

An updated systematic review and meta-analysis of fecal microbiota transplantation for the treatment of ulcerative colitis

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Abstract

Background: Fecal microbiota transplantation (FMT) as a promising therapy for ulcerative colitis (UC) remains controversial. We conducted a systematic review and meta-analysis to assess the efficiency and safety of FMT as a treatment for UC.

Methods: The target studies were identified by searching PubMed, EMBASE, the Cochrane Library, Web of Science, and ClinicalTrials and by manual supplementary retrieval. We conducted a general review and quantitative synthesis of included studies. We used the RevMan and Stata programs in the meta-analysis. The outcomes were total remission, clinical remission, steroid-free remission, and serious adverse events. We also performed subgroup analyses based on different populations.

Results: A total of 34 articles were included in the general review. Only 16 articles, including 4 randomized controlled trials, 2 controlled clinical trials, and 10 cohort studies, were selected for the meta-analysis. We found that donor FMT might be more effective than placebo for attaining total remission (risk ratio [RR]: 2.77, 95% confidence interval [CI]: 1.54–4.98; $P = .0007$), clinical remission (RR: 0.33, 95% CI: 0.24–0.41; $P < .05$), and steroid-free remission (RR: 3.63, 95% CI: 1.57–8.42; $P = .003$), but found no statistically significant difference in the incidence of serious adverse events (RR: 0.88, 95% CI: 0.34–2.31, $P = .8$). The subgroup analyses revealed significant differences between the pooled clinical remission rates for different regions, degrees of severity of the disease, and patients with steroid- or nonsteroid-dependent UC.

Conclusions: FMT can achieve clinical remission and clinical response in patients with UC.

Abbreviations: cap-FMT = capsule-delivered fecal microbiota transplantation, CCTs = controlled clinical trials, d-FMT = donor FMT, RCTs = randomized controlled trials, SAEs = serious adverse events, UC = ulcerative colitis.

Keywords: efficiency, fecal microbiota transplantation, safety, systematic review, meta-analysis, ulcerative colitis

1. Introduction

Ulcerative colitis (UC), a type of inflammatory bowel disease, often begins in the rectum, extends to the left hemicolon, and gradually affects the proximal colon and even the whole colon. UC is characterized by a long course and recurrent occurrence, and its main symptoms are abdominal pain, diarrhea, and bloody stool. The morbidity rate of UC has been increasing in developing countries, including South America, Asia, and Africa, although the incidence rate is stabilizing in Western countries, whose burden remains high owing to the prevalence of the disease exceeding 0.3%.^[1] The precise etiology of

UC is still uncertain, and its incidence is caused by many factors, including genetic susceptibility, epithelial barrier defects, immune response disorders, and environmental factors.^[2] Intestinal microbiological imbalance plays a vital role in the development of UC, in a cause-and-effect relationship.

The treatment of UC is based on the severity of the disease, which is typically classified as remission, mild, moderate, or severe.^[3] Routine treatment includes administration of aminosalicylic acids, glucocorticoids, antibiotics, immunosuppressants, and biological agents. Patients with severe acute UC, who fail to respond to medical therapy adequately, should be considered for surgical treatment.^[4] However, the currently

TH, JX, and MW contribute equally.

This study was supported by the National Natural Science Foundation of China (81570783), National Key R&D Program of China (2016YFC1302201), the Key Program of the Natural Science Foundation of Gansu Province, China (18JR3RA366), and the Open Fund of State Key Laboratory of Cancer Biology, China (CBSKL201718).

The authors have no conflicts of interest to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Supplemental Digital Content is available for this article.

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How to cite this article: Huang T, Xu J, Wang M, Pu K, Li L, Zhang H, Liang Y, Sun W, Wang Y. An updated systematic review and meta-analysis of fecal microbiota transplantation for the treatment of ulcerative colitis. *Medicine* 2022;101:30(e29790).

Received: 26 February 2021 / Received in final form: 7 May 2022 / Accepted: 26 May 2022

<http://dx.doi.org/10.1097/MD.00000000000029790>

available treatment is limited and has many adverse effects that are difficult to solve.

With the increasing recognition of the role of intestinal microbiological imbalance in the pathogenesis of UC, many microbial regulatory therapies have been developed, such as probiotic therapy and fecal microbiota transplantation (FMT). In terms of microbial therapeutics, FMT appears to hold the most promise.^[5] However, the efficacy of FMT in patients with UC is uncertain. FMT has been proved to be effective for treating recurrent *Clostridium difficile* infection; therefore, it is attractive to explore the role of FMT in the treatment of UC.

The healthy intestinal microbiome exhibits a considerable functional diversity; one of the crucial functions is priming the immune system of the host.^[5,6] Multiple studies have shown that the type, number, and spatial distribution of the intestinal microbiome vary widely between healthy hosts and patients with UC. FMT restores the diversity of the intestinal microbial population by transplanting fecal microbiota from healthy individuals into the body of the patients. Furthermore, it establishes a trans-kingdom equilibrium between intestinal bacteria, viruses, and fungi, facilitating the recovery of microbial homeostasis.^[7] Paramsothy et al^[8] showed that microbial diversity increased and persisted after FMT among patients.

Many studies have investigated the efficacy and safety of FMT for UC, including 4 high-quality randomized controlled trials (RCTs), multiple controlled clinical trials (CCTs), cohort studies, and case studies. However, their results were inconsistent and sample sizes were relatively small. Moreover, no meta-analyses or systematic reviews have been conducted to date on the efficacy and safety of FMT for UC in the Chinese population, UC at different degrees of severity, and steroid-dependent UC. To include new studies, assess whether the outcomes had changed, and analyze on the basis of new factors, different populations, and outcome indicators, we conducted this research to update and improve the existing systematic reviews and meta-analyses of the efficacy and safety of FMT in UC.

2. Materials and methods

2.1. Search strategy

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, Cochrane, and Meta-analysis Of Observational Studies in Epidemiology guidelines.^[9-11] The protocol for this research was registered in the International Prospective Register of Systematic Reviews (CRD42020164915). Computer-based and manual retrieval were performed. Only human studies were included, without language restrictions. Literature searches in Medline/PubMed (from 1948 to December 2019), EMBASE (from 1947 to December 2019), the Cochrane Library (for all years), Web of Science (from 1950 to December 2019), and ClinicalTrials (for all years) were performed through December 2019. Google Scholar (for all years) was used for the supplementary retrieval. Other studies were manually searched for references to related articles.

We performed the first step of the search using the following keywords: “fecal,” “faecal,” “feces,” “faeces,” “fecal flora,” “faecal flora,” “stool,” “excreta,” “excrement*,” “ordure,” “microflora,” “microorganic,” “microb*.” The second step of the search was performed using the following keywords: “transplant*,” “transfusion,” “transfer*,” “implant*,” “instillation,” “donor*,” “enema*,” “reconstitution,” “infusion*,” “therap*.” Each first-step keyword was combined with each second-step keyword. “Fecal microbiota transplantation,” “FMT,” and “bacteriotherapy” were searched separately. The results were combined with the following terms: “UC,” “ulcerative colitis,” “UC, ulcer colonitis,” “colitis, ulcerative,” “inflammatory bowel disease, ulcerative colitis type,” “idiopathic proctocolitis,” “colitis gravis”^[12] (Appendix 1, Supplemental Digital Content, <http://links.lww.com/MD/G816>).

Two investigators (H.T.B. and W.M.Y.) performed the search independently, and no discrepancy was found in the literature search results.

2.2. Study selection

We established strict inclusion and exclusion criteria according to the participants, interventions, comparisons, outcomes criteria. The EndNote X9 software was used to manage the articles searched from the database. Study selection was performed independently by 2 investigators (H.T.B. and W.M.Y.). For the study, all types of interventional studies were eligible, including RCTs, CCTs, cohort studies, and case studies (case series and case reports). The included studies met the following criteria: included adults and children diagnosed as having UC using any recognized diagnostic criterion; used FMT as the intervention delivered through all possible variation routes (i.e., colonoscopy, nasoduodenal tube, enema, or capsules); and controlled trials that used FMT administered by other routes, placebo, and no treatment as comparators. Studies that met any of the following criteria were excluded: patients with any other disease coexisting with UC and cannot be separated from UC; nonhuman clinical trials, general reviews, conference abstracts, editorials, guidelines, and letters; and any studies with <8 participants (calculated in accordance with the statistical number of each type of study, not the number of participants included originally).

2.3. Quality assessment

The Cochrane risk-of-bias tool was used to assess the risk of bias in the RCTs.^[10] The risk of bias was assessed in 7 different items using the tool. The specific items are described in Table 5. The risk of overall bias for a study was determined to be high if 1 item was high in 1 study.

The Newcastle-Ottawa Scale was used to assess the risk of bias in CCT and cohort studies with no control group.^[13] Using the assessment tool, we graded the selection of ascertainment of exposure, comparability of the study group, and outcome for each report, with 8 subitems. Studies with ≥6 stars were considered to have a low risk of bias; those with 4 or 5 stars, as a moderate risk of bias; and those with ≤3 stars, as a high risk of bias.^[14] We excluded studies with a high risk of bias.

Case series and case reports were only included in the general review and were not assessed. Two independent authors (X.J.L. and W.M.Y.) assessed the article quality. Any differences were settled by consensus.

2.4. Data extraction

Data extraction was performed independently by 2 researchers (X.J.L. and W.M.Y.). The following information was extracted in an Excel spreadsheet: author, year of publication, country, type of study, number of participants, characteristics of the participants (age, disease course, and disease severity), FMT procedures (process condition, frequency, choice of donor, route of instillation, etc), the end point or follow-up timing, the definition of outcomes (steroid-free remission, clinical remission, clinical response, endoscopic remission, etc), fecal characteristics, and severe adverse effects. Any discrepancy in data extraction was resolved by consensus and consulting the third investigator (H.T.B.).

2.5. Statistical analyses

Patient groups, intervention, and outcome measures must be comparable to perform a meta-analysis. Data from individual trials were combined, and a meta-analysis was performed only if the data were considered amenable. Subgroup analyses based on region, patients with steroid- or nonsteroid-dependent UC,

and UC severity was performed. We performed funnel plots for the assessment of publication bias when we identified at least 10 studies. For the identified studies, we used the Egger test for the evaluation of publication bias.

For RCTs and CCTs, statistical analyses were performed with RevMan 5.1 (Review Manager [RevMan] [Computer program] Version 5.1). The results of the dichotomy were estimated using the pooled risk ratio (RR) with the 95% confidence interval (CI). For cohort studies, analyses were performed with the Stata 15.0 statistical package using the metan command. A single-rate meta-analysis was used to estimate the reported effect. We used a random-effects model because it provides a more conservative estimate than a fixed-effects model. We tested for heterogeneity between the studies using the χ^2 test and I^2 statistics. In the Q test, a P value of $<.05$ was considered statistically significant. The χ^2 test indicated substantial heterogeneity between the studies when the P value was $<.1$. The I^2 value was used to assess the degree of heterogeneity, with score discrimination of 0% to 39%, 40% to 59%, and 60% to 100%, consistent with low, moderate, and substantial heterogeneity, respectively.

3. Results

3.1. Search results

A total of 7742 potential articles were identified after the preliminary retrieval. The retrieval results included 7736 articles from 5 electronic databases and 6 articles from other sources. Through manual retrieval, 3 articles were retrieved from references of relevant articles and 3 from original studies included in other meta-analyses. After duplicates were removed and titles and abstracts were screened, we calculated that 40 articles with access to the full text were needed. We excluded 6 studies after reading their full texts. Of these studies, 3 included populations that did not meet the participants, interventions, comparisons, outcomes criteria,^[15–17] and 3 duplicated data from other studies practically.^[18–20] We performed a qualitative synthesis of the remaining 34 studies. Sixteen studies were included in the meta-analysis after excluding 21 studies. The flow diagram of the study selection process for the systematic review and meta-analysis is shown in Figure 1.

3.2. Study characteristics

A total of 34 studies published between 2016 and 2019 were finally analyzed, including RCTs ($n = 5$), CCTs ($n = 2$), cohort studies ($n = 17$), case series ($n = 2$), and case reports ($n = 8$). The total number of patients in all the studies was 852, with the number of patients in individual studies ranging from 1 to 129. These reports were from 12 different countries. The top 3 countries that contributed to the number of reports were China ($n = 7$), the United States ($n = 6$), and Japan ($n = 6$).

Eight studies involved a study population with moderate-to-severe active UC (Mayo score ≥ 6), including 6 cohort studies and 2 case reports. The other studies included patients with either mild-to-moderate UC or unrecorded disease severity. Another 8 studies involved pediatric patients with UC, including 1 RCT, 3 cohort studies, and 4 case reports. The rest of the studies involved adults with UC. Eight studies involved patients with refractory UC, including 1 CCT, 3 cohort studies, and 4 case reports. Eight studies included patients with steroid-dependent UC, including 3 RCTs, 3 cohort studies, and 2 case reports.

Three major FMT routes were used, including colonoscopy, retention enema, and nasoduodenal tube. Two studies used a capsule-delivered FMT (cap-FMT). The first case report of the use of cap-FMT in the treatment of UC was published in 2017. In addition, a cohort study of cap-FMT for UC was published in

2019, in which cap-FMT was performed as maintenance therapy after the initial colonoscopic FMT.

The end points reported in each study varied. Clinical remission and response were the 2 most common outcomes. Five studies that used steroid-free remission as outcome were reported, including 2 RCTs, 2 cohort studies, and 1 case report. In 2 studies, including 1 RCT and 1 cohort study, the follow-up period was >1 year (>12 months), and the outcome was the efficacy of FMT for maintaining the long-term remission of patients with UC.

The patients were pretreated with antibiotics in the 2 CCTs. A total of 63 patients with active UC (FMT after antibiotic pretreatment vs antibiotic pretreatment only) were included in the 2 CCTs, divided into an FMT group (54%) and an AB group (antibiotic pretreatment only; 46%). Table 1 provides a detailed description of the characteristics of the studies. Of the 10 case studies, 4 reported cases of refractory UC and 2 reported cases of steroid-dependent UC.

3.3. Randomized controlled trials

The 4 RCTs were reported from 2015 to 2019. A total of 277 patients with mild-to-moderate active UC (Mayo score range: 3–10) were included, with the patient populations of the individual studies ranging from 48 to 81. The included patients were at least 20 years old, and 140 patients (50.5%) were randomly allocated to the donor FMT (d-FMT) group and 137 (49.5%), to the placebo group. FMT was performed more than twice in all the 4 trials. The patients and stool donors were not related in the 4 trials. To minimize the risk of disease transmission, strict screening criteria were applied to potential donors in the 4 trials. Two trials^[21,22] used a single donor for the FMT, and 2 trials^[8,23] used pooled donors for the FMT. The stool samples^[23] were processed under anaerobic conditions only in 1 trial and under aerobic conditions in 3 trials. The follow-up time points were 7, 8, 8, and 12 weeks, respectively. Microbiota analyses of stool samples were performed in all the 4 trials. Stable dosing of UC maintenance therapies (oral 5-aminosalicylates, glucocorticoids, thiopurines, etc) was permitted in the 4 trials, except that the use of any steroids was stopped before reaching the outcome points in 2 trials.^[8,23] Table 1 provides a detailed description of the characteristics of the studies. In the 4 RCTs, the primary outcome was remission (clinical remission with endoscopic remission or response); therein, the primary outcome of 2 trials was steroid-free remission^[8,23]; that is, the patients stopped using any steroids before reaching the outcome points. The secondary outcomes included clinical remission, clinical response, endoscopic remission or response, and serious adverse events (SAEs). The definitions of the outcomes are shown in Table 2.

3.4. Cohort studies

Seventeen cohort studies were reported from 2013 until 2019. A total of 358 patients from the study populations of the individual studies, which ranged from 4 to 109 patients, were included. The study populations included children and adults. Six studies had mild-to-moderate UC (Mayo score range: 3–10). Five studies included patients with moderate-to-severe UC (Mayo score range: 6–12). Six other studies did not record the severity of the disease. Colonoscopy was the most common route of FMT. The frequencies of FMT were once and many times. The stool donor was a single donor in 5 studies and pooled donors in 7 studies. Fresh stool was used in 12 studies, and frozen stool was used in 2 studies. We also counted the number of participants according to sex, the course of the disease, and the follow-up period. The detailed information is shown in Table 3. Two studies did not record the incidence of outcome events and mentioned only the mean Mayo scores of the patients with UC before and

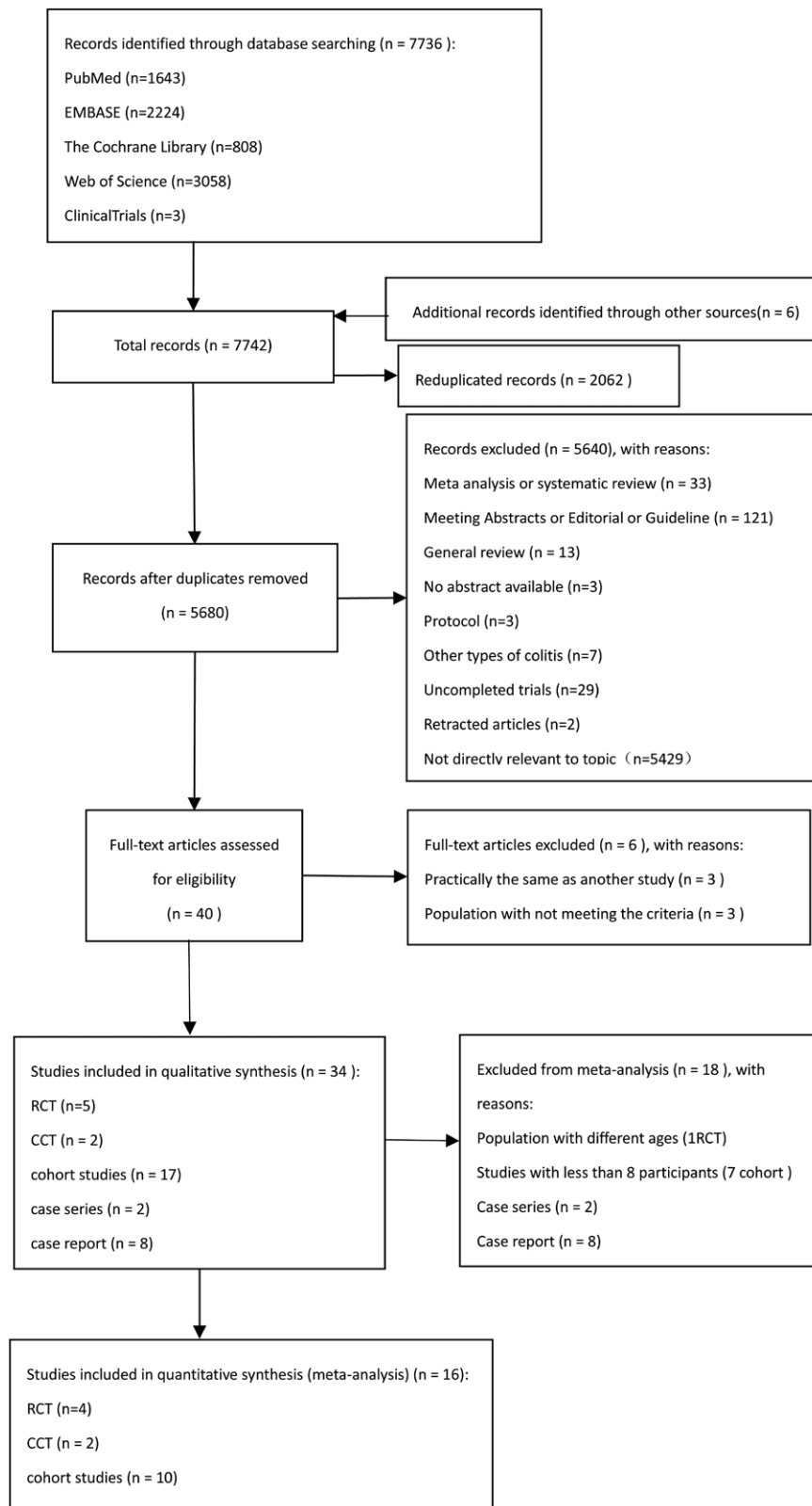


Figure 1. Flow diagram of the study selection process for the systematic review and meta-analysis. CCT = controlled clinical trial, RCT = randomized controlled trial.

after FMT. The results showed that the patients' Mayo scores decreased after treatment. One study did not record the clinical remission rate. Four studies were conducted with <8 participants. The remaining 10 studies were included in the quantitative synthesis. The definitions of outcomes are shown in Table 4.

3.5. Risk of bias of individual studies

The risk assessment of bias of the RCTs is shown in Table 5. Three RCTs received a high-quality score for all the items. One RCT was of unclear quality due to the blinded outcome assessment and incomplete outcome data, and the other items were of

Table 1
Characteristics of included RCTs and CCTs.

Study	Year	Country	Study Type	Age (yr)	Severity of the disease		Course of the disease (yr)		Patients (group)			Route	Frequency	Endpoint (wk)	Donor	Relationship	Stool	Process condition
					Mild-moderate	Severe	FMT	Placebo	FMT	Placebo	FMT							
Costello et al ^[23]	2019	Australia	RCT	≥18	Mild-moderate	Mean 4.9 (1.6–9.6)	Mean 5.8 (2.4–11)	Autologous stool	38	35	Colonoscopy	Three times in a week	8	Pooled donors	Unrelated	Frozen	Anaerobic	
Mozayedi et al ^[21]	2015	Canada	RCT	≥18	Mild-moderate	7.9±5.6	7.0±6.8	Water	38	37	Retention enema	Once per week for 6 wk	7	Single donor	Unrelated	Fresh; frozen	Aerobic	
Paramsothy et al ^[8]	2017	Australia	RCT	18–75	Mild-moderate	Mean 5.8 (3.4–9.0)	Mean 5.8 (2.7–9.4)	Isotonic saline adding brown food colorant, odorant, and glycerol cryoprotectant	41	40	Colonoscopy+ enemas	A total of 40 times	8	Pooled donors	Unrelated	Frozen	Aerobic	
Rossen et al ^[22]	2015	The Netherlands	RCT	≥18	Mild-moderate	NR	NR	Autologous stool	23	25	Nasoduodenal tube	A total of twice, interval of 3 wk	12	Single donor	Unrelated	Fresh	Aerobic	
Ishikawa et al ^[27]	2017	Japan	CCT	≥20	Mild-severe	NR	NR	Antibiotic (amoxicillin, fosfomycin, and metronidazole)	17	19	Colonoscopy	Once	4	Single donor	Related	Fresh	NR	
Kump et al ^[28]	2018	Austria	CCT	16–80	NR	8±8	7±6	Antibiotic	17	10	Endoscopy	Five times per 2 wk intervals	12	Single donor	Related; unrelated	Frozen	NR	

CCT = controlled clinical trial, NR = not recorded, RCT = randomized controlled trial.

high quality. Four RCTs were determined to be of high methodological quality. The risk assessments of bias of the CCTs and cohort studies are shown in Tables 6 and 7, respectively. Two CCTs and 9 cohort studies had a low risk of bias. Six cohort studies had a moderate risk of bias. None of the studies had a high risk of bias.

3.6. Statistical analyses

We conducted a meta-analysis of 4 high-quality RCTs. Overall, total remission was achieved in 39 (28%) of the 140 patients in the d-FMT group and in 13 (9%) of the 137 patients in the placebo group. The pooled RR for total remission (clinical remission with endoscopic remission or response) was 2.77 (95% CI: 1.54–4.98). A statistically significant difference was found between the d-FMT and placebo groups ($P = .0007$), and no or low heterogeneity was observed between the 4 trials ($P = .53$, $I^2 = 0\%$; Fig. 2). These results are consistent with those of previous studies.^[24,25] The number of studies was too small to make the statistical assessment of publication bias reasonable.

We also conducted a meta-analysis of 2 CCTs with patients pretreated with antibiotics. The pooled results showed that clinical remission was achieved in 10 (29%) of the 34 patients in the FMT group and in 3 (10%) of the 29 patients in the AB group. No significant difference was found between the 2 groups in clinical remission, with an RR of 2.58 (95% CI: 0.84–7.91; Fig. 3). The results also showed a low heterogeneity between the 2 trials ($I^2 = 0\%$, $P = .55$). The results differed from those of a previous study that showed a significant difference (odds ratio = 6.18, 95% CI: 1.7–22.49) between the FMT and AB groups and low heterogeneity ($P = .17$, $I^2 = 48\%$) between the 2 trials.^[26] The number of studies was too small to make the statistical assessment of publication bias reasonable.

For the cohort studies, 10 eligible studies were quantitatively evaluated. One cohort study was excluded automatically because the number of events was 0. For the 9 studies included, the meta-analysis based on the random-effects model revealed that the overall clinical remission rate of the 9 studies was 0.33 (95% CI: 0.24–0.41), which was statistically significant ($z = 7.44$, $0.000 = P < .05$) and suggests that FMT was effective in the treatment of UC, attaining a clinical remission rate of 33% (Fig. 4A). In the heterogeneity test, the Q test result was $I^2 = 43.5\%$ ($0.078 = P < .1$), which suggests a moderate heterogeneity between the included studies. Thus, we continued to conduct a sensitivity analysis to investigate the causes of the heterogeneity. After the sensitivity analysis, none of the studies interfered with the results of the meta-analysis, which meant that the results were stable (Fig. 4B). As the number of included studies was <10, potential publication bias was assessed using the Egger test. The result of the Egger test was 0.754 ($P > .05$), which indicated no publication bias in the studies included in the meta-analysis (Fig. 4C).

3.7. Subgroup analyses

Steroid-free remission was achieved in 23 (29%) of the 79 patients who received d-FMT and in 6 (8%) of the 75 who received placebo (RR: 3.63, 95% CI: 1.57–8.42). A statistically significant difference was found between the d-FMT and placebo groups ($P = .003$), and no or low heterogeneity was observed between the 2 trials ($I^2 = 0\%$, $P = .97$; Fig. 5). The meta-regression analysis revealed significant correlations among the regions, degrees of severity of diseases, and patients with steroid- or nonsteroid-dependent UC ($P < .5$). We continued to conduct a subgroup analysis.

The efficacy rate of FMT varied between mild-to-moderate and moderate-to-severe UC when the patients were subdivided according to disease severity (Fig. 6A). The pooled clinical remission rate for mild-to-moderate UC was 0.46 (95%

Table 2
Definition and data extraction of measured outcomes in RCTs and CCTs.

Study	Costello et al ^[23]	Moayyedi et al ^[21]	Paramsothy et al ^[9]	Rossen et al ^[22]	Ishikawa et al ^[27]	Kump et al ^[26]
The primary outcome	Steroid-free remission	Remission	Steroid-free remission	Remission	NR	NR
Definition total remission	Total Mayo ≤ 2 with endoscopic Mayo ≤ 1	Total Mayo < 3 with endoscopic Mayo = 0	Total Mayo ≤ 2 with subscores of ≤ 1 endoscopic subscore ≥ 1 point reduction	SCCAI ≤ 2 with ≥ 1 point reduction in the combined endoscopic Mayo score of sigmoid and rectum	NR	Total score ≤ 2
Total remission	FMT 12 Placebo 3	9 2	11 3	7 5	NR NR	NR NR
Definition clinical remission	Total Mayo score ≤ 2	Total Mayo score < 3	Total Mayo score ≤ 2 with subscores of ≤ 1	SCCAI ≤ 2	CAI ≤ 3	Total Mayo ≤ 2
Clinical remission	FMT 18 Placebo 6	9 2	18 8	7 8	6 3	4 0
Definition clinical response	≥ 3 -point reduction in Mayo score	≥ 3 -point reduction in Mayo score	≥ 3 -point reduction in Mayo score or $\geq 50\%$ reduction from baseline in combined rectal bleeding plus stool frequency subscores	≥ 1.5 -point reduction on the SCCAI	CAI ≤ 10 -point and ≥ 3 -point reduction	≥ 3 -point reduction in Mayo score
Clinical response	FMT 21 Placebo 8	15 9	22 9	11 13	14 13	10 1
Definition endoscopic response	Endoscopic Mayo score ≤ 1	Endoscopic Mayo score = 0	Endoscopic Mayo score = 0	NR	NR	NR
Endoscopic remission	FMT 4 Placebo 0	9 2	5 3	2 2	NR NR	NR NR
Definition endoscopic response	3 (1 worsening colitis, 1 C difficile colitis requiring colectomy, 1 pneumonia)	3 (2 patchy inflammation of the colon and rectal abscess formation, 1 C difficile infection)	≥ 1 -point reduction in endoscopic Mayo subscore	≥ 1 -point reduction in endoscopic Mayo subscore	NR	1 (worsening colitis)
Serious adverse effects	2 (both worsening colitis)	2 (1 worsening colitis, 1 patchy inflammation of the colon and rectal abscess formation)	1 (needed hospitalization)	2 (NR)	NR	5 (3 C difficile infection, 1 antibiotic-associated diarrhea, 1 worsening colitis)

CAI = Lichtiger's Clinical Activity Index, CCT = controlled clinical trial, C difficile, Clostridium difficile, FMT = fecal microbiota transplantation, NR = not recorded, RCT = randomized controlled trial, SCCAI = Simple Clinical Colitis Activity Index.

Table 3
Characteristics of included cohort studies.

Study	Year	Country	Age (yr)	Male, N (%)	Severity of the disease	Course of the disease	Patients (n)	Route	Frequency	Follow-up	Donor	Stool
Tian et al ^[29]	2019	China	18–75	11 (55%)	NR	4.5	20	Gastroduodenal tube	5 times, interval of 3 wk	12 wk	Single donor	Fresh
Sood et al ^[30]	2019	India	18–75	24 (58.54%)	Mild-moderate	4.6 ± 4.2	41	Colonoscopy	7 times (at weeks 0, 2, 6, 10, 14, 18, and 22)	24 wk	NR	Fresh
Ding et al ^[31]	2019	China	8–74 (mean 40.0 ± 14.3)	65 (59.6%)	Moderate-severe	6.5 ± 5.5	109	Midgut/nasojejunal; colonic TET	Twice (1–9)	12–68 mo	Pooled donors	Fresh
Adler et al ^[32]	2019	United States	25–70 (mean 47)	8 (62%)	NR	NR	13	Colonoscopy	6 times	6 wk	Pooled donors	Fresh
Karolewska-Bochenek et al ^[33]	2018	Poland	10–17	2 (25%)	NR	5.25	8	Nasoduodenal tube or gastroscopy	8 times	33 d	Pooled donors	Fresh
Uygun et al ^[34]	2017	Turkey	19–58 (mean 34.6 ± 10.3)	14 (46.7%)	Moderate-Severe	5.3 ± 3.3	30	Colonoscopy	Once or twice	12 wk	Pooled donors	Fresh
Nishida et al ^[35]	2017	Japan	>15 (mean 39.6 ± 16.9)	28 (68.2%)	Mild-moderate	91.2 ± 103.3 M	41	Colonoscopy	NR	8 wk	Single donor	Fresh
Mizuno et al ^[36]	2017	Japan	17–48 (mean 31)	7 (70%)	Moderate-severe	4.5	10	Colonoscopy	Once	12 wk	Pooled donors	Frozen
Jacob et al ^[37]	2017	United States	23–71 (mean 38.4)	12 (60%)	NR	NR	20	Colonoscopy	Once	4 wk	Pooled donors	NR
Vermeire et al ^[38]	2016	Belgium	30–53 (mean 39.9)	6 (75%)	NR	6.88	8	Nasojejunal tube	Twice	>6 mo	Single donor	Fresh
Wei et al ^[39]	2015	China	26–70 (mean 47)	3 (27.3%)	Mild-moderate	4.5	11	Colonoscopy	NR	4 wk	Single donor	Frozen
Dammen et al ^[40]	2015	United States	25–61 (mean 36)	2 (28.6%)	Mild-moderate	16.57	7	Colonoscopy	Once	3 mo	Single donor	Fresh
Cui et al ^[41]	2015	China	11–48 (mean 31.7)	11 (73.3%)	Moderate-severe	4.2	15	Gastroscopy	Once or twice	3–18 mo	NR	NR
Suskind et al ^[42]	2014	United States	13–16 (mean 14.5 ± 1.7)	4 (100%)	Mild-moderate	1	4	Gastroscopy	Once	12 wk	NR	NR
Kunde et al ^[43]	2013	United States	7–21	6 (60%)	Mild-moderate	3.51	10	Fecal enemas	5 times	6 wk	NR	Fresh
Kurpp et al ^[44]	2013	Austria	17–52 (mean 36)	3 (50%)	NR	5.5	6	Colonoscopy	Once	3 mo	Pooled donors	Fresh
Angelberger et al ^[45]	2013	Austria	22–51 (mean age 34.2)	3 (60%)	Moderate-severe	4.1	5	Nasojejunal tube and enema	3 times	7 mo	NR	Fresh

M = month, NR = not recorded; TET = transendoscopic enteral tubing.

Table 4

Definition and data extraction of measured outcomes in cohort studies.

Study	Definition clinical remission	Clinical remission rate (%)	Definition clinical response	Clinical response rate (%)	Definition endoscopic remission	Serious adverse effects
Tian et al ^[29]	NR	NR	NR	NR	NR	0
Sood et al ^[30]	Mayo score ≤2, with subscore ≤1	46.3	Reduction of Mayo score ≥30% and ≥3	75.6	Mayo endoscopy subscore ≤1	0
Ding et al ^[31]	Partial Mayo score ≤1	1M:25.7 3M:20.2 6M:13.8	A decrease of ≥2 and ≥30%, with a decrease in the rectal bleeding subscore of ≥1 or an absolute rectal bleeding subscore of ≤1	1M:74.3 3M:51.4 6M:28.4	NR	1
Adler et al ^[32]	NR	NR	NR	NR	NR	0
Karolewska-Bochenek et al ^[33]	PUCAI score <10	37.5	A decrease of ≥15 points in PUCAI	87.5	NR	0
Bochenek et al ^[33]	Mayo score ≤2 and complete mucosal healing (Mayo endoscopy subscore ≤1)	43.3	A decrease in the Mayo score ≥30% and ≥3	70	Mayo endoscopy subscore ≤1	0
Uygun et al ^[34]	Mayo score of ≤2, with no subscore >1	0	A decrease in the full Mayo score of ≥3 or a decrease in the Mayo clinical score of ≥2 with a decrease in the rectal bleeding subscore of ≥1	26.8	Mayo endoscopy subscore ≤1	0
Nishida et al ^[35]	Mayo score ≤2	NR	NR	9	NR	0
Mizuno et al ^[36]	Mayo score ≤2 and no subscore >1	15	A decrease of Mayo score ≥3 and a bleeding subscore ≤1	35	NR	0
Jacob et al ^[37]	NR	25	NR	25	Mayo endoscopy subscore ≤1	0
Vermeire et al ^[38]	Mayo score <2	A decrease in Mayo score of >1	54.5	100	NR	0
Wei et al ^[39]	A total UCDAI score of ≤2 and subscore ≤1	14.3	Decrease in total UCDAI score of ≥3	14.3	NR	0
Dammen et al ^[40]	The absence of diarrhea and blood (Montreal classification S0)	28.6	A persistent steroid-free clinical improvement	85.7	NR	0
Cui et al ^[41]	PUCAI score of <10	0	NR	0	NR	0
Suskind et al ^[42]	PUCAI <10	33	Decrease in PUCAI by >15	67	NR	0
Kunde et al ^[43]	Mayo score ≤2	0	A decrease in Mayo score of ≥3	33.3	NR	0
Kump et al ^[44]	Mayo score ≤2 with subscore ≤1	0	A decrease of ≥3 and ≥30%, with a decrease in the rectal bleeding subscore of ≥1 or an absolute rectal bleeding subscore of ≤1	20	NR	0
Angelberger et al ^[45]						

NR = not recorded, PUCAI = Pediatric Ulcerative Colitis Activity Index, UCDAI = ulcerative colitis disease activity index.

Table 5

The Cochrane risk-of-bias tool for assessing risk of bias of RCTs.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personal	Blinding of outcome assessment	Incomplete outcome data	Selection reporting	Other sources of bias
Moayyedi et al ^[21]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Rossen et al ^[22]	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk
Paramsothy et al ^[8]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Costello et al ^[23]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

RCT = randomized controlled trial.

Table 6
Newcastle-Ottawa Scale for assessing quality of CCTs.

Study (yr)	Selection			Comparability		Outcome			NOS score
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur (28 d)	Adequacy of follow-up of cohorts	
Ishikawa et al (2017) ^[27]	—	—	*	*	*	*	*	—	5
Kump et al (2018) ^[28]	—	*	*	*	*	*	*	—	6

* = yes, _ = no, CCT = controlled clinical trial, NOS = Newcastle-Ottawa Scale.

Table 7
Newcastle-Ottawa Scale for assessing quality of cohort studies.

Study (yr)	Selection			Comparability		Outcome			NOS score
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur (4 wk)	Adequacy of follow-up of cohorts	
Tian et al (2019) ^[29]	—	—	*	*	*	*	—	—	4
Sood et al (2019) ^[30]	—	—	*	*	*	*	*	*	6
Ding et al (2019) ^[31]	—	—	*	*	*	*	*	*	6
Adler et al (2019) ^[32]	—	—	*	*	*	*	*	—	5
Karolewska-Bochenek et al (2018) ^[33]	—	—	*	*	*	*	—	—	4
Uygun et al (2017) ^[34]	—	—	*	*	*	*	*	*	6
Nishida et al (2016) ^[35]	—	—	*	*	*	*	*	*	6
Mizuno et al (2017) ^[36]	—	—	*	*	*	*	*	*	6
Jacob et al (2017) ^[37]	—	—	*	*	*	*	*	—	5
Vermeire et al (2015) ^[38]	—	—	*	*	*	*	*	*	6
Wei et al (2015) ^[39]	—	—	*	*	*	*	*	*	6
Damman et al (2015) ^[40]	—	—	*	*	*	*	*	*	6
Cui et al (2015) ^[41]	—	—	*	*	*	—	*	*	5
Suskind et al (2014) ^[42]	—	—	*	*	*	*	*	*	6
Kunde et al (2013) ^[43]	—	—	*	*	*	*	*	—	5
Kump et al (2013) ^[44]	—	—	*	*	*	*	*	*	6
Angelberger et al (2013) ^[45]	—	—	*	*	*	*	*	*	6

*** = yes, " _ " = no.

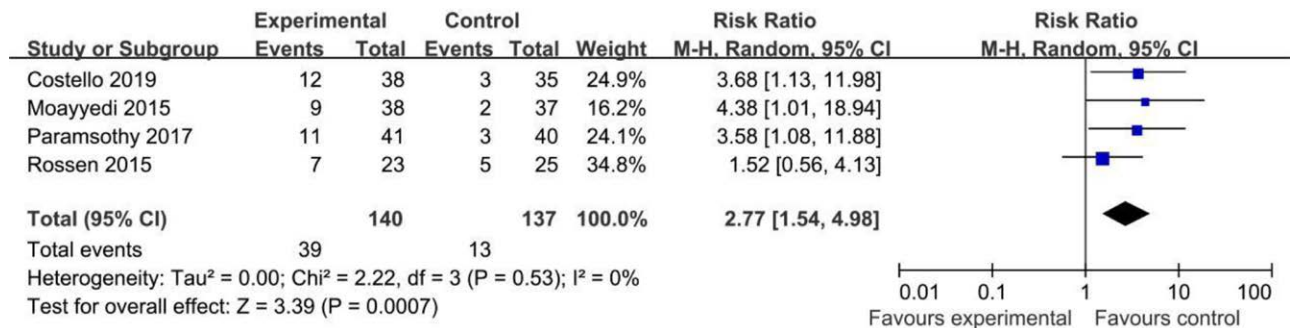


Figure 2. Forest plot of the RCTs that reported total remission rates. CI = confidence interval, RCT = randomized controlled trial.

CI: 0.33–0.58), and the results showed no or low heterogeneity for the subgroups ($I^2 = 0\%$, 0.615 [$P > .1$]). The pooled clinical remission rate for moderate-to-severe UC was 0.31 (95% CI: 0.20–0.42), and the results showed no or low heterogeneity for the subgroups ($I^2 = 36.2\%$, 0.209 [$P > .1$]).

The efficacy rate of FMT varied among the regions when the studies were subdivided into China, Asia except for China, and non-Asian countries (Fig. 6B). The pooled clinical remission rate in Asia, excluding China, was 0.45 (95% CI: 0.33–0.57), and the results showed no or low heterogeneity for the subgroups

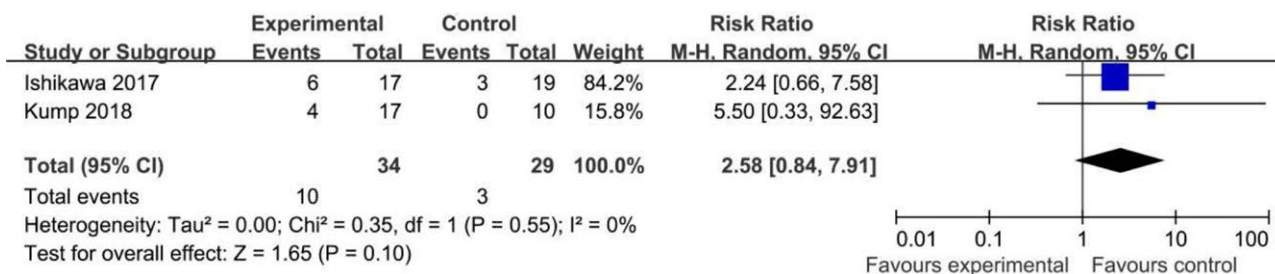


Figure 3. Forest plot of the CCTs that reported clinical remission rates in patients pretreated with antibiotics. CCT = controlled clinical trial, CI = confidence interval.

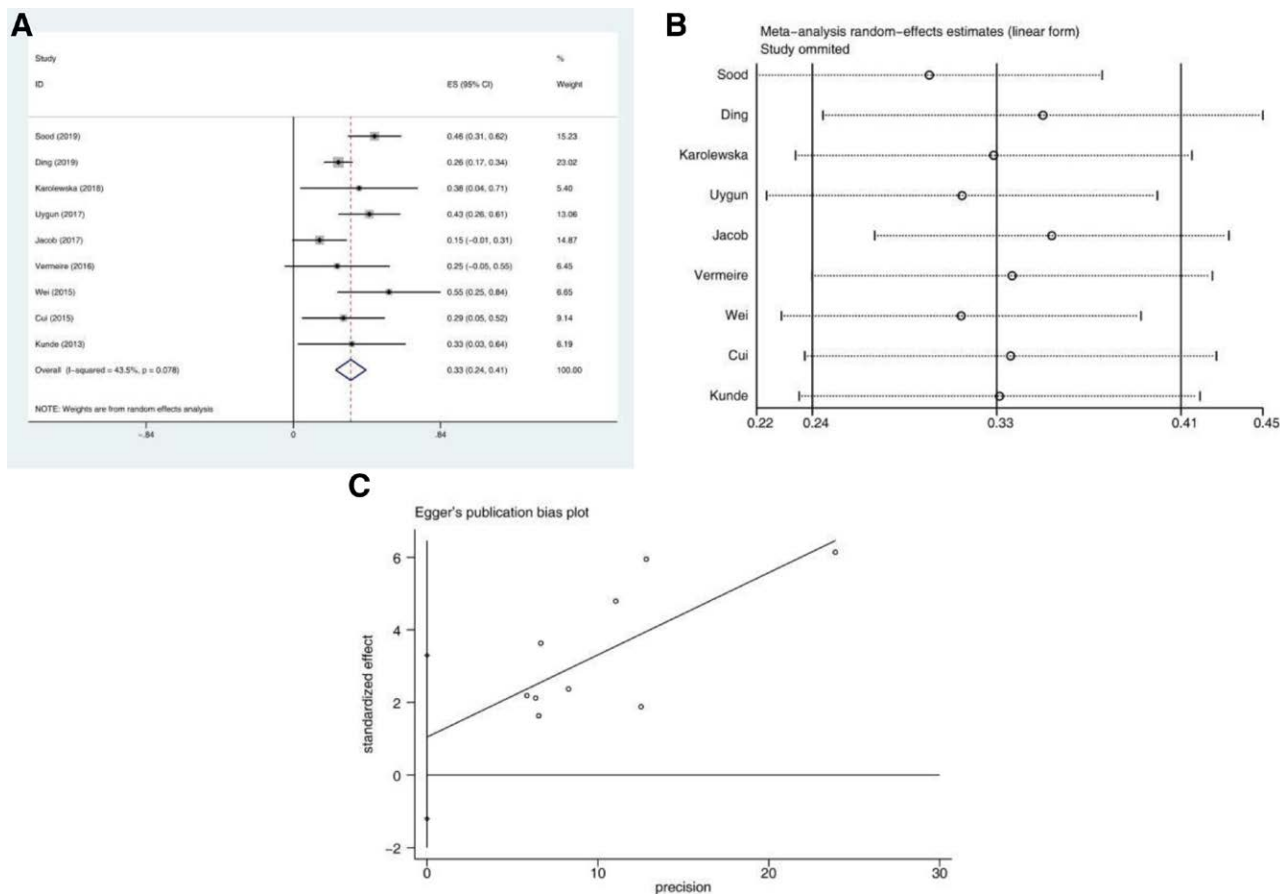


Figure 4. Cohort studies that reported clinical remission: (A) forest plot of the clinical remission rates; (B) random-effects estimate plot; and (C) Egger publication bias plot.

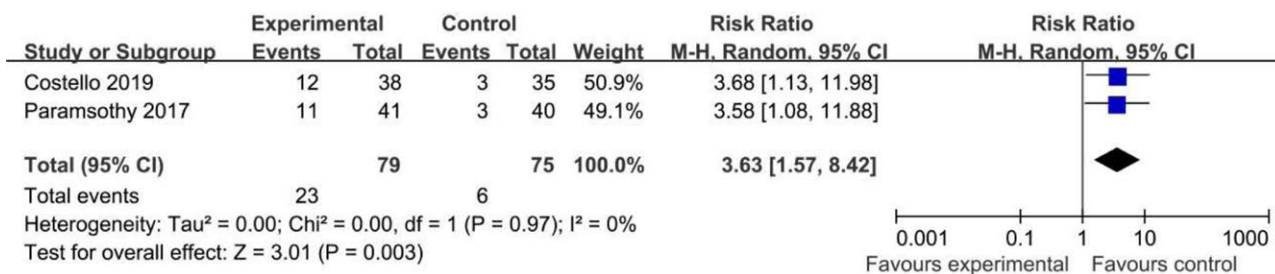


Figure 5. Forest plot of the RCTs that reported steroid-free remission. CI = confidence interval, RCT = randomized controlled trial.

(I² = 0%, 0.801 [P > .1]). The pooled clinical remission rate in China was 0.31 (95% CI: 0.17–0.46), and the results showed a moderate heterogeneity for the subgroups (I² = 41.7%, 0.180

[P > .1]). The pooled clinical remission rate in the non-Asian studies was 0.22 (95% CI: 0.10–0.34), and the results showed no or low heterogeneity for the subgroups (I² = 0%, 0.542 [P > .1]).

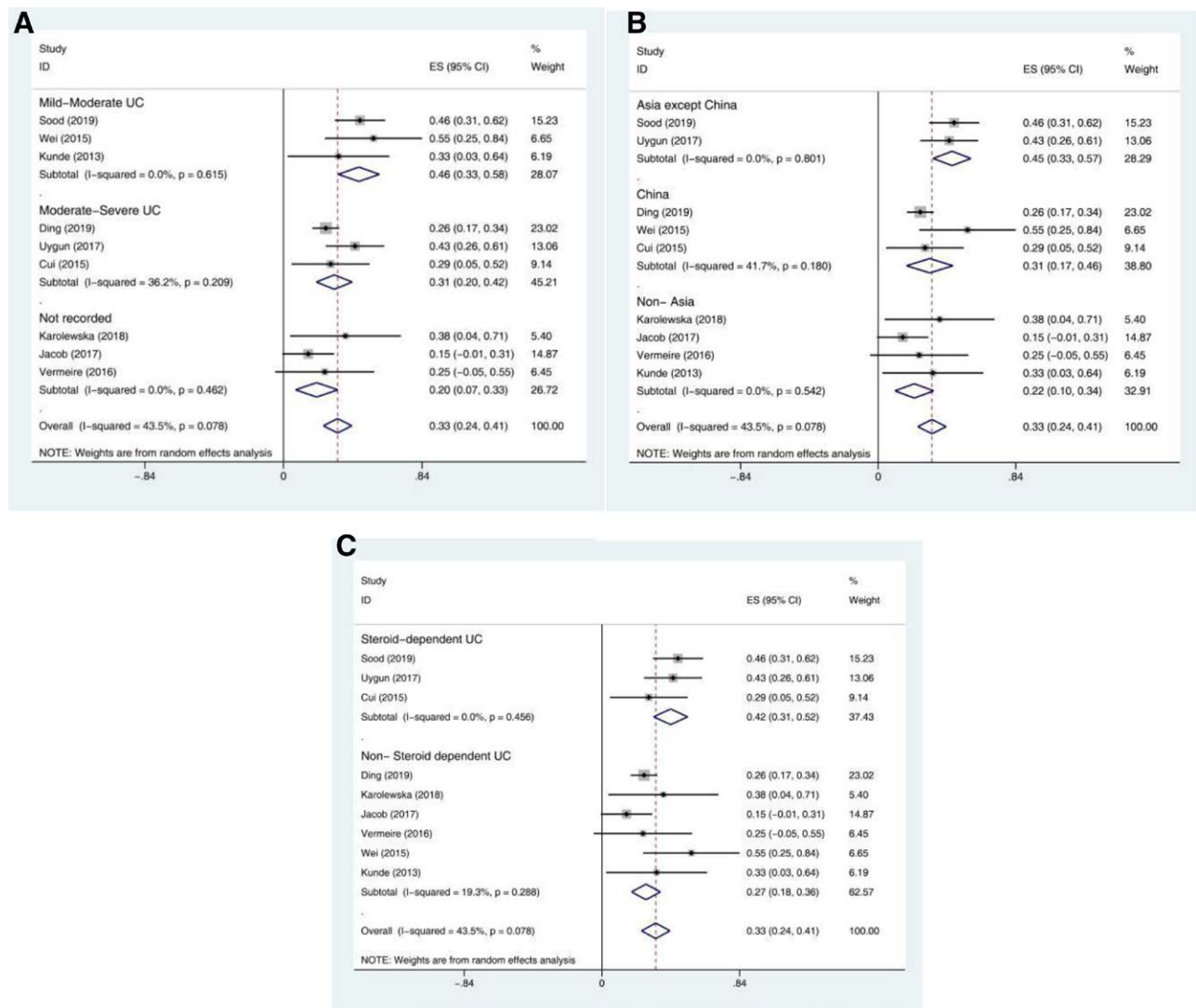


Figure 6. Subgroup analysis of UC patients for clinical remission in cohort studies: (A) the difference between mild-moderate UC and moderate-severe UC patients; (B) the difference between UC patients from China, Asia except China, and non-Asia; and (C) the difference between steroid-dependent UC and non-steroid-dependent UC patients. CI = confidence interval, UC = ulcerative colitis.

We further subdivided the studies according to patients with steroid- or nonsteroid-dependent UC. The pooled clinical remission rate for steroid-dependent UC was 0.42 (95% CI: 0.31–0.52), and the results showed no or low heterogeneity for the subgroups ($I^2 = 0\%$, 0.456 [$P > .1$]). The pooled clinical remission rate for nonsteroid-dependent UC was 0.27 (95% CI: 0.18–0.36), and the results showed a low heterogeneity for the subgroups ($I^2 = 19.3\%$, 0.288 [$P > .1$]; Fig. 6C).

3.8. Safety

Two (1 CCT and 1 case series) of the 34 studies did not report SAEs. We counted SAEs in the other 32 studies. No SAE was found in the case studies. Only 1 case of SAE (myasthenia gravis) was found in the 17 cohort studies. Other SAEs were found in all the 4 RCTs and 1 CCT. Detailed information on the SAEs is shown in Tables 2 and 4.

Compared with FMT, AB was poorly tolerated in 1 CCT (RR = 0.12, 95% CI: 0.02–0.87). The total incidence rate of SAEs was 7% (11/157 patients) in the d-FMT group and 8% (12/147 patients) in the placebo group. The pooled RR for total SAEs was 0.88 (95% CI: 0.34–2.31). No statistically significant

differences were found between the d-FMT and placebo groups ($P = .8$), and low heterogeneity was observed between the 5 trials ($P = .28$, $I^2 = 20\%$; Fig. 7).

4. Discussion

In a meta-analysis of the 4 high-quality RCTs that have been conducted to date, d-FMT was significantly more effective than placebo for the induction of clinical remission with endoscopic remission or response in patients with UC, which is similar to the results of the studies by Costello et al^[24] and Narula et al.^[25] We also synthesized the clinical remission rate in the cohort studies. The pooled result of clinical remission suggested that FMT was effective for the treatment of UC.

Our study also showed differences in the significance of steroid-free remission. d-FMT was significantly more effective than placebo for the induction of steroid-free remission of active UC. The results differ from those of a previous study, which showed no statistically significant difference in steroid-free remission (odds ratio = 2.08; 95% CI: 0.41–10.5; $P = .37$; $I^2 = 69\%$).^[26] This result may be of significance for adjusting patients' treatment plans after FMT.

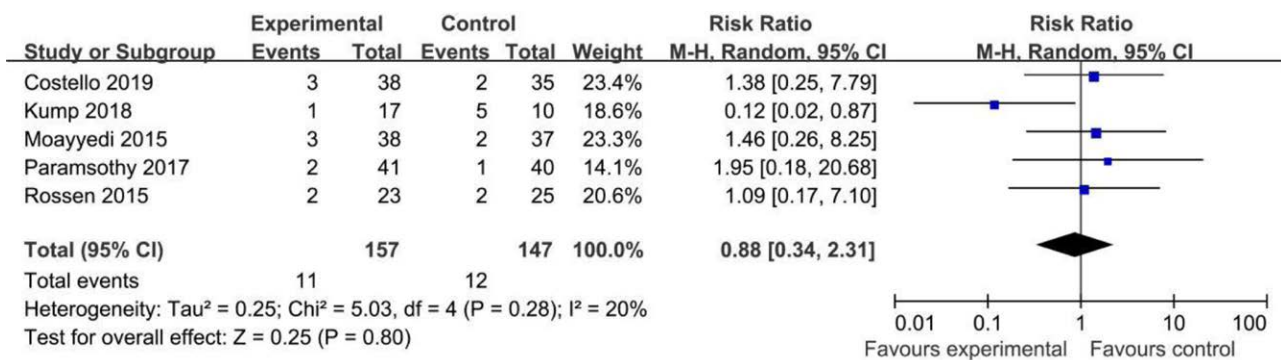


Figure 7. Forest plot of severe adverse events after FMT. CI = confidence interval, FMT = fecal microbiota transplantation.

To our knowledge, this systematic review and meta-analysis study is the first to investigate the effectiveness of FMT in patients with UC from different regions, the severity of the disease, and steroid-dependent UC. The meta-regression analysis revealed significant correlations for different regions, degrees of disease severity, and patients with steroid- or nonsteroid-dependent UC. Subsequently, we synthesized the results of the cohort study by performing a subgroup analysis because no RCTs or CCTs were conducted in the Chinese population, patients with moderate-to-severe UC, or steroid-dependent patients. The pooled clinical remission rate appeared to have increased in the order of non-Asia, China, and Asia excluding China, which seemed much higher for mild-to-moderate UC than for moderate-to-severe UC, and for steroid-dependent UC than for nonsteroid-dependent UC. This may provide a new idea for the treatment of UC according to different populations.

As for the question of sample size, some studies were first registration trials. Safety assessment should be given priority in accordance with the requirements of the ethics committee. An effectiveness assessment was secondary; thus, the number of patients included was <8. When counting the serious adverse effects after FMT, we did not limit the number of patients included in the study. This is also the first study to synthesize the evidence from all types of studies that investigated the severe adverse events due to FMT for the treatment of UC, including CCTs, cohort studies, and case studies not included in previous studies.^[25,26] The pooled results showed no statistically significant difference in severe adverse events among the patients who received FMT. This result is consistent with the results of a previous systematic review and meta-analysis of RCTs by Narula et al^[25] and Lam et al.^[26] Overall, FMT was safe and well tolerated in patients with UC. However, few data are available on its long-term safety, and further validation is needed.

Antibiotic pretreatment was used to improve the efficacy of FMT.^[27] Antibiotic treatment without FMT resulted in only short-term improvement of disease activity and was poorly tolerated, with the emergence of infections with intestinal pathogens such as *C difficile*. Furthermore, microbial richness decreased in the long term. The persistent antimicrobe-associated dysbiosis found in the AB group was reversed by FMT.^[27,28] Kump et al^[28] assumed that these adverse events were caused by a loss of intestinal colonization resistance. A higher clinical response was observed in the FMT group than in the AB group after treatment, but no statistically significant difference was found. A possible reason for this result is that the different types of fecal microbiota from the donors in the 2 groups may have caused mixed bias. The results differ from those of a previous study that showed a significant difference in clinical response between the FMT and AB groups.^[26]

A previous meta-analysis revealed that the optimal FMT delivery was through the colonoscopy route.^[46] Zhang et

al^[47] performed a meta-analysis that indicated that the clinical remission rate was significantly higher in the lower digestive tract than in the upper digestive tract. However, the FMT colonoscopy route may be burdensome for long-term therapy, and cap-FMT is preferred by patients with recurrent *C difficile* infection.^[48] Cap-FMT, after multiple routes such as colonoscopy, retention enema, and nasoduodenal tube, is becoming an increasingly more promising new type of FMT route for improving intestinal flora. One study reported a case of UC successfully treated with oral lyophilized full-spectrum microbiota.^[49] Compared with interventional FMT, cap-FMT is more convenient, has fewer adverse effects, and is easier for patients to accept.^[48] It is also more suitable as a therapy for long-term maintenance remission.^[32] Cap-FMT may improve the overall quality of life of patients with UC. This strategy may provide a novel and safe treatment for patients with UC before treatment with corticosteroids, immunosuppressants, or biologics. Ongoing prospective studies, including 1 RCT (ACTRN12619000611123) registered in the Australian New Zealand Clinical Trials Registry that aimed to prospectively detect the effect of orally administered encapsulated lyophilized FMT for patients with UC^[28] and another RCT (NCT04034758) that was registered in ClinicalTrials.gov using the standardized quantitative multidonor intestinal microbiota capsule, will help determine the short- or long-term effects and safety of Cap-FMT.^[46] The FMTs were divided into single and multiple FMTs. The results of a meta-analysis suggested that remission improved with an increased number of FMT infusions.^[47] More RCTs of cap-FMT are urgently needed to advance the application of cap-FMT in clinical practice.

For patients with UC who achieve remission after multisession FMT, FMT can also be used as a therapy for maintenance of long-term remission. Only a few studies have investigated maintenance remission, long-term efficacy, and safety. One RCT was performed in India, and the outcome was observation of the effectiveness of FMT in the maintenance of long-term remission in UC. Currently, the trial is the first and only report on the efficiency of FMT in the maintenance of long-term remission in UC. Patients with UC attained clinical remission after multiple sessions of FMT. The outcome of the maintenance of clinical remission at 48 weeks was achieved in 27 (87.1%) of 31 patients who received FMT and in 20 (66.7%) of 30 patients allocated placebo (Yates-corrected chi-square = 2.54, $P = .111$), which indicated that FMT might help sustain long-term clinical remission in patients with UC.^[15]

Relatively few studies have been conducted on children in this area. FMT is safe to use in children, but its effectiveness for the treatment of UC is inconsistent in the different studies to date.^[51,52] Owing to tolerance problems, only a single FMT is usually performed in children, which may be one of the reasons why the effectiveness of FMT in the treatment of UC in children is not considerable.

Donor selection, stool, and process conditions vary in different studies. This also makes interpretation of the pooled results more difficult. One meta-analysis revealed that the optimal FMT donor was an unrelated donor,^[46] but Zhang et al^[47] considered that the effectiveness of FMT is not related to a specific donor. A trend was observed in a meta-analysis that the clinical remission rate after FMT using frozen stool was higher than that after FMT using fresh stool in the treatment of UC.^[51] The abundance of *Faecalibacterium prausnitzii*, an anti-inflammatory commensal bacterium associated with inflammatory bowel disease, decreased with oxygen exposure.^[52] The RCT performed by Costello et al^[23] was the first study to investigate the effectiveness of FMT under anaerobic conditions in UC, which showed that treatment with FMT using an anaerobically prepared donor was effective and safe. Notably, if oxygen-sensitive bacteria or their metabolites contribute to the clinical effectiveness of FMT, preserving their activity may enhance clinical efficiency. More RCTs are needed to investigate the frequency of FMT administration, donor selection, and standardization of microbiome analysis.

An international panel of experts indicated that the different results of FMT were related to the differences in the composition and function of recipient microbiota and the physiological and genetic factors related to the donor and recipient.^[7] Bacteria can produce short-chain fatty acids, such as butyrate, which regulate adaptive immune responses.^[53] Shinohara et al^[54] found that butyrate is impaired in patients with UC. Treatment with FMT may restore butyrate levels in patients with UC. Costello et al^[23] mentioned that changes in fecal butyrate concentration from baseline were not significantly different between patients who received d-FMT and those who received cap. This makes the different results difficult to explain.

Increasing evidence proves that competition between bacteria plays a dominant role in many environments.^[55] Microbial flora in the gut not only releases toxins to kill opponents but also transmits defense systems to each other; therefore, new bacteria must prevail if they are to survive.^[56] That is, UC can be treated and health can be promoted by regulating intestinal microbes, but this is not easy. The gut flora of each person has a unique set of survival rules. The implication is that simply transplanting fecal microbiota may not change the gut flora over a long time. Of utmost importance is the need to determine the rules of bacteria colonization in the intestine, develop a personalized analysis for different people to improve intestinal flora, facilitate the recovery of microbial homeostasis, achieve long-term remission in patients with UC, and reduce adverse reactions.

Our study has the following limitations: first, if only high methodological quality studies were included in this meta-analysis, the sample size of the study will be relatively small. Therefore, moderate-methodological-quality cohort studies were also included in the meta-analysis, which may lead to potential outcome bias. Second, we only performed subgroup analyses of populations and outcomes, and various other unreported factors may have affected the overall results, including donor selection, stool, and process conditions. Clinical trials that clearly report these factors are urgently needed in the future to determine the best conditions for FMT.

5. Conclusions

FMT provides a reliable therapy for adult UC, especially in Asian patients with mild-to-moderate and steroid-dependent UC. FMT can achieve clinical remission and may achieve steroid-free remission in patients with UC. The efficacy of FMT in children with UC is uncertain. Many routes can be used to deliver FMT, and capsule-delivered FMT may become more common in the future.

Author contributions

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