Using probiotics alone could improve the eradication rate, but the effect was not satisfied, which also indicated the characteristics of probiotics as an adjuvant for eradication treatment.[83] Excluded the effects of using probiotics alone, a potential mechanism was that probiotics helped to reduce the load of *H pylori* before eradication and continued to remove residual *H pylori* after eradication.[7] Although previous studies supported this result,[19,84] our study had a more detailed subgroup on the timing and duration of probiotic addition.

We analyzed the incidence of 6 common side effects in the probiotic group. Taste disturbance was the most common side effect, whereas vomiting and diarrhea were relatively less frequent. This difference may explain why probiotics reduced antibiotic-related gastrointestinal side effects, but the mitigation of taste disturbance was not good.[10,11,85]

In terms of the efficacy and safety of probiotics in eradicating *H pylori*, the results from previous meta-analyses were similar to the present study.[18,19,83,86–89] However, some studies did not address the timing and duration of probiotic addition, and excluded the bismuth quadruple regime. In contrast, our study had the following strengths. First, we used the network

meta-analysis method to rank the subgroup results that were not able to directly compared, and the timing of probiotic supplementation was more comprehensive. Second, we investigated the situation of eradicating *H pylori* in China and abroad. Last, we also analyzed the occurrence of common side effects such as diarrhea, abdominal pain, nausea, taste disturbance, vomiting, and constipation.

This study also had some limitations. First, a high heterogeneity was observed on the analysis of total side effects. Although we had used a meta-regression analysis to assess heterogeneity, the source of heterogeneity could not be completely explained. The data on side effects were collected during the follow-up period. Therefore, subjectivity and inconsistency may cause substantial heterogeneity. Second, the small sample size of the study would lead to an overestimation of treatment effects. Last, the subjects analyzed in the present study did not include children. Therefore, more studies with larger sample sizes and higher-quality trials were needed for further analysis.

5. Conclusions

Probiotics improved the eradication rate and reduced side effects when assisting with the eradication of *H pylori*. The use of probiotics before and throughout the eradication treatment, and the use of probiotics for more than 2 weeks exerted a better eradication effect. Probiotics combined with the bismuth quadruple regimen was the best combination. *Lactobacillus* and multiple strains were the better choices for probiotic strains. The eradication effect reported in China was better than the rates reported in other countries.

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Writing – review & editing: Xiaoguang Shi, Jialing Shi, Xue Huang.

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