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Meta-analysis of the effectiveness of combined enteral nutrition therapy for inflammatory bowel disease

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Abstract

Background: So far, there are still many difficulties in the treatment of inflammatory bowel disease (IBD), among which enteral nutrition (EN) is the most valuable and controversial treatment. Therefore, this study will compare the effectiveness of conventional medication with EN in the treatment of inflammatory bowel disease.

Methods: Searching the Pubmed, Embase, Web of Science, Cochrane Library, Clinical trial, CNKI, Chinese biomedical literature, VIP, and Wanfang databases, Randomized controlled trials and cohort studies on conventional drug + EN and conventional drug therapy for IBD were also retrieved, The data of their efficiency and nutritional status (hemoglobin, albumin, and body mass index) were extracted independently, After a qualitative evaluation of the included literature. The meta-analysis was performed using the RevMan5.3 software.

Results: A total of 33 study articles were included, including 2466 IBD patients, 1248 patients in the test group (conventional drugs combined with EN), and 1218 patients in the control group (conventional drugs). The meta-analysis showed that the clinical response of conventional drugs with EN for IBD was higher than the conventional drug group (RR = 1.25, 95% CI: 1.17–1.34, $Z = 6.37$, $P < .00001$); incidence of total adverse effects: compared with the combination group (RR = 0.98, 95% CI: 0.64–1.48, $Z = 0.11$, $P = .91$). Nutritional status: hemoglobin, albumin, and body mass index in the combined EN group were significantly higher than those in the control group.

Conclusion: For IBD patients (including UC and CD), the combination of conventional drugs and EN was more effective than conventional drug treatment alone, hemoglobin, albumin and body mass index were significantly higher than conventional drug treatment alone, and the difference in adverse reactions was not significant. However, the current research evidence is not enough to fully prove the reliability of the combination therapy, and further studies need to be verified in the future.

Abbreviations: ADA = adalimumab, BMI = body mass index, CD = Crohn's disease, CI = confidence interval, CNKI = China National Knowledge Infrastructure, EEN = Exclusive Enteral Nutrition, EN = enteral nutrition, ESPEN = European Society for Parenteral and Enteral Nutrition, IBD = inflammatory bowel disease, IFX = infliximab, iNOS = inducible nitric oxide synthase, MD = mean difference, MPO = myeloperoxidase, NOS = Newcastle–Ottawa Scale, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT = randomized controlled trial, RR = relative risk, TNBS = 2,4,6-trinitrobenzenesulfonic acid, TNF = tumor necrosis factor, UC = ulcerative colitis, VIP = Very Important Paper (Database).

Keywords: enteral nutrition, inflammatory bowel disease, meta-analysis

1. Introduction

Inflammatory bowel disease (IBD) is a chronic nonspecific intestinal inflammatory disease in the department of gastroenterology. IBD can be divided into ulcerative colitis (UC) and Crohn's disease (CD), and patients usually develop intestinal symptoms such as abdominal pain, diarrhea, dyspepsia, and blood in the stool, some may have parenteral manifestations. The pathogenesis of this disease is complex, and it is considered to be the result of multifactor interaction of genes, environment, immunity and microorganisms.[1] Clinically, the drug treatment of inflammatory bowel disease mainly includes 5-aminosalicylic acid, glucocorticoids, immunosuppressants, biological agents and others.[2] While there has been some evidence of efficacy with

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

The research did not involve in any human or animal research, therefore there was no ethical approval from any ethics committee.

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conventional medication treatment, many people return after a time of remission. The length of the treatment regimen, which might occasionally last a lifetime, has a substantial influence on disease management.

Patients with IBD are at high risk of malnutrition, mainly nutritional deficiency, which can be by decreased body mass, decreased muscle mass, negative nitrogen balance, hypoproteinemia, micronutrient deficiency, anemia, low bone mass, and osteoporosis.[3–5] Malnutrition in IBD patients can have a serious impact on the recovery, affect the quality of life of patients, and is also an important factor for the poor prognosis of IBD. The efficacy of supportive nutrition therapy for IBD has been recognized as crucial to the current treatment of IBD. Nutritional support includes enteral nutrition (EN) and parenteral nutrition support. At present, many studies have proved that the enteral nutrition (EN) is more effective on IBD than parenteral nutrition, which may be related to lower incidence of complications and lower treatment cost; In addition, EN is currently considered the basic nutritional factor of intestinal mucosa, which also prevents bacterial displacement and maintains gastrointestinal function.[5] The ESPEN guidelines also recommend that EN should always be prioritized over parenteral nutrition for IBD,[6] unless completely contraindicated.

EN provides essential nutrients directly to the body and intestinal mucosa, regulate intestinal flora, reduce inflammation of intestinal mucosa, improve intestinal permeability, and promote intestinal mucosa healing, and play an important role in inducing and maintaining IBD remission, as well as reducing postoperative recurrence. Numerous studies have demonstrated that total EN therapy is an effective treatment measure for pediatric CD patients, and it has been recommended as the first-line treatment. However, for adult CD patients, the British Society of Gastroenterology recommends steroids, immunosuppressants or surgical as preferred treatments, with Exclusive Enteral Nutrition (EEN) reserved for cases where 5-aminosalicylic acid is ineffective or contraindicated due to steroids.[7] The treatment of IBD currently remains great challenges, and EN remains a controversial but promising treatment modality for adult IBD patients.[8] The effectiveness and safety of EN, especially when paired with conventional therapy, are gaining attention despite the difficulties in treating IBD and the debates surrounding it.. This study aims to evaluate, the efficacy and safety of this combines approach, as well as its impact on nutritional status, through comprehensive meta-analysis to inform future clinical treatment.

2. Data and methods

PRISMA criteria were adhered to in this meta-analysis, and the PRISMA Statement checklist for reporting systematic reviews was used. The research did not involve any human or animal research, therefore there is no ethical approval from any ethics committee.

2.1. Literature search

Search the Chinese and English databases: CNKI, Wanfang database (WanFang), VIP database (VIP), PubMed, Embase, Cochrane Library, Web of Science. The time limit for database searches extended until August 2023. For Chinese databases, search terms included: inflammatory bowel disease, Crohn's disease, ulcerative colitis, enteral nutrition. For English databases, search terms included: inflammatory bowel disease, ulcerative colitis, Crohn's disease, enteral nutrition, elemental diet, medical foods, and polymeric diet. Cohort studies and randomized controlled trials were included, both in Chinese and English.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria. Study type: randomized controlled trial and cohort studies investigating conventional drugs combined with EN for IBD. Subjects: patients diagnosed with IBD, aged 18 years regardless of gender, race or nationality. Interventions: comparison between a test group receiving conventional drugs combined with EN and a control group receiving conventional drugs alone; control group for IBD alone. clear efficacy criteria in the study.

2.2.2. Exclusion criteria. Any of the following cases in the study was excluded: non-IBD patients; studies involving children as subjects; reviews, letters to the editor, and case analysis; repeated the published literature.

2.3. Data extraction

The relevant data for inclusion in the study comprised the research topic, year, population characteristics, sample size, follow-up time, intervention measures, efficacy indicators, and results. Two independent researchers extracted the data and, in case of disagreement, discussed the issues or solicit opinions from a third party.

2.4. Literature evaluation

The literature quality of the included randomized controlled trials was evaluated by 2 evaluators against the risk of bias criteria in the Cochrane systematic evaluation manual. The literature quality of the cohort study was evaluated using the Newcastle Ottawa scale.

2.5. Statistical analysis

Data analysis was performed using the RevMan 5.3 software. The Q test was used to assess heterogeneity among studies: when $I^2 \leq 50\%$, $P \geq .1$, less heterogeneity of included studies; when $I^2 > 50\%$, $P < .1$, more heterogeneity of included studies, indicated that source of heterogeneity should be analyzed for subgroup analysis and the study results should be interpreted. Since various baseline treatment drugs may cause heterogeneity, random effects models were employed. For the analysis relative risk (RR), mean difference (MD) and 95% confidence intervals (Cis) were calculated for categorical data, with $P < .05$ indicating statistically significance.

3. Results

3.1. Literature search

A total of 7329 articles were retrieved using Endnote to remove duplicate literature, abstracts, and full articles; 33 studies were included (13 studies for UC, 16 studies for CD, 4 studies did not distinguish IBD types; 22 Chinese articles, and 11 English articles). The literature screening process is shown in Figure 1.

3.2. Basic characteristics and quality evaluation of the literature

A total of 2466 subjects were included, 1248 in the test group (conventional drug + EN) and 1218 in the control group (conventional drug). The types of patients had definite IBD (Table 1). Among them, RCT 18, 15 cohort studies; literature quality evaluation: 11 high qualities, 22 moderate qualities (Table 1).

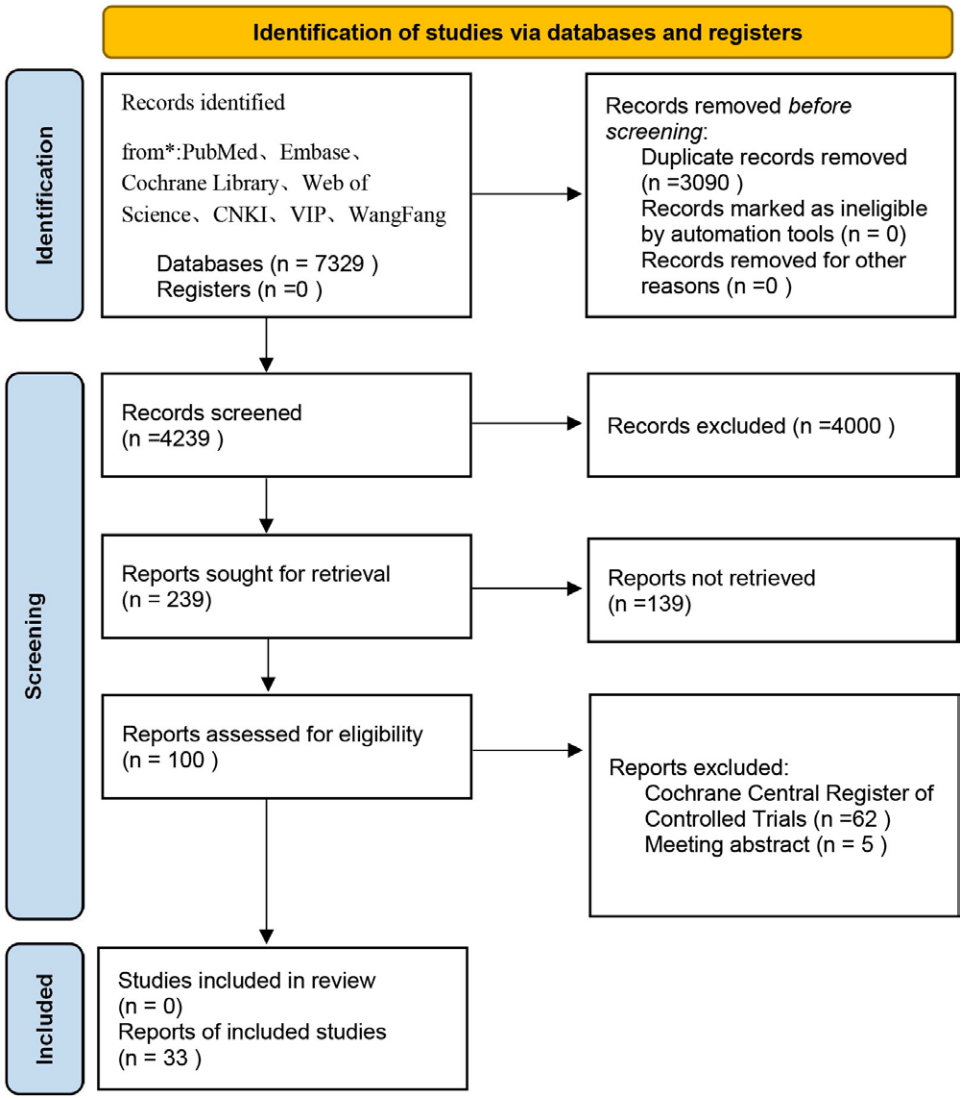

Figure 1. Flow chart of literature screening.

3.3. Meta-analytic result

3.3.1. Effective rate. A sum of 25 studies on IBD[9–19,22–34,38] reported effective rates with low heterogeneity between studies ($P = .02$, $I^2 = 41\%$) using random effects model analysis, conventional drugs combined with EN were significantly more effective in IBD than in conventional drugs alone, with statistically significant differences (RR = 1.25, 95% CI: 1.17–1.34, $Z = 6.37$, $P < .00001$; Fig. 2). Among them, 11 studies on UC[9–19] showed high heterogeneity ($P = .002$, $I^2 = 64\%$). Meta-analysis using random effects model showed that the clinical response rate of conventional therapy combined with EN for UC was statistically significant (RR = 1.29, 95% CI: 1.13~1.47, $Z = 3.82$, $P = .0001$; Fig. 2).

Among them, 13 studies[22–34] on CD showed little heterogeneity between ($P = .24$, $I^2 = 20\%$). The random effects model analysis showed the clinical response rate of CD compared with conventional treatment alone (RR = 1.22, 95% CI: 1.12–1.32, $Z = 4.77$, $P < .00001$; Fig. 2).

3.3.2. Subgroup analysis (effective rate). Among them, 11 studies[9–19] on the English literature in meta-analysis using random-effects models showed that the clinical response rate of conventional therapy combined with EN was significantly higher and statistically significant (RR = 1.22, 95% CI: 1.08–1.39, $Z = 3.19$, $P = .001$). Among them, 14 studies[22–34,36] on the Chinese literature conducted in meta-analysis using random effects models showed that the clinical response rate of conventional therapy combined with EN was significantly higher, with statistically significant differences (RR = 1.27, 95% CI: 1.16–1.38, $Z = 5.25$, $P < .0001$).

Among the 20 studies[11–19,22–32] on high NOS, random-effects models showed significant clinical response compared with EN alone (RR = 1.25, 95% CI: 1.14–1.37, $Z = 4.88$, $P < .0001$). Among them, 6 studies on middle NOS,[23–28] using meta-analysis using random-effects models, showed that the clinical response rate of conventional therapy combined with EN was significantly higher and statistically significant (RR = 1.21, 95% CI: 1.10–1.32, $Z = 4.09$, $P < .0001$).

Among these, 10 studies[24–30,34–36] with 30 days' follow-up using a random-effects model, the clinical response of conventional therapy combined with EN was statistically significant (RR = 1.32, 95% CI: 1.18–1.47, $Z = 4.88$, $P < .0001$). Among them, 15 studies[9–16,22–28] with follow-up time < 30 days in meta-analysis showed that the clinical response rate of conventional therapy combined with EN was significantly higher, with statistically significant differences (RR = 1.21, 95% CI: 1.11–1.32, $Z = 4.31$, $P < .0001$).

Among these, 10 studies[11–19,22] of Infliximab (IFX) + EN/IFX using meta-analysis showed that the clinical response rate of

Table 1

Basic characteristics and literature quality of the included literature.

Author	Year	Object of study	N (test group/control group)	Age (test group/control group)	Intervention (test group/control group)	Follow-up time (test group/control group)	NOS	Outcome
Horiuchi[9]	2016	UC	16/10	The median age was 39 yr	IFX + EN/IFX	2 wk	High	1
Sahu[10]	2021	Severe UC	32/30	32.8 ± 10.8/37.9 ± 13.1	Glucocorticoids + EN/glucocorticoids	7 d	High	1–4
Lu[11]	2016	Moderate to severe UC	25/21	42.1 ± 7.8/41.2 ± 7.2	Mesalazine + Probiotics + EN/Mesalazine + Probiotics	4 wk	High	1, 3, 4
Gong[12]	2009	Mild to moderate UC	13/11	44.25 ± 17.69/38.6 ± 10.69	Mesalazine + EN/Mesalazine	14 d	Middle	1
Zhuang[13]	2020	Moderate to severe UC	43/42	44.08 ± 5.72/43.03 ± 5.65	Mesalazine + Probiotics + EN/Mesalazine + probiotics	4 wk	High	1, 3–5
Yang[14]	2016	UC	59/62	35.6 ± 10.4/36.2 ± 11.4	Compound glutamine + EN/compound glutamine	4 Wk	High	1, 2, 4, 5
Bai[15]	2016	UC	27/25	45.15 ± 13.64/42.48 ± 12.22	Conventional drugs + EN/conventional drugs	≥8 wk	High	1–4
Che[16]	2013	Mild to moderate UC	50/55	42.2 ± 14.6/43.5 ± 15.4	Conventional drugs + EN/conventional drugs	20 d	High	1, 3, 4
Xin[17]	2014	UC	23/22	44 ± 16/46 ± 14	Mesalazine + EN/Mesalazine	7–30 d	Middle	1, 2
Deng[18]	2015	Mild to moderate UC	16/17	39.21 ± 10.13/37.86 ± 9.82	Mesalazine + EN/Mesalazine	2 wk	High	1, 2
Cheng[19]	2020	UC	45/45	40.15 ± 3.22/40.05 ± 3.15	Compound glutamine + EN/compound glutamine + EN	4 wk	High	1, 3, 4
Pan[20]	2018	Moderate to severe CD	24/25	35 ± 13.7/36 ± 14.8	Basic treatment + EN/basic treatment	1 mo	High	3–5
Wang[21]	2019	Moderate to severe CD	56/34	44.68 ± 14.12/49.47 ± 16.19	Conventional drugs + EN/conventional drugs	5–25 d	Middle	3–5
Hirai[22]	2013	Moderate to severe CD	45/57	35.7 ± 1.5/31.2 ± 1.3	IFX + EN/IFX	(78 ± 3) wk	High	1, 2
Hirai[23]	2019	CD	37/35	31.6 ± 12.5/31.9 ± 12.4	ADA or IFX + EN/ADA or IFX	2 yr	High	1
Yoshimura[24]	2014	Moderate to severe CD	42/34	None	ADA + EN/ADA	4 wk	High	1
Kamata[25]	2014	Moderate to severe CD	28/97	36.9 ± 7.6/36.1 ± 10.9	IFX + EN/IFX	(799 ± 398)d/(771 ± 497)d	High	1
Sazuka[26]	2012	Moderate to severe CD	29/45	31.2	IFX + EN/IFX	85 wk	High	1
Ono[27]	2015	Moderate to severe CD	42/38	None	IFX + EN/IFX	3 yr	High	1
Matsumoto[28]	2005	Moderate to severe CD	49/12	33/32	IFX + EN/IFX	2 wk	High	1
Yamamoto[29]	2010	Moderate to severe CD	32/24	31 ± 1.6/33 ± 1.6	IFX + EN/IFX	56 wk	High	1
Tanaka[30]	2006	Moderate to severe CD	51/59	None	IFX + EN/IFX	16 wk	High	1
Zhang[31]	2019	CD	40/40	38.52 ± 1.54/38.56 ± 1.68	Mesalazine + prednisone + EN/Mesalazine + prednisone	2 wk	Middle	1
Shi[32]	2020	Mild to moderate CD	45/44	32.2 ± 10.3/31.2 ± 11.0	IFX + EN/IFX	12 wk	Middle	1–5
Hu[33]	2015	Moderate to severe CD	30/30	32.1 ± 8.4/32.6 ± 8.2	IFX + EN/IFX	6 wk	Middle	1, 2, 5
Zhao[34]	2015	CD	46/46	38.8 ± 7.4/39.3 ± 7.6	Mesalazine + prednisone + EN/Mesalazine + prednisone	14 d	Middle	1, 4
Zhu[35]	2005	CD	31/8	11–69 (35 ± 13)	hormone + EN/hormone	4 wk	Middle	3, 4
Gong[36]	2009	CD	42/20	34.2 ± 13.3/36.2 ± 12.2	TWP + EN/TWP	12 wk	High	3–5
Qu[37]	2019	CD	48/48	38.45 ± 5.40/39.42 ± 5.27	Parenteral nutrition at 4 wk before surgery + EN/parenteral nutrition at 4 wk before surgery	3 mo	High	2–5
Xia[38]	2020	IBD	41/41	37.53 ± 8.33/39.85 ± 7.69	Mesalazine + prednisone + EN/Mesalazine + prednisone	None	High	1
Wang[39]	2016	IBD	57/57	21–65 (43.61 ± 1.70)	Basic treatment + EN/basic treatment	None	High	2, 4, 5
Peng[40]	2020	IBD	43/43	44.21 ± 5.68/42.83 ± 4.29	Mesalazine or prednisone + EN/Mesalazine or prednisone	4 wk	High	4
Fan[41]	2016	IBD	41/41	45.21 ± 1.9	Basic treatment + EN/basic treatment	None	Middle	2, 4, 5

Note: 1 = effective rate, 2 = the incidence of adverse reactions, 3 = hemoglobin levels, 4 = albumin, 5 = BMI.

ADA = Adamumab, BMI = body mass index, CD = Crohn's disease, EN = enteral nutrition, IBD = inflammatory bowel disease, IFX = Infliximab, NOS = The Newcastle–Ottawa Scale, TWP = Tripteryium Wilfordii Polyglycosidium, UC = ulcerative colitis.

conventional therapy compared with EN was statistically significant (RR = 1.27, 95% CI: 1.17–1.39, $Z = 5.59$, $P < .0001$). Among them, 2 studies on conventional drugs + EN/conventional drugs, using meta-analysis using random-effects models, showed that the clinical response rate of conventional therapy combined with EN was significantly higher, with no statistically significant difference (RR = 1.43, 95% CI: 0.92–2.23, $Z = 1.57$, $P = .12$). Among these, 5 studies[9–13] on

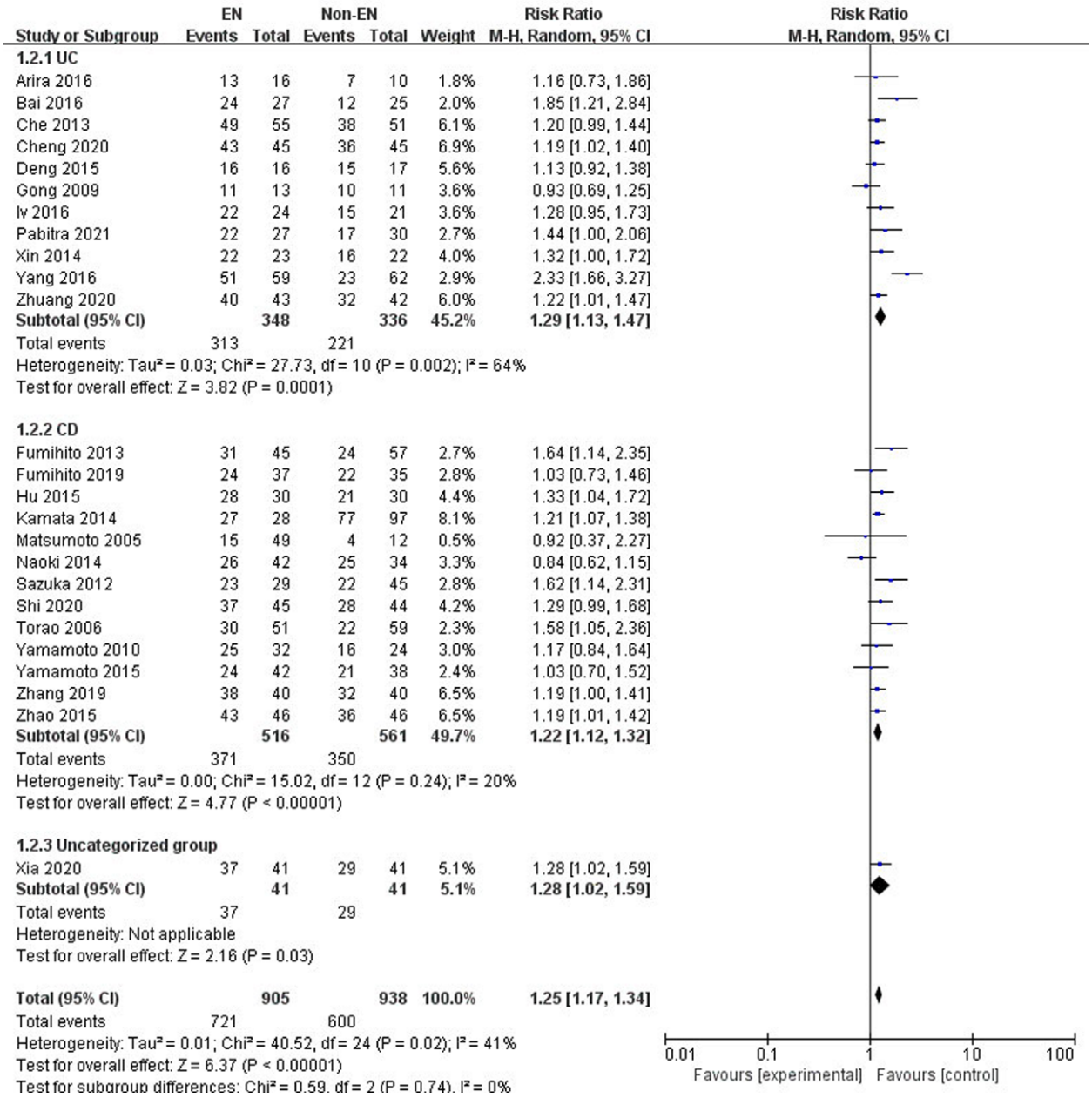

Figure 2. Results of the efficient meta-analysis. CD = Crohn's disease, UC = ulcerative colitis.

Mesalazine + Probiotics + EN/Mesalazine + Probiotics, meta-analysis using random effects model, showed that the clinical response rate of conventional therapy compared with EN was statistically significant (RR = 1.22, 95% CI: 1.12–1.33, Z = 4.40, $P < .0001$). Two studies[11,12] of ADA + EA/ADA in meta-analysis using random-effects models showed that the clinical response rate combined with EN was lower than that alone and not significant (RR = 0.92, 95% CI: 0.73–1.16, Z = 0.69, $P = .49$). Three of the studies[16–18] on Mesalazine + EN/Mesalazine in meta-analysis using random effects models showed that clinical response with EN was higher than that (RR = 1.13, 95% CI: 0.95–1.33, $Z = 1.41$, $P = .16$; Table 2).

3.3. Comparison of the incidence of adverse reactions

A total of 11 studies[10,14,15,17,18,22,32,33,37,39,41] compared the incidence of adverse reactions with heterogeneity test ($P = .03$, $I^2 = 50\%$), considering that heterogeneity originated from patient IBD, different types, treatment follow-up time, EN support, and severity of adverse reactions. Meta-analysis using random effects models showed that there was no significant difference in the incidence of adverse effects (RR = 0.98, 95% CI: 0.64–1.48, $Z = 0.11$, $P = 0.91$; Fig. 3).

3.4. Comparison of the nutritional status situation

3.4.1. Hemoglobin levels. Eight articles on UC[10,11,13,15,16,19–21] and 4 projects on CD[31,34–36] documented post-treatment hemoglobin levels, with heterogeneity tests between studies ($P = .03$, $I^2 = 48\%$), considering the heterogeneity derived from disease severity, basic treatment agents, and follow-up time among studies. Using the random effects model analysis, the results showed that the hemoglobin level after IBD with EN was significantly higher than in the conventional drug treatment

alone, statistically significant (MD = 7.25, 95% CI: 3.55~10.95, $Z = 3.84$, $P = .0001$; Fig. 4).

3.4.2. Albumin levels. Nine articles on UC,[10,11,13–16,19–21] 5 items on CD,[32,34–37] and 3 unclassified IBD articles[39–41] studied post-treatment albumin, with high heterogeneity between studies ($P < .00001$, $I^2 = 91\%$), considering the heterogeneity originated from the disease severity, basic treatment agents and follow-up duration of the studies. Using random effects model analysis, the results showed that the albumin level after IBD with EN was significantly higher than in IBD group, statistically significant (MD = 5.39, 95% CI: 3.60–7.17, $Z = 5.90$, $P < .00001$; Fig. 5).

3.4.3. Body mass index. Four articles on UC,[13,14,20,21] 4 articles on CD,[32,33,36,37] and 2 unclassified IBD articles[39,41] studied the BMI after treatment, with high heterogeneity between studies ($P < .00001$, $I^2 = 92\%$), considering the heterogeneity originated from the disease severity, basic treatment, and follow-up time of each study. Using a random effects model analysis, the results showed that the BMI level after IBD with EN was significantly higher than in the IBD group, statistically significant (MD = 2.22, 95% CI: 1.18–3.26, $Z = 4.18$, $P < .0001$; Fig. 6).

Table 2

Subgroup analysis based on NOS, Chinese and English literature, follow-up period, measures in effective rate.

Subgroup		I^2 (%)	95% CI	*P* value
Literature	English (N = 11)	34	1.22 [1.08, 1.39]	.13
	Chinese (N = 14)	52	1.27 [1.16, 1.38]	.01
NOS	High (N = 19)	52	1.25 [1.14, 1.37]	.003
	Middle (N = 6)	0	1.21 [1.10, 1.32]	.5
Measures	IFX + EN/IFX (N = 11)	0	1.27 [1.17, 1.39]	.52
	Conventional drugs + EN/ conventional drugs (N = 2)	73	1.43 [0.92, 2.23]	.12
	Mesalazine + probiotics + EN/ Mesalazine + probiotics (N = 5)	0	1.22 [1.12, 1.33]	.98
	ADA + EN/ADA (N = 2)	0	0.92 [0.73, 1.16]	.39
	Mesalazine + EN/Mesalazine (N = 5)	32	1.13 [0.95, 1.33]	.23
Follow up day	≥30 d (N = 10)	29	1.32 [1.18, 1.47]	.18
	<30 d (N = 15)	47	1.21 [1.11, 1.32]	.02

ADA = Adamumab, CI = confidence interval, EN = enteral nutrition, IFX = Infliximab, NOS: = The Newcastle–Ottawa Scale.

3.5. Sensitivity analysis and publication bias

In the response rate analysis, among the 11 UC studies included, there was a great heterogeneity among the studies. According to the statistical graph shift, the suggestion of Yang et al[14] study may have a high risk of bias, so the sensitivity analysis of meta-analysis results was conducted after excluding this study (Fig. 7).The findings of the before and after analysis revealed little changes, and the heterogeneity test indicated lowered heterogeneity among studies ($P = .38$, $I^2 = 6\%$). The possible reasons were as follows: Disease severity, basic interventions, therapeutic drugs and doses were not completely consistent among studies. A funnel plot analysis was performed for the total response rate, which showed a mild asymmetry, suggesting a potential publication bias (Fig. 8).

4. Discussion

Inflammatory bowel disease (IBD) is a chronic, recurrent, inflammatory disease of the digestive tract. IBD incidence has been rising in recent years due to a number of causes, including nutrition.[42] There is a correlation between an increased risk of IBD and Western diets, particularly those with a high n-6/n-3 fatty acid ratio. Dietary variables, the gut microbiota, and the mucosal system may interact to cause IBD.[43] Meanwhile, malnutrition, as one of the complications of IBD, has the prevalence of between 20% and 85%.[5] A systematic review reported that up to 60% of IBD patients decreased muscle mass[44] compared to healthy subjects; in a Romanian study, the prevalence of BMI was 30.6%[45]; in a Serbian study, of 76 IBD patients (23 CD and 53 UC), 68.4% were malnourished and 31.6% were severely malnourished.[46] The causes of malnutrition in IBD patients are multifaceted, including discomfort from symptoms like abdominal pain, nausea, reduced oral nutrition intake due to hospitalization, complications from small intestinal bacterial overgrowth and motility issues, and the direct impacts of the disease such as increased intestinal and nutrient loss.[5,6] In recent years, due to the increasing incidence of IBD and its impact on quality of life and the huge burden on society-economy, more attention has been paid to its treatment plan. Nutritional support has also become one of its important ways.

In IBD treatment, nutritional support often prioritizes EN, which can not only improve the malnutrition status of patients, regulate inflammatory reactions, promote the healing of diseased intestinal mucosa, and play an important role in the treatment of IBD. Enteral nutrition(EN) may reduce the degree of disease activity and promote mucosal healing by regulating

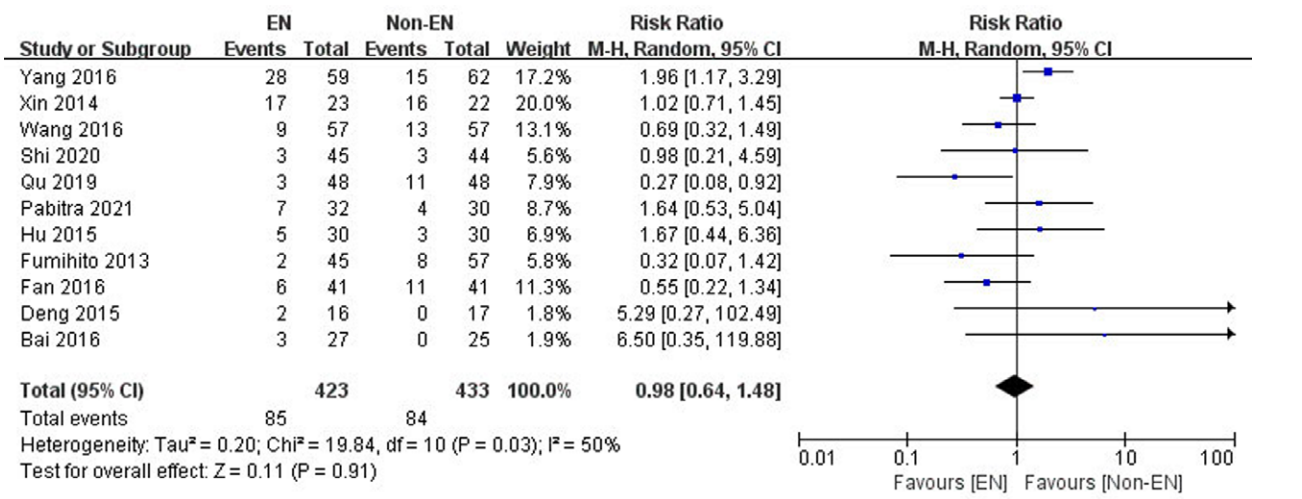

Figure 3. Meta-analysis results of adverse reaction rates.

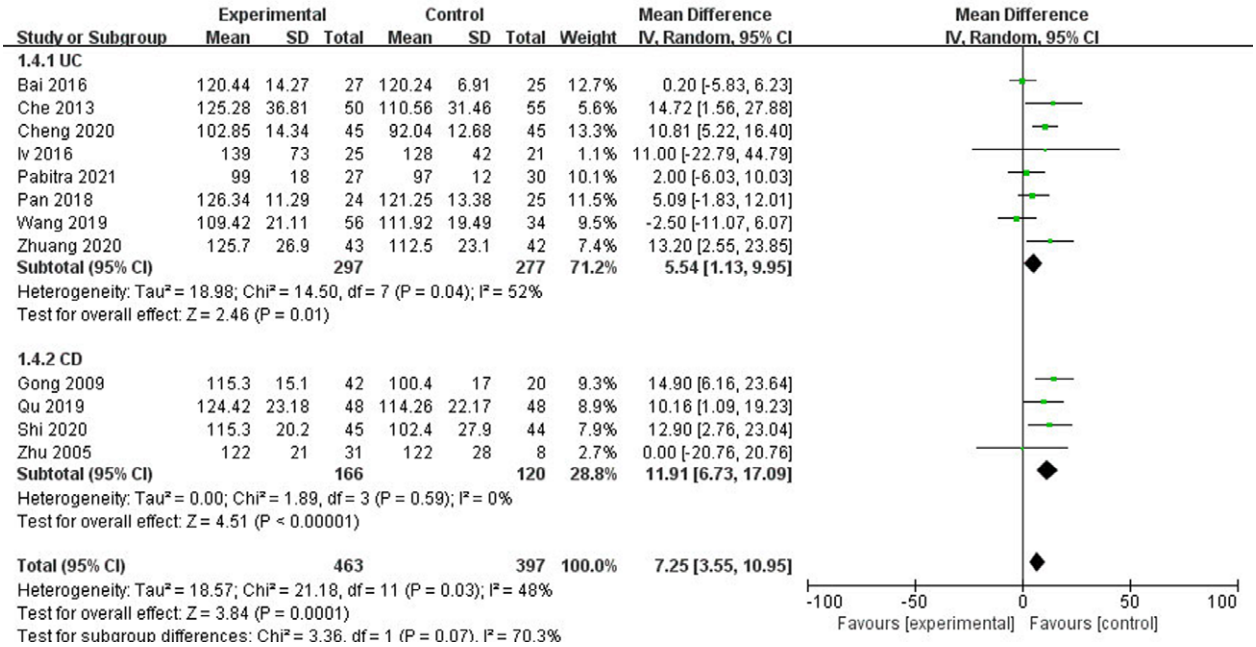

Figure 4. Results of a meta-analysis of hemoglobin levels after treatment. CD = Crohn's disease, UC = ulcerative colitis.

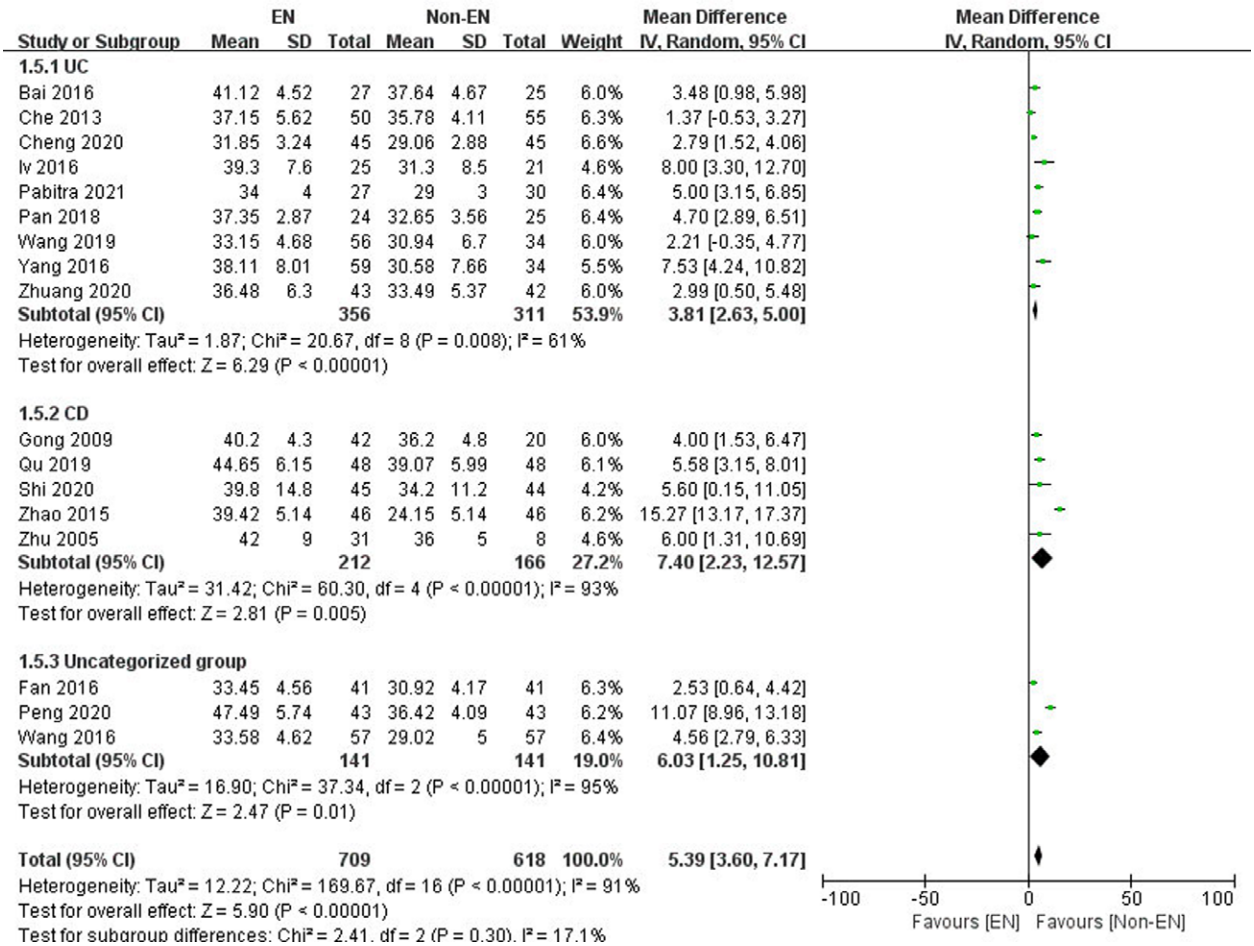

Figure 5. Results of the meta-analysis of albumin levels after treatment. CD = Crohn's disease, UC = ulcerative colitis.

intestinal flora, regulating intestinal mucosal immune response and inflammatory response, repairing epithelial barrier, restoring mesenteric fat abnormalities, and affecting antioxidant enzymes.[47] Yu [48] study found that EN was effective in improving weight loss, colon length shortening, loose stools and blood in the stool. Furthermore, it also improved the signs of TNBS

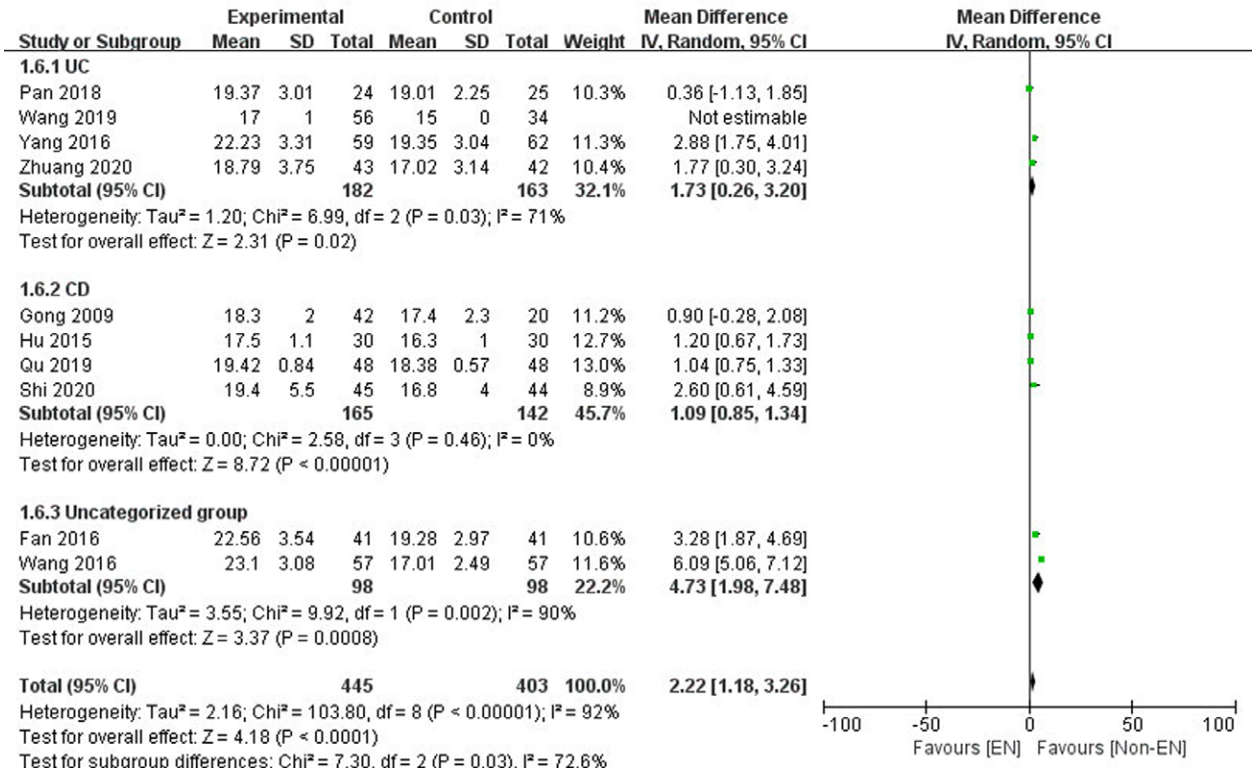

Figure 6. Results of a meta-analysis of body mass index after treatment. CD = Crohn's disease, UC = ulcerative colitis.

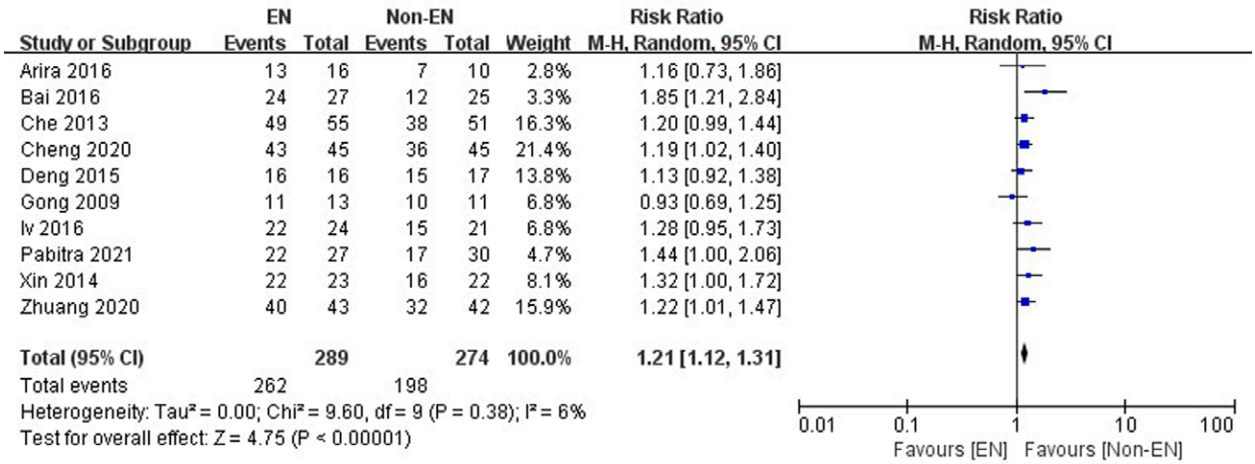

Figure 7. Clinical effective meta-analysis results. UC = ulcerative colitis.

induced colitis, as histopathological analysis showed that EN reduced the pathological damage of colon tissue, and inhibited the activity of myeloperoxidase (MPO) and nitric oxide synthase (iNOS), along with cytokine secretion in colon tissue.

Exclusive enteral nutrition (EEN) has been recommended as the first-line treatment for pediatric CD patients. For adults IBD patients, EN is selected when glucocorticoid therapy is intolerated.[49] While some guidelines recommend EN along with other drugs for[50] in remission. However, in Japan, EEN therapy has become the first-line treatment in adult CD patients, with EN also being widely employed in the maintenance phase treatment.[51]

In addition, the efficacy of EN in treating UC remains controversial, despite an increasing number of studies exploring its application. Abigail Marsh conducted a systematic evaluation[52] of 10 different dietary management (including enteral nutrition, total parenteral nutrition, exclusion diet, and standard oral diet) in inpatient and outpatient adult active UC found no strong evidence supporting the use of any specific dietary prescription to improve clinical outcomes in patients with active UC. Chen and Dong study on enteral nutrition combined with compound glutamine in UC[53] showed that the levels of TNF-α and IL-8 were significantly reduced in the combination treatment group, and lower than that of the control group (compound glutamyl group), statistically significant ($P < .05$). The total effective rate of the combination group was 95.56%, significantly higher than 80.00% in the control group. Zhang[54] conducted a study with 70 cases of ulcerative enteritis patients, randomly dividing them into control group (conventional treatment) and observation group (based on the control group and parenteral, enteral high nutrition therapy), 2 groups of 35 cases, after the corresponding

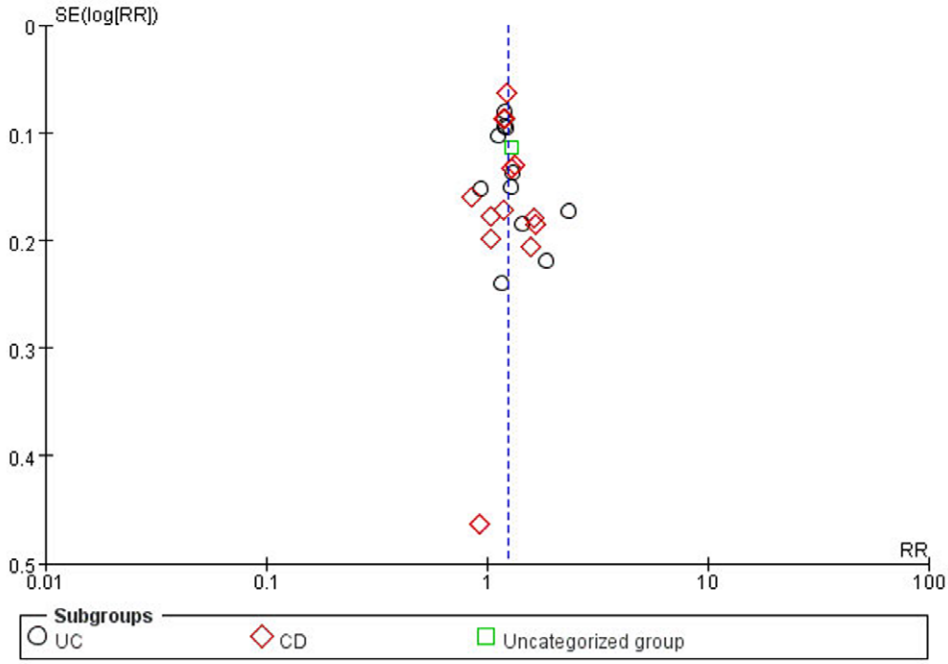

Figure 8. Total efficiency comparison funnel plot.

treatment, in the observation group total efficiency and treatment satisfaction is significantly better than the control group, the contrast between the 2 groups the difference is significant, has the corresponding statistical significance, $P < .05$.

A previous meta-analysis of IFX with EN for CD showed that IFX combined with EN was more effective, with lower recurrence rate, and no significant difference in adverse effects.[55] This meta-analysis involved a comprehensive search of domestic and foreign database, including more studies and cases, a total of 33 articles, 11 literature quality evaluation for high quality, 22 literature quality evaluation for middle quality, analysis compared the clinical efficiency of combined therapy and conventional treatment, nutritional status improvement and adverse reactions, and the CD and UC patients respectively, the results show that. The results showed that the combination of EN for IBD treatment was more effective than conventional drug treatment group (RR = 1.25, 95% CI: 1.17~1.34, $Z = 6.37$, $P < .00001$). And it was statistically significant in both the UC and CD subgroups (UC group: RR = 1.29, 95% CI: 1.13~1.47, $Z = 3.82$, $P = .0001$; CD group: RR = 1.22, 95% CI: 1.12~1.32, $Z = 4.77$, $P < .00001$). It was beneficial to improve the nutritional status of patients. BMI, hemoglobin and albumin in the test group were higher than that in the control group. And the total incidence of adverse reactions between the 2 groups was not significant (RR = 0.98, 95% CI: 0.64–1.48, $Z = 0.11$, $P = .91$).

Meanwhile, this study conducted subgroup analysis of NOS, Chinese and English literature, follow-up time, and intervention measures, the results show that, the overall efficacy of conventional drugs with EN for IBD was better than the conventional drug alone group (RR = 1.24, 95% CI: 1.20~1.28, $Z = 12.79$, $P < .00001$), There was no significant difference only in the conventional drugs + EN/conventional drugs, ADA + EN/ADA, and Mesalazine + EN/Mesalazine subgroups.

This study has some limitations. Although included in RCT, it was mainly in Chinese. Most studies were included in China, only 1 in India; other included studies were cohort studies, and some studies did not mention patient compliance. Some included literature for IBD induced remission, some studies to maintain remission, some studies failed to clarify disease severity, the IBD treatment duration, EN preparation types, dosages, administration methods, and evaluation of active IBD remission criteria, studies have certain heterogeneity, failed to perform further subgroup analysis due to the limited number of the included literature. In order to comprehensively evaluate the role of enteral nutrition in the treatment of IBD, further meta-analysis is needed to design and implement more randomized controlled trials of higher quality. In conclusion, conventional drugs combined with EN has better clinical efficacy than conventional drug treatment of IBD (including CD and UC), can better improve the nutritional status of patients, and has good safety, which can provide certain guidance for the induction and maintenance of IBD remission. However, the broader adoption of EN combination therapy in clinical practice requires larger scale, multi-center clinical research, to further prove its clinical efficacy, no, incidence of good response, and nutritional status improvement, and guidance in the induction and maintenance of disease remission in the timing of the EN treatment, nutritional support and nutritional dose, etc.

Author contributions

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