World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 July 26; 12(21): 4691-4702

DOI: 10.12998/wjcc.v12.i21.4691

ISSN 2307-8960 (online)

META-ANALYSIS

Efficacy and safety of fecal microbiota transplantation for treatment of ulcerative colitis: A post-consensus systematic review and meta-analysis

Jin-Tao Zhang, Nan Zhang, Xue-Tao Dong, Xiao-Ran Wang, Hong-Wen Ma, Yan-Di Liu, Mu-Ran Li

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Tung TH

Received: March 27, 2024

Revised: May 28, 2024

Accepted: June 19, 2024

Published online: July 26, 2024

Processing time: 95 Days and 22.8 Hours

Jin-Tao Zhang, Department of Clinical Medicine, School of Medicine, Nankai University, Tianjin 300071, China

Nan Zhang, Xue-Tao Dong, Xiao-Ran Wang, Hong-Wen Ma, Yan-Di Liu, Mu-Ran Li, Department of Gastroenterology, Tianjin Union Medical Center, Tianjin 300122, China

Corresponding author: Mu-Ran Li, MD, Chief Doctor, Department of Gastroenterology, Tianjin Union Medical Center, No. 190 Jieyuan Road, Hongqiao District, Tianjin 300122, China. muranli@126.com

Abstract

BACKGROUND

Numerous studies have assessed the efficacy and safety of fecal microbiota transplantation (FMT) as a therapy for ulcerative colitis (UC). However, the treatment processes and outcomes of these studies vary.

AIM

To evaluate the efficacy and safety of FMT for treating UC by conducting a systematic meta-analysis.

METHODS

The inclusion criteria involved reports of adult patients with UC treated with FMT, while studies that did not report clinical outcomes or that included patients with infection were excluded. Clinical remission (CR) and endoscopic remission (ER) were the primary and secondary outcomes, respectively.

RESULTS

We included nine studies retrieved from five electronic databases. The FMT group had better CR than the control group [relative risk (RR) = 1.53; 95% confidence interval (CI): 1.19-1.94; $P < 0.0008$]. ER was statistically significantly different between the two groups (RR = 2.80; 95%CI: 1.93-4.05; $P < 0.00001$). Adverse events did not differ significantly between the two groups.

CONCLUSION

FMT demonstrates favorable performance and safety; however, well-designed randomized clinical trials are still needed before the widespread use of FMT can be recommended. Furthermore, standardizing the FMT process is urgently

needed for improved safety and efficacy.

Key Words: Fecal microbiota transplantation; Randomized clinical trials; Remission; Ulcerative colitis; Meta-analysis

Core Tip: We conducted a meta-analysis on the use of fecal microbiota transplantation (FMT) for treating ulcerative colitis (UC), marking the first meta-analysis following the Rome consensus by experts in inflammatory bowel disease. This study stands out as it contributes to the establishment of standard procedures for FMT in UC treatment and facilitates its clinical application. Through a comprehensive analysis of existing research data, we found that FMT holds significant potential in UC treatment and has shown promising efficacy to a certain extent. This finding provides robust support for expanding clinical practices while also suggesting further avenues for research to elucidate the mechanisms and optimal therapeutic strategies of FMT in UC treatment.

Citation: Zhang JT, Zhang N, Dong XT, Wang XR, Ma HW, Liu YD, Li MR. Efficacy and safety of fecal microbiota transplantation for treatment of ulcerative colitis: A post-consensus systematic review and meta-analysis. *World J Clin Cases* 2024; 12(21): 4691-4702

URL: https://www.wjgnet.com/2307-8960/full/v12/i21/4691.htm

DOI: https://dx.doi.org/10.12998/wjcc.v12.i21.4691

INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) characterized by chronic inflammation of the colon and rectum, accompanied by an alternating pattern of relapse and remission. Common symptoms include diarrhea, abdominal pain, and the presence of blood in the stool[1]. Since the 1990s, the incidence of UC has increased in newly industrialized regions such as Asia and South America[2]. The pathogenesis of UC is not fully understood but is currently believed to be genetically and environmentally driven, leading to immune dysfunction and abnormal effects on intestinal microbes[3]. Dysbiosis observed in UC is characterized by specific changes in the intestinal bacterial makeup including a decrease in the population of *Bacteroidetes* and certain groups of *Firmicutes* (such as *Clostridium* IXa and IV groups, *Bifidobacteria*, *Lactobacillus*, and *Faecalibacterium prausnitzii*) and an increase in *Proteobacteria* and *Actinobacteria*. The dysbiosis of microbes with related metabolic pathways and molecular mechanisms is crucial in intestinal immunity in patients with UC[4]. Fecal microbiota transplantation (FMT) is the process of transplanting feces from a healthy donor into an unhealthy recipient, used clinically as a therapy for *Clostridium difficile* infection (CDI). FMT can restore microbial diversity and correct dysbiosis[5]. The success of FMT in treating CDI has attracted much attention, and many have hypothesized its effectiveness for IBD treatment.

Promising results have been published by various retrospective trials on FMT for IBD treatment, particularly in patients diagnosed with UC. Bennett was the first to perform FMT for UC treatment[6]. Several trials on FMT for UC treatment, mostly one-armed cohort studies or case series, have yielded satisfactory results. The first two randomized controlled trials (RCTs) evaluating the efficacy and safety of FMT for the treatment of UC were published in 2015[7,8]. To date, several relevant RCTs have been conducted. However, the treatment methods used varied in these trials, with results that are not easily generalizable. Therefore, the non-standardization of FMT processes must be resolved. The first international Rome consensus on the use of FMT in IBD treatment was recently published, recommending an optimal FMT framework to promote future quality management[9]. Notably, previous systematic reviews and meta-analyses have not proposed to standardize the process of FMT for the treatment of IBD, as the first meta-analysis after this consensus, this study aimed to evaluate the efficacy and safety of FMT for UC treatment to advance FMT process standardization, help implement large-sample and multi-center RCTs, and, ultimately, apply the technology to clinical practice.

MATERIALS AND METHODS

Search strategy

All studies published in PubMed, Cochrane, EMBASE, Wanfang Data, and China National Knowledge Infrastructure by November 2023 were searched using specific search strategies adjusted to individual databases. Table 1 presents the search strategies for these databases. This study considered only original research published in English or Chinese. Two investigators conducted a literature search and assessed the findings, with any discrepancies discussed and resolved by a senior researcher.

Table 1 PubMed search strategy

Query search term
1 Colitis, Ulcerative [Mesh]
2 Ulcerative Colitis [Title/Abstract] OR Inflammatory Bowel Disease, Ulcerative Colitis Type [Title/Abstract]
3 1 OR 2
4 Fecal Microbiota Transplantation [Mesh]
5 Fecal Microbiota Transplant [Title/Abstract] OR Fecal Transplant [Title/Abstract] OR Donor Feces Infusion [Title/Abstract] OR Intestinal Microbiome Transplant [Title/Abstract] OR Intestinal Microbiota Transplantation [Title/Abstract] OR Microbiota Transfer [Title/Abstract] OR Fecal Fecal Transplantation [Title/Abstract]
6 4 OR 5
7 randomized controlled trial [Publication Type] OR randomized [Title/Abstract] OR placebo [Title/Abstract]
8 3 AND 6 AND 7

Inclusion and exclusion criteria

We included: (1) Randomized controlled trials; (2) studies with adult participants aged 18–70 years with UC; (3) studies on FMT-based intervention administered orally *via* colonoscopy, nasogastric tube, nasoduodenal tube, and nasojejunal tube or by enema; and (4) studies with explicitly described endpoints. We excluded: (1) Animal or *in vitro* studies; (2) studies in languages other than English or Chinese; (3) studies that included patients with co-infections; (4) studies without a separate report data on patients with UC or studies containing data from multiple overlapping studies; and (5) reviews and meta-analyses.

Quality assessment

Two authors independently assessed the quality of each study, and divergences were resolved through discussion. Methodological quality was evaluated using the Cochrane risk-of-bias tool, which assesses seven areas: (1) Generating random sequences (potentially introducing selection bias); (2) concealing allocation (potentially introducing selection bias); (3) blinding participants and personnel (potentially introducing performance bias); (4) blinding outcome assessment (potentially introducing detection bias); (5) incomplete outcome data (potentially introducing attrition bias); (6) selective reporting (potentially introducing reporting bias); and (7) other biases. The level of risk of bias was evaluated and categorized as "low," "high," or "unclear."

Data extraction

Duplicates of the retrieved articles were imported and removed using Zotero (version 6.0.30). Two authors independently read the titles and abstracts of these papers, and eligible papers were screened according to the inclusion criteria. Finally, all papers were reviewed in full. The information obtained included specific details such as the name of the author, year of publication, country of origin, type of patients involved, FMT method, control mode used, method of delivery, type of donor, time of evaluation, number of clinical remissions (CR) observed, number of endoscopic remissions (ER) observed, and number of adverse reactions reported. Subsequently, the data were arranged in tables for convenience.

Statistical analysis

We used Review Manager software (version 5.4.1) to perform a meta-analysis and compare the rates of remission and adverse reactions between the FMT and control groups. We combined the risk ratio (RR) and 95% confidence interval (CI) for the data analysis. To evaluate statistical heterogeneity for each meta-analysis, we used the Cochran Q test (χ^2) and I^2 method. A P value < 0.1 in the Q test indicated statistical significance. In such cases, fixed-effect models were employed; otherwise, random-effect models were used. The I^2 method was used to assess the level of heterogeneity, with scores of 0%–30%, 30%–60%, 50%–90%, and 75%–100% indicating low, moderate, substantial, and considerable heterogeneity, respectively. Furthermore, we conducted subgroup analyses based on different factors such as delivery route, control mode, and pre-FMT treatment. All statistical tests were two-tailed, with a significance level of $P < 0.05$.

RESULTS

Search results

Our search yielded 484 potentially relevant studies. After removing duplicates, 265 articles were evaluated. After the two authors independently screened the titles and abstracts of the articles, 13 full-text articles were retrieved, four of which were excluded. The meta-analysis included a total of nine RCTs that examined the efficacy of FMT in individuals diagnosed with UC[7,8,10-16]. Figure 1 presents a flowchart illustrating the literature screening process.

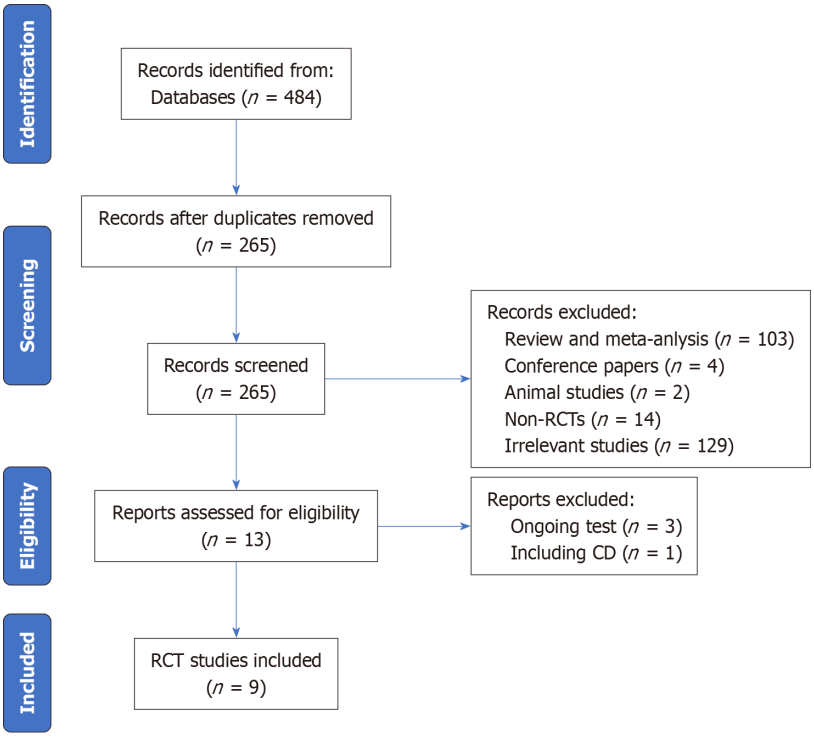


Figure 1 Flowchart of the literature screening process. RCT: Randomized clinical trial.

Characteristics of the included studies

An overview of the characteristics of the studies included in this meta-analysis is presented in Tables 2 and 3. These studies, published between 2015 and 2022, were all RCTs, focusing specifically on patients with mild-to-moderate UC, with Mayo scores of 4–10 and an endoscopic Mayo sub-score of 1. Regarding transplantation methods, the studies used several modalities such as colonoscopy, enema, and nasoduodenal tubes. Both single and multiple donors were used in the studies, with control groups receiving placebo, autologous FMT, 5-aminosalicylic acid (5-ASA), and standard drug therapy. However, in most of the studies included, CR (Mayo score of ≤ 2) and ER (endoscopic Mayo score of ≤ 1) were the primary and secondary outcomes, respectively. The follow-up period ranged from 7 to 48 weeks, focusing more on 8 and 12 weeks.

Quality assessment

To evaluate the reliability of the included studies, we used the Cochrane risk-of-bias tool (Figures 2 and 3). A few studies did not indicate how random sequencing was generated during this evaluation, and allocation was concealed. Additionally, blinding was not fully performed in some studies, resulting in an unclear risk of selection bias and a high risk of performance and detection bias. However, we determined that all included studies had a low risk of attrition and reporting biases.

Meta-analysis of CR

All the included studies report data on CR. In the FMT group, CR was achieved in 157 of 261 patients (60.15%) compared with 100 of 259 patients (38.61%) in the control group. To assess the relationship between CR and FMT, we used a random-effects model while considering the heterogeneity of risk (χ^2 = 13.95; P = 0.08; I^2 = 43%). The combined RRs and corresponding 95%CIs were calculated, as shown in Figure 4. The findings indicated that the FMT group exhibited better CR than the control group (RR = 1.53, 95%CI: 1.19–1.94, P < 0.0008). Publication bias was not assessed because qualitative and quantitative studies have sensitivities < 10[17].

Subgroup analyses based on CR

To further evaluate how the various methods used in the studies affected the efficacy of FMT, we performed subgroup analyses of CR. These analyses targeted various factors including delivery route, control mode, and pre-FMT therapy. Based on these factors, the participants were categorized into three groups. The delivery route determined the composition of the initial group; Moayyedi *et al*[7] and Zhang *et al*[11] administered FMT *via* an enema, Rossen *et al*[8] administered FMT *via* nasoduodenal tube, and others administered FMT *via* colonoscopy. In comparison, the results (Figure 5A) of the enema group were not statistically significant (RR = 2.07; 95%CI: 0.57-7.51; P = 0.27) and were highly heterogeneous (χ^2 = 3.34; P = 0.07; I^2 =70%). The group that received colonoscopy infusion exhibited favorable outcomes in UC treatment (RR = 1.41; 95%CI: 1.01–1.96; P = 0.006). Based on the control mode, the sham FMT/water method (RR = 4.61; 95%CI: 1.25-16.94; P = 0.02) had better effects than standard medical therapy (SMT) (RR = 1.34; 95%CI: 1.11–1.62; P = 0.002), while the effect of autologous fecal microbiota (RR = 1.17; 95%CI: 0.78–1.77; P = 0.44) was not statistically

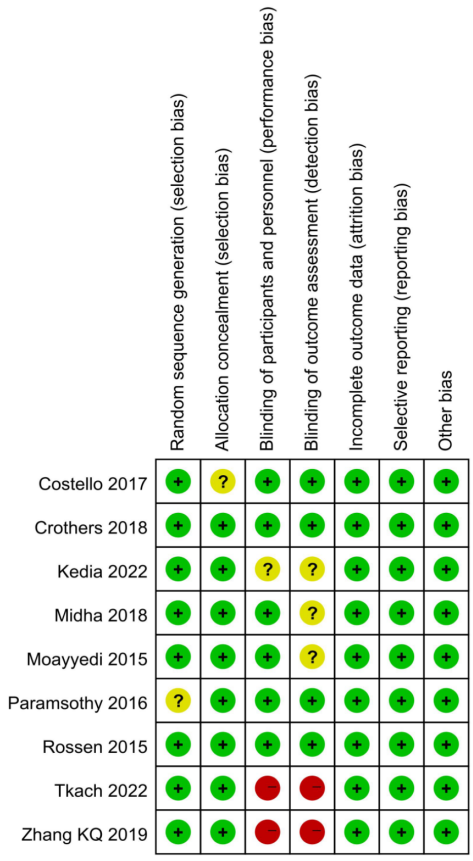


Figure 2 Quality assessment of the studies.

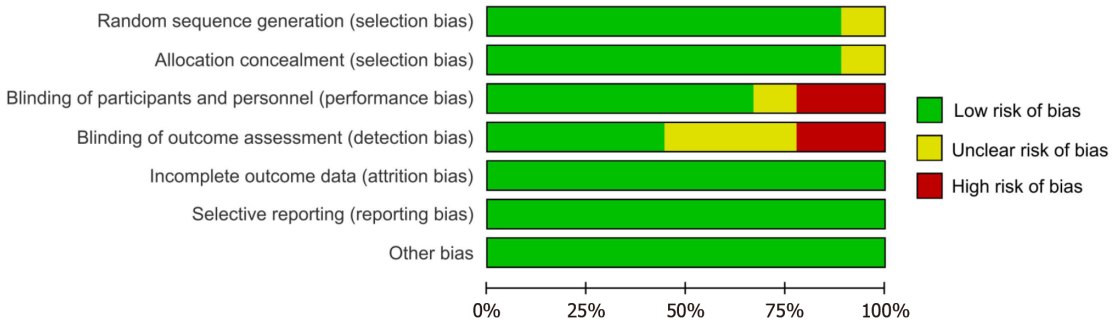


Figure 3 Percentage risk of bias in the studies.

significant (Figure 5B). These results showed that FMT was more effective than sham FMT/water, but a comparison with SMT requires further justification. Regarding the analysis based on pre-FMT therapy, there was no significant difference between the 5-ASA group (RR = 1.31; 95%CI: 1.11–1.54; P = 0.001) and the non-5-ASA group (RR = 1.85; 95%CI: 1.28–2.68; P = 0.001) are shown in Figure 5C.

Meta-analysis of ER

Six of the studies had data on ER. In the FMT group, 77 of 182 patients achieved ER (43.40%) compared with 27 of 177 patients in the control group (15.25%). The result of the analysis (Figure 6) showed a statistically significant difference (RR = 2.80; 95%CI: 1.93–4.05; P < 0.00001) with low heterogeneity (χ^2 = 4.83; P = 0.44; I^2 = 0%).

Meta-analysis of adverse reactions

Kedia *et al*[13] did not report adverse effects; therefore, we only considered the remaining eight studies while analyzing adverse reaction analyses. Among the 221 patients in the FMT group, 21 (9.29%) experienced adverse reactions compared with 13 of the 228 (5.70%) patients in the control group. However, the findings were not statistically significant (RR = 1.64, 95%CI: 0.85-3.17, P = 0.14), indicating no significant difference in the occurrence of adverse reactions between the FMT and control groups. Furthermore, the meta-analysis revealed minimal variation among the studies (χ^2 = 1.07, P = 0.96, I^2 = 0%) (Figure 7).

Table 2 Characteristics of the included studies

Ref.	Study design	Intervention		Control mode	Outcomes				
		FMT			CR (*n*/total)		Adverse events	Follow up (weeks)	Reference standard of CR
		pre-FMT therapy	Delivery route		FMT	Control			
Moayyedi *et al* [7], 2015	Double-blind, RCT	NR	Enema	Water enema	9/36	2/35	5	7	Mayo score ≤ 2, endoscopic Mayo score of 0
Rossen *et al*[8], 2015	Double-blind, RCT	Bowel lavage	Via naso-duodenal tube	AFM	7/17	5/20	4	12	SCCAI scores ≤ 2, Mayo endoscopic score decrease ≥ 1
Paramsothy *et al*[15], 2016	Double-blind, RCT	NR	Colonoscopic infusion	NR	18/41	8/40	3	8	Mayo score ≤ 2 points with subscores ≤ 1
Costello *et al* [16], 2017	Double-blind, RCT	NR	Colonoscopic infusion	AFM	19/35	17/34	5	8	Mayo score of ≤ 2 with an endoscopic Mayo score of ≤ 1
Crothers *et al* [10], 2018	Double-blind, RCT	7 days of antibiotics	Colonoscopic infusion and daily FMTc	Sham FMT	2/7	0/8	NR	12	> 3 point reduction in Mayo score
Midha *et al* [14], 2018	Double-blind, RCT	NR	NR	NR	12/14	4/14	0	48	Mayo score = 1
Zhang *et al* [11], 2019	RCT	Sulfapyridine 0.75 g, qid	Enema	Sulfapyridine 0.75 g, qid	48/50	35/50	9	NR	NR
Kedia *et al*[13], 2022	Open-labeled RCT	FMT + UC-SAID	Colonoscopic infusion	SMT	21/35	10/31	NR	8	Decline in SCCAI > 3
Tkach *et al* [12], 2022	RCT	Mesalazine 1 g, tid	Colonoscopic infusion	SMT	21/26	19/27	8	8	Partial Mayo score ≤ 2

NR: No report; AFM: Autologous fecal microbiota; SMT: Standard medical therapy; CR: Clinical remission; SCCAI: Simple clinical colitis activity index; UC-SAID: Ulcerative colitis-specific anti-inflammatory diet.

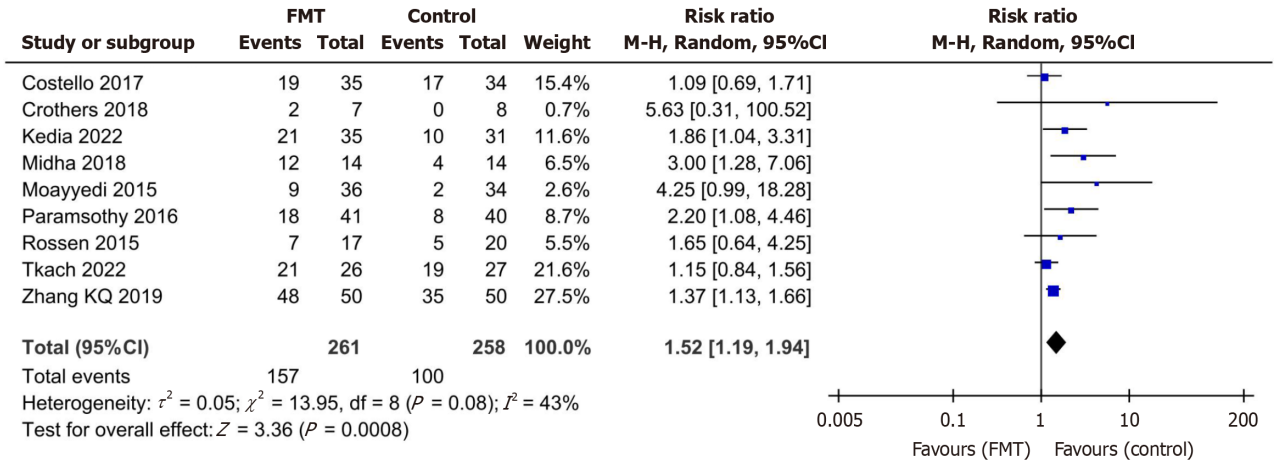


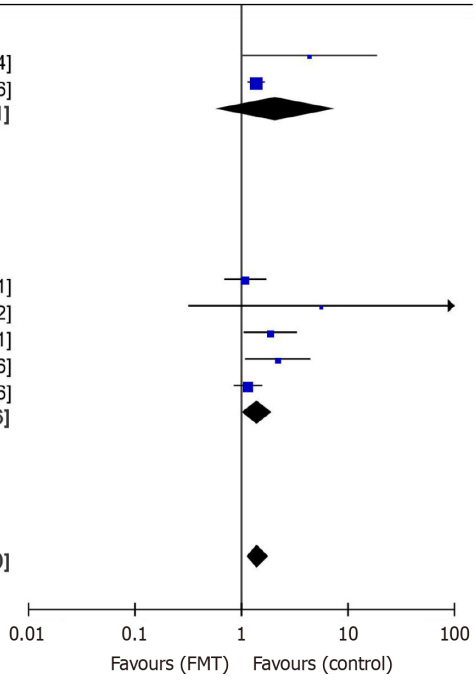
Figure 4 Forest plot of the result of the meta-analysis of clinical remission.

DISCUSSION

Although the mechanism by which dysbiosis of the intestinal flora affects UC has not been fully explored, there is evidence that they are correlated[18]. FMT has emerged as a means of modifying the intestinal microbiome and has already been used clinically for CDI, with several studies confirming its potential in treating UC[19]. This study aimed to investigate the efficacy and safety of FMT for UC treatment. We analyzed data from nine RCTs involving 580 patients. The results indicated that the FMT group experienced notably higher rates of CR and ER than the control group. These

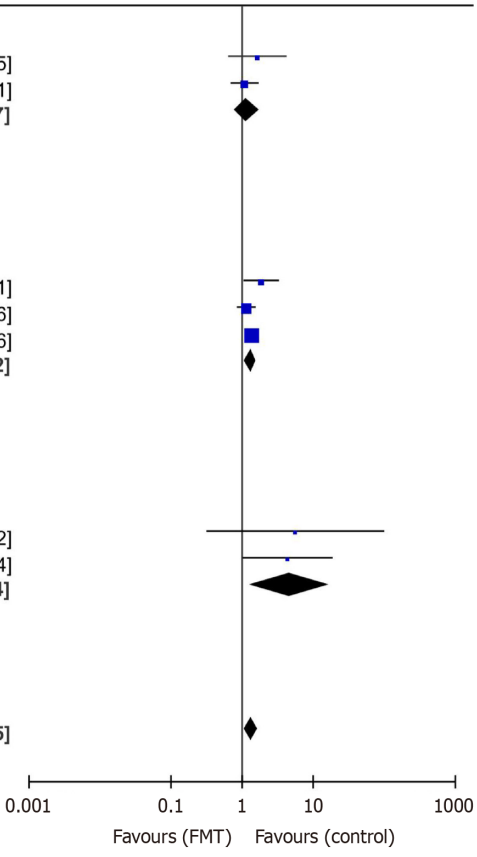
A

Study or subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95%CI
1.2.1 enema						
Moayyedi 2015	9	36	2	35	2.5%	4.38 [1.02, 18.84]
Zhang KQ 2019	48	50	35	50	33.8%	1.37 [1.13, 1.66]
Subtotal (95%CI)		**86**		**85**	**36.3%**	**2.07 [0.57, 7.51]**
Total events	57		37			
Heterogeneity: τ^2 = 0.66; χ^2 = 3.34, df = 1 (P = 0.07); I^2 = 70%						
Test for overall effect: Z = 1.11 (P = 0.27)						
1.2.2 colonoscopic infusion						
Costello 2017	19	35	17	34	16.9%	1.09 [0.69, 1.71]
Crothers 2018	2	7	0	8	0.7%	5.63 [0.31, 100.52]
Kedia 2022	21	35	10	31	12.2%	1.86 [1.04, 3.31]
Paramsothy 2016	18	41	8	40	8.9%	2.20 [1.08, 4.46]
Tkach 2022	21	26	19	27	25.0%	1.15 [0.84, 1.56]
Subtotal (95%CI)		**144**		**140**	**63.7%**	**1.41 [1.01, 1.96]**
Total events	81		54			
Heterogeneity: τ^2 = 0.05; χ^2 = 6.74, df = 4 (P = 0.15); I^2 = 41%						
Test for overall effect: Z = 2.02 (P = 0.04)						
Total (95%CI)		**230**		**225**	**100.0%**	**1.42 [1.12, 1.80]**
Total events	138		91			
Heterogeneity: τ^2 = 0.03; χ^2 = 9.96, df = 6 (P = 0.13); I^2 = 40%						
Test for overall effect: Z = 2.87 (P = 0.004)						
Test for subgroup differences: χ^2 = 0.32, df =1 (P = 0.57), I^2 = 0%						



B

Study or subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95%CI
1.3.1 AFM						
Costello 2017	7	17	5	20	4.1%	1.65 [0.64, 4.25]
Rossen 2015	19	35	17	34	15.0%	1.09 [0.69, 1.71]
Subtotal (95%CI)		**52**		**54**	**19.1%**	**1.17 [0.78, 1.77]**
Total events	26		22			
Heterogeneity: τ^2 = 0.00; χ^2 = 0.62, df = 1 (P = 0.43); I^2 = 0%						
Test for overall effect: Z = 0.77 (P = 0.44)						
1.3.2 SMT						
Kedia 2022	21	35	10	31	10.1%	1.86 [1.04, 3.31]
Tkach 2022	21	26	19	27	26.0%	1.15 [0.84, 1.56]
Zhang KQ 2019	48	50	35	50	42.6%	1.37 [1.13, 1.66]
Subtotal (95%CI)		**111**		**108**	**78.6%**	**1.34 [1.11, 1.62]**
Total events	90		64			
Heterogeneity: τ^2 = 0.01; χ^2 = 2.46, df = 2 (P = 0.29); I^2 = 19%						
Test for overall effect: Z = 3.04 (P = 0.002)						
1.3.3 Sham FMT/Water						
Crothers 2018	2	7	0	8	0.5%	5.63 [0.31, 100.52]
Moayyedi 2015	9	36	2	35	1.8%	4.38 [1.02, 18.84]
Subtotal (95%CI)		**43**		**43**	**2.3%**	**4.61 [1.25, 16.94]**
Total events	11		2			
Heterogeneity: τ^2 = 0.00; χ^2 = 0.02, df = 1 (P = 0.88); I^2 = 0%						
Test for overall effect: Z = 2.30 (P = 0.02)						
Total (95%CI)		**206**		**205**	**100.0%**	**1.35 [1.11, 1.65]**
Total events	127		88			
Heterogeneity: τ^2 = 0.01; χ^2 = 7.61, df = 6 (P = 0.27); I^2 = 21%						
Test for overall effect: Z = 2.97 (P = 0.003)						
Test for subgroup differences: χ^2 = 3.86, df =2 (P = 0.15), I^2 = 48.1%						



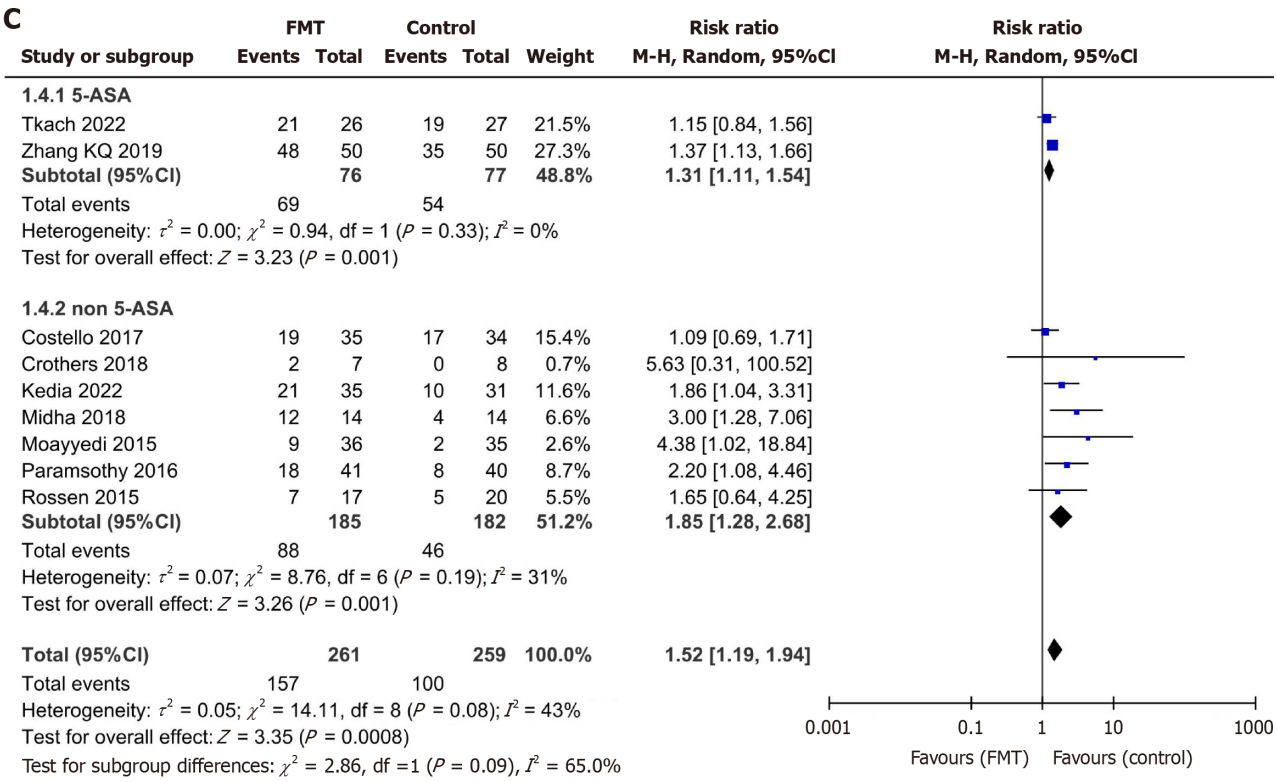


Figure 5 Subgroup analysis of clinical remission based on the delivery route (A), the control mode (B) and pre-fecal microbiota transplantation therapy (C).

findings were statistically significant with minimal variations, demonstrating the potential of FMT for UC treatment. However, several issues still require further research including the selection of fecal donors, choice of delivery route, and handling of the pre-FMT.

The choice of FMT donor may significantly impact the efficacy of FMT in UC treatment[20]. Kazerouni and Wein[21] predicted that collecting stools from multiple donors could improve remission rates. Paramsothy *et al*[15] reported that FMT from multi-donors achieved post-FMT remission rates (FMT, 27% *vs* placebo, 8%, $P = 0.02$) similar to those from single-donors. Therefore, further research is needed to determine whether FMT from multi-donors or a single donor is more effective. However, similar genetics and environments may lead to alterations in the microbiota of related donors, even though fecal microbiota transplant donors for UC do not have UC. In this case, alterations in the microbiota of the related donor may lead to a relapse of UC in the patient; therefore, unrelated donors may be preferred for UC treatment. Donors related to the recipients may share similarities because of shared genes or environment, and using their feces may make the treatment well tolerated but potentially less effective. In such cases, the fecal flora of unrelated individuals may be more effective[22]. Certain studies have discovered "super-donors," whose fecal material results in significantly more successful outcomes than other donors. However, evidence for "super-donors" remains limited, and more research is needed to fully understand and validate this phenomenon[23]. As the number of RCTs included was insufficient to perform a relevant study, we did not obtain results on donor selection.

The effect of the delivery method of FMT on the treatment of UC remains inconclusive. Notably, there are two main ways to deliver FMT for the treatment of UC: Through the upper gastrointestinal (GI) tract, which involves methods such as gastroscopy and the use of nasogastric or nasojejunal tubes, and through the lower GI, involving techniques such as colonoscopy and retention enemas. Previous studies on FMT for CDI concluded that patients who received FMT *via* the lower GI route received larger amounts or concentrations of FMT than those who received FMT *via* the upper GI route [24]. Some hypotheses indicate that administration *via* the upper GI tract exposes the FMT to gastric acid, potentially affecting its efficacy[25]; however, another study revealed that this effect may not be significant[26]. Our study revealed that subgroup analyses of enema were not statistically significant (RR = 2.07; 95%CI: 0.57-7.51; $P = 0.27$) with high heterogeneity ($\chi^2 = 3.34$; $P = 0.07$; $I^2 = 70\%$). We hypothesized that the source of heterogeneity stemmed from dissimilar treatment methods among researchers. Zhang *et al*[11] used 5-ASA in the experimental and control groups. whereas Moayyedi *et al*[7] did not. Although analysis of the group using colonic infusion showed positive results in treating UC (RR = 1.40; 95%CI: 1.05-1.87; $P = 0.006$), the results of Rossen *et al*[8] using nasoduodenal tubes were not significant (RR = 1.65; 95%CI: 0.64-4.25; $P = 0.30$). Therefore, it is necessary to conduct additional trials and studies to determine the optimal delivery route.

Pre-FMT included antibiotic or 5-ASA treatments. To compare the effects of 5-ASA treatment on efficacy, we performed a subgroup analysis, which showed no significant difference between the 5-ASA and non-5-ASA groups. Combining different treatments may be more effective than FMT alone. Although dysbiosis correction alone can benefit certain patients, it may not sufficiently cure the disease owing to its complex pathogenesis[27]. UC has a complex pathogenesis,

Table 3 Efficacy and safety data of the included studies

Ref.	Patients		ER		AEs	
	FMT (*n*)	Control (*n*)	FMT (*n*)	Control (*n*)	FMT (*n*)	Control (*n*)
Moayyedi *et al*[7], 2015	36	35	NA	NA	3	2
Rossen *et al*[8], 2015	17	20	NA	NA	2	2
Paramsothy *et al*[15], 2016	41	40	7	3	2	1
Costello *et al*[16], 2017	35	34	19	6	3	2
Crothers *et al*[10], 2018	7	8	3	0	0	0
Midha *et al*[14], 2018	14	14	8	0	0	0
Zhang *et al*[11], 2019	50	50	29	15	5	4
Kedia *et al*[13], 2022	35	31	13	3	NA	NA
Tkach *et al*[12], 2022	26	27	NA	NA	6	2

Efficacy and safety data of the studies. NA: Not available; ER: Endoscopic remission; AEs: Adverse events.

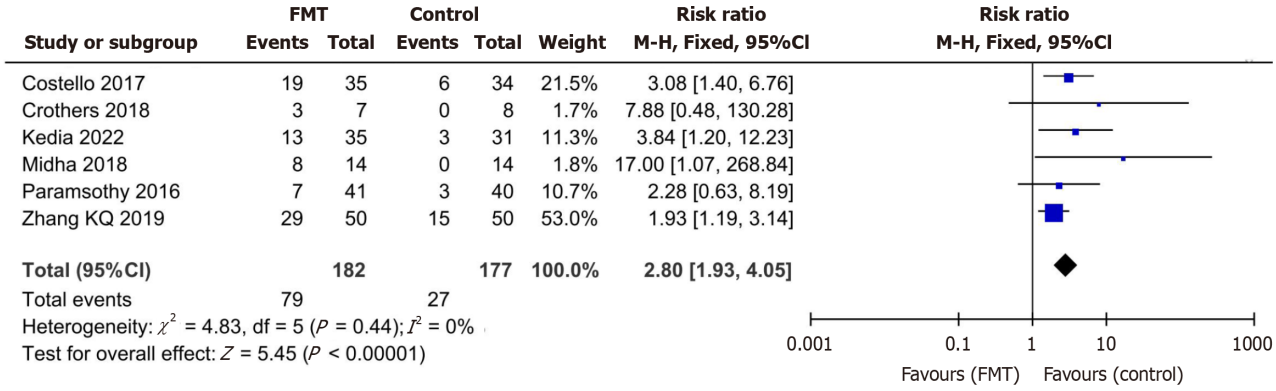


Figure 6 Forest plot for meta-analysis of endoscopic remission.

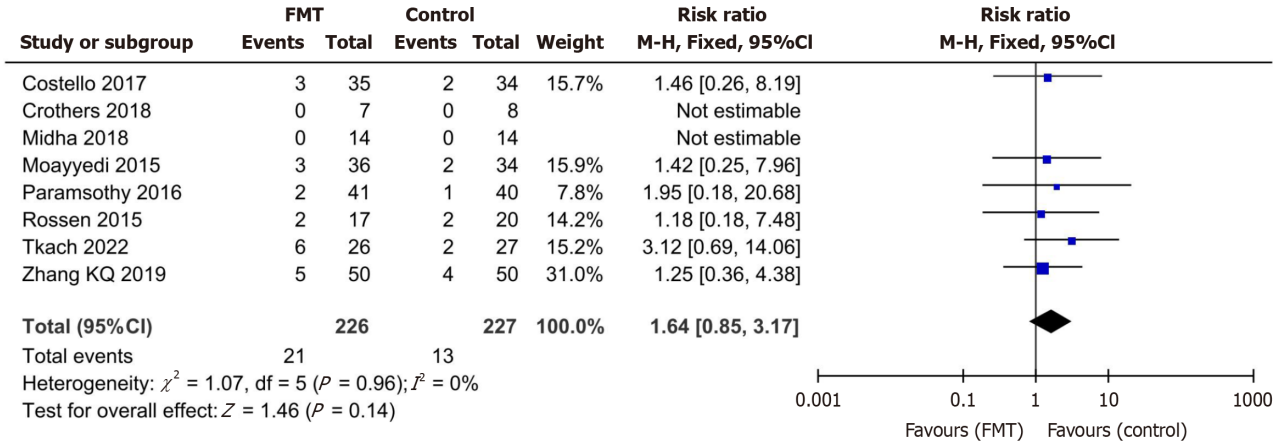


Figure 7 Forest plot for meta-analysis of adverse reactions.

and dysbiosis is not directly associated with it[28]. Ishikawa *et al*[29] combined FMT with a triple-antibiotic therapy. This method of using antibiotic pretreatment to reshape the gut flora to match the donor's flora showed a higher CR rate (43.8%) than the conventional FMT (42.1%). Further research based on pre-antibiotics is needed to confirm their effectiveness.

The altered gut flora in patients who underwent FMT is a concern. Several studies have found differences in the composition and diversity of the gut flora between patients with UC and healthy individuals. These studies showed that patients with UC have fewer *Bacteroides*, *Clostridium* XIV, and *Firmicutes* and higher numbers of *Clostridium cluster* IX, *Bacteroides*, and *Proteobacteria*[8,30,31]. A previous study confirmed that individuals who responded to FMT showed significant changes in bacterial profiles similar to those of the donor microbiota[20]. However, another study demonstrated that most species diversity observed post-transplantation was initially linked to species initially present in the recipient[32].

However, the adverse effects of FMT remain a crucial issue. A meta-analysis of 129 studies showed that 19% of the adverse reactions (diarrhea, bloating, and abdominal pain) associated with FMT were mild, and 1.4% of patients who received FMT developed severe adverse reactions (including infection and death)[33]. Our analysis revealed that the occurrence of adverse reactions was not significantly different between the two groups. To improve the safety of FMT, clinicians should rigorously screen donors to prevent fecal transmission of infectious pathogens to recipients[34]. In addition, we believe that the standardization of FMT processes is a way to improve its safety.

Compared with previous meta-analyses, our study incorporated the most recent relevant studies, most importantly, our study will promote the establishment of a standardized protocol for FMT in the treatment of IBD, which will lead to the implementation of more multi-center, large-scale RCTs and provide more evidence-based evidence for clinical practice; however, it still has limitations. One crucial aspect is the subjective nature of assessing methodological quality, reporting quality, and assessing the quality of the evidence. Consequently, the outcomes may differ based on the judgment calls made by individual researchers when evaluating each factor. Furthermore, there is a lack of standardization in the definitions of FMT-related variables. Data on these variables are often not reported in publications, and no universal trial design exists. Factors such as patient and donor preparation, dosage, route of administration, and follow-up duration varied considerably. Finally, we did not perform a funnel plot analysis, Begg's test, or Egger's test because the included studies were few, which would have led to inadequate testing for publication bias.

CONCLUSION

In conclusion, FMT is a promising treatment for UC that enhances CR and ER rates. However, the limited number of insufficient RCTs with large sample sizes and inconsistencies in trial standards need to be addressed.

ACKNOWLEDGEMENTS

We thank Dr. Cui-Ping Bao for reviewing the manuscript.

FOOTNOTES

Author contributions: Li MR outlining and coordinating the work of co-authors; Zhang JT and Zhang N performed the research and analyzed the data; Zhang JT, Zhang N, Dong XT, Wang XR, Ma HW and Liu YD wrote and edit the manuscript; All authors have read and agreed to the published version of the manuscript.

Supported by the Tianjin Health Science and Technology Project, No. TJWJ2021MS011.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country of origin: China

ORCID number: Mu-Ran Li 0000-0003-1225-2304.

S-Editor: Gong ZM
L-Editor: A
P-Editor: Zheng XM

REFERENCES

1 **Gros B**, Kaplan GG. Ulcerative Colitis in Adults: A Review. *JAMA* 2023; **330**: 951-965 [PMID: 37698559 DOI: 10.1001/jama.2023.15389]

2 **Ng SC**, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JJY, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2017; **390**: 2769-2778 [PMID: 29050646 DOI: 10.1016/S0140-6736(17)32448-0]

3 **Chang JT**. Pathophysiology of Inflammatory Bowel Diseases. *N Engl J Med* 2020; **383**: 2652-2664 [PMID: 33382932 DOI: 10.1056/NEJMra2002697]

4 **Cheng YW**, Fischer M. Fecal Microbiota Transplantation for Ulcerative Colitis. Are We Ready for Primetime? *Gastroenterol Clin North Am* 2020; **49**: 739-752 [PMID: 33121693 DOI: 10.1016/j.gtc.2020.08.006]

5 **Carlucci C**, Petrof EO, Allen-Vercoe E. Fecal Microbiota-based Therapeutics for Recurrent Clostridium difficile Infection, Ulcerative Colitis and Obesity. *EBioMedicine* 2016; **13**: 37-45 [PMID: 27720396 DOI: 10.1016/j.ebiom.2016.09.029]

6 **Bennet JD**, Brinkman M. Treatment of ulcerative colitis by implantation of normal colonic flora. *Lancet* 1989; **1**: 164 [PMID: 2563083 DOI: 10.1016/s0140-6736(89)91183-5]

7 **Moayyedi P**, Surette MG, Kim PT, Libertucci J, Wolfe M, Onischi C, Armstrong D, Marshall JK, Kassam Z, Reinisch W, Lee CH. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. *Gastroenterology* 2015; **149**: 102-109.e6 [PMID: 25857665 DOI: 10.1053/j.gastro.2015.04.001]

8 **Rossen NG**, Fuentes S, van der Spek MJ, Tijssen JG, Hartman JH, Duflou A, Löwenberg M, van den Brink GR, Mathus-Vliegen EM, de Vos WM, Zoetendal EG, D'Haens GR, Ponsioen CY. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. *Gastroenterology* 2015; **149**: 110-118.e4 [PMID: 25836986 DOI: 10.1053/j.gastro.2015.03.045]

9 **Lopetuso LR**, Deleu S, Godny L, Petito V, Puca P, Facciotti F, Sokol H, Ianiro G, Masucci L, Abreu M, Dotan I, Costello SP, Hart A, Iqbal TH, Paramsothy S, Sanguinetti M, Danese S, Tilg H, Cominelli F, Pizarro TT, Armuzzi A, Cammarota G, Gasbarrini A, Vermeire S, Scaldaferri F. The first international Rome consensus conference on gut microbiota and faecal microbiota transplantation in inflammatory bowel disease. *Gut* 2023; **72**: 1642-1650 [PMID: 37339849 DOI: 10.1136/gutjnl-2023-329948]

10 **Crothers J**, Kassam Z, Smith M, Phillips M, Vo E, Velez M, Cohn AH, Fortner K, Del Rio Guerra R, Chu N, Nguyen LT, Elliott RJ, Wong WF, Lavoie B, Callas P, Budd R, Wilcox R, Alm E, Mawe GM, Moses PL, Collins C. Tu1893 - A Double-Blind, Randomized, Placebo-Control Pilot Trial of Fecal Microbiota Transplantation Capsules from Rationally Selected Donors in Active Ulcerative Colitis. *Gastroenterology* 2018; **154**: S1050-S1051 [DOI: 10.1016/S0016-5085(18)33519-4]

11 **Zhang KQ**, Jiang Q, Zhang HB. [Effect of fecal microbiota transplantation on gastrointestinal function and intestinal flora in patients with ulcerative colitis]. *Shijie Huaren Xiaohua Zazhi* 2019; **27**: 68-72 [DOI: 10.11569/wcjd.v27.i1.68]

12 **Tkach S**, Dorofeyev A, Kuzenko I, Falalyeyeva T, Tsyryuk O, Kovalchuk O, Kobyliak N, Abenavoli L, Boccuto L. Efficacy and safety of fecal microbiota transplantation *via* colonoscopy as add-on therapy in patients with mild-to-moderate ulcerative colitis: A randomized clinical trial. *Front Med (Lausanne)* 2022; **9**: 1049849 [PMID: 36714101 DOI: 10.3389/fmed.2022.1049849]

13 **Kedia S**, Virmani S, K Vuyyuru S, Kumar P, Kante B, Sahu P, Kaushal K, Farooqui M, Singh M, Verma M, Bajaj A, Markandey M, Sachdeva K, Das P, Makharia GK, Ahuja V. Faecal microbiota transplantation with anti-inflammatory diet (FMT-AID) followed by anti-inflammatory diet alone is effective in inducing and maintaining remission over 1 year in mild to moderate ulcerative colitis: a randomised controlled trial. *Gut* 2022; **71**: 2401-2413 [PMID: 35973787 DOI: 10.1136/gutjnl-2022-327811]

14 **Midha V**, Singh A, Mahajan R, Mehta V, Khattar H, Narang V, Sood A. IDDF2018-ABS-0221 Maintenance with faecal microbiota transplantation enhances deep remission in patients with ulcerative colitis in clinical remission. *Clin Gastroenterol* 2018; **67** [DOI: 10.1136/gutjnl-2018-IDDFabstracts.162]

15 Inflammatory Bowel Disease Clinical. *J Gastroenterol Hepatol* 2016; **31** Suppl 2: 127-155 [PMID: 27709671 DOI: 10.1111/jgh.13522]

16 **Costello SP**, Waters O, Bryant RV, Katsikeros R, Makanyanga J, Schoeman M, Mountifield RE, Tee D, Howell S, Hughes PA, Conlon M, Roberts-thomson IC, Andrews JM. Short Duration, Low Intensity, Pooled Fecal Microbiota Transplantation Induces Remission in Patients with Mild-Moderately Active Ulcerative Colitis: A Randomised Controlled Trial. *Gastroenterology* 2017; **152**: S198-S199 [DOI: 10.1016/S0016-5085(17)30969-1]

17 **Ioannidis JP**, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. *CMAJ* 2007; **176**: 1091-1096 [PMID: 17420491 DOI: 10.1503/cmaj.060410]

18 **Guo XY**, Liu XJ, Hao JY. Gut microbiota in ulcerative colitis: insights on pathogenesis and treatment. *J Dig Dis* 2020; **21**: 147-159 [PMID: 32040250 DOI: 10.1111/1751-2980.12849]

19 **Green JE**, Davis JA, Berk M, Hair C, Loughman A, Castle D, Athan E, Nierenberg AA, Cryan JF, Jacka F, Marx W. Efficacy and safety of fecal microbiota transplantation for the treatment of diseases other than Clostridium difficile infection: a systematic review and meta-analysis. *Gut Microbes* 2020; **12**: 1-25 [PMID: 33345703 DOI: 10.1080/19490976.2020.1854640]

20 **Vermeire S**, Joossens M, Verbeke K, Wang J, Machiels K, Sabino J, Ferrante M, Van Assche G, Rutgeerts P, Raes J. Donor Species Richness Determines Faecal Microbiota Transplantation Success in Inflammatory Bowel Disease. *J Crohns Colitis* 2016; **10**: 387-394 [PMID: 26519463 DOI: 10.1093/ecco-jcc/jjv203]

21 **Kazerouni A**, Wein LM. Exploring the Efficacy of Pooled Stools in Fecal Microbiota Transplantation for Microbiota-Associated Chronic Diseases. *PLoS One* 2017; **12**: e0163956 [PMID: 28068341 DOI: 10.1371/journal.pone.0163956]

22 **Kelly CR**, Kahn S, Kashyap P, Laine L, Rubin D, Atreja A, Moore T, Wu G. Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms, and Outlook. *Gastroenterology* 2015; **149**: 223-237 [PMID: 25982290 DOI: 10.1053/j.gastro.2015.05.008]

23 **Wilson BC**, Vatanen T, Cutfield WS, O'Sullivan JM. The Super-Donor Phenomenon in Fecal Microbiota Transplantation. *Front Cell Infect Microbiol* 2019; **9**: 2 [PMID: 30719428 DOI: 10.3389/fcimb.2019.00002]

24 **Quraishi MN**, Widlak M, Bhala N, Moore D, Price M, Sharma N, Iqbal TH. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory Clostridium difficile infection. *Aliment Pharmacol Ther* 2017; **46**: 479-493 [PMID: 28707337 DOI: 10.1111/apt.14201]

25 **Damman CJ**, Miller SI, Surawicz CM, Zisman TL. The microbiome and inflammatory bowel disease: is there a therapeutic role for fecal microbiota transplantation? *Am J Gastroenterol* 2012; **107**: 1452-1459 [PMID: 23034604 DOI: 10.1038/ajg.2012.93]

26 **Shi Y**, Dong Y, Huang W, Zhu D, Mao H, Su P. Fecal Microbiota Transplantation for Ulcerative Colitis: A Systematic Review and Meta-Analysis. *PLoS One* 2016; **11**: e0157259 [PMID: 27295210 DOI: 10.1371/journal.pone.0157259]

27 **Zhang X**, Tian H, Chen Q, Qin H, Li N. Fecal microbiota transplantation: standardization or diversification? *Sci China Life Sci* 2019; **62**: 1714-1716 [PMID: 31813093 DOI: 10.1007/s11427-019-1592-8]

28 **Ni J**, Wu GD, Albenberg L, Tomov VT. Gut microbiota and IBD: causation or correlation? *Nat Rev Gastroenterol Hepatol* 2017; **14**: 573-584 [PMID: 28743984 DOI: 10.1038/nrgastro.2017.88]

29 **Ishikawa D**, Zhang X, Nomura K, Seki N, Haraikawa M, Haga K, Shibuya T, Kim YG, Nagahara A. A Randomized Placebo-Controlled Trial of Combination Therapy With Post-triple-antibiotic-therapy Fecal Microbiota Transplantation and Alginate for Ulcerative Colitis: Protocol. *Front Med (Lausanne)* 2022; **9**: 779205 [PMID: 35273972 DOI: 10.3389/fmed.2022.779205]

30 **Nemoto H**, Kataoka K, Ishikawa H, Ikata K, Arimochi H, Iwasaki T, Ohnishi Y, Kuwahara T, Yasutomo K. Reduced diversity and imbalance of fecal microbiota in patients with ulcerative colitis. *Dig Dis Sci* 2012; **57**: 2955-2964 [PMID: 22623042 DOI: 10.1007/s10620-012-2236-y]

31 **Andoh A**, Ida S, Tsujikawa T, Benno Y, Fujiyama Y. Terminal restriction fragment polymorphism analyses of fecal microbiota in five siblings including two with ulcerative colitis. *Clin J Gastroenterol* 2009; **2**: 343-345 [PMID: 26192610 DOI: 10.1007/s12328-009-0106-8]

32 **Damman CJ**, Brittnacher MJ, Westerhoff M, Hayden HS, Radey M, Hager KR, Marquis SR, Miller SI, Zisman TL. Low Level Engraftment and Improvement following a Single Colonoscopic Administration of Fecal Microbiota to Patients with Ulcerative Colitis. *PLoS One* 2015; **10**: e0133925 [PMID: 26288277 DOI: 10.1371/journal.pone.0133925]

33 **Marcella C**, Cui B, Kelly CR, Ianiro G, Cammarota G, Zhang F. Systematic review: the global incidence of faecal microbiota transplantation-related adverse events from 2000 to 2020. *Aliment Pharmacol Ther* 2021; **53**: 33-42 [PMID: 33159374 DOI: 10.1111/apt.16148]

34 **Khanna S**, Kraft CS. Fecal Microbiota Transplantation: Tales of Caution. *Clin Infect Dis* 2021; **72**: e881-e882 [PMID: 32991697 DOI: 10.1093/cid/ciaa1492]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com