

# A Meta-analysis of efficacy and safety of Banxia Xiexin decoction on ulcerative colitis

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**Abstract:** Objective: To evaluate the clinical efficacy and safety of Banxia Xiexin Decoction in the treatment of ulcerative colitis(UC). Methods: The Cochrane Library, PubMed, Embase, CBM, CNKI, VIP and Wanfang databases were searched by computer, and the clinical randomized controlled trials(RCTs) of Banxia Xiexin Decoction in the treatment of UC were included with the method of manual retrieval. The retrieval time was from the establishment of each database to March 16,2021. Meta-analysis was completed Rev Man 5.3. Results: This study included 16 articles,1332 patients. Meta-analysis showed that the total effective rate was [RR = 1.29, 95%CI:1.23~1.36,Z=9.82(P <0.01)];The cure rate [RR=1.72,95%CI:1.43~2.06,Z=5.79(P <0.01)];The incidence of adverse reactions was [RR=1.2 9,95%CI:0.27~0.65,Z=3.88(P=0.0001)];Symptom disappearance time ①Abdominal pain disappearance time: [MD =-4.45, 95%CI:-5.03~-3.86,Z=14.99(P <0.01)],②Diarrhea disappearance time: [MD=- 2.7 0,95%CI:-3.27~-2.13, Z=9.28(P <0.01)],③Skeptics tool disappearance time: [MD=-2.55, 9 5%CI:-3.09~-2.02,Z=9.32(P <0.01)];The levels of inflammatory factors TNF - $\alpha$  and IL- 1 ①TNF - $\alpha$ : [MD=-5.3 6,95%CI:-7.70~-3.02,Z=4.49(P < 0.01)], ② IL-1 :[MD =-0.41, 9 5%CI:-0.77~-0.06,Z=6.50(P =0.02)]; Conclusions: Curative Effect and Safety of Modified Banxia Xiexin Decoction on UC.

**Keywords:** Banxia Xiexin Decoction, ulcerative colitis, Meta-analysis

## 1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease caused by the interaction between genetic background and environmental factors. The etiology and pathogenesis of UC are not yet clear <sup>[1]</sup>, which involves genetic susceptibility, epithelial barrier defects, immune response disorders and environmental factors <sup>[2]</sup>, and is characterized by recurrent and remission alternation in clinic. In recent years, the incidence of UC in China has shown a significant upward trend, which is related to the improvement of people's living standards and the change of diet structure <sup>[3]</sup>. The disease is difficult to treat and has a high incidence [4]. At present, the main drug for the treatment of UC in clinic is 5-aminosalicylic acid (5-ASA) [5]. The frequent use of this drug leads to increased adverse reactions and poor therapeutic effect. However, the adverse reactions of traditional Chinese medicine in the treatment of UC are small, drug dependence is low, and the price is low. Therefore, many UC patients choose to use traditional Chinese medicine. At present, the clinical efficacy of traditional Chinese medicine in the treatment of UC is also recognized [6]. Banxia Xiexin Decoction is a classical prescription derived from Treatise on Febrile Diseases. It uses the method of pungent opening and bitter descending to treat the symptoms of diarrhea, abdominal pain, fullness of stuffiness, internal urgency and weight loss. Experiments and clinical show that Banxia Xiexin Decoction has advantages in the treatment of UC. In order to clarify the efficacy and safety of Banxia Xiexin Decoction in the treatment of UC, based on the idea of evidence-based medicine, Meta analysis method is used to systematically evaluate its safety, so as to provide more reliable evidence for clinical treatment.

## 2. Data and methods

### 2.1 Literature search

Through electronic database retrieval and manual retrieval, the retrieval databases include Cochrane Library, PubMed, Embase, China Biomedical Database (CBM), China Journal Full-text Database (CNKI), VIP database and Wan Fang Data. The combination of keywords and free words is adopted, and the Chinese retrieval words are Banxia Xiexin Decoction and ulcerative colitis. The key words in English were "Pinellia xiexin decoction" and "Ulcerative colitis". The search language is limited to Chinese and English, and all searches are databaseed until 16 March 2021. The PubMed search strategy is shown in **Figure 1**.

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#1 "Colitis, Ulcerative"[Mesh]
#2 "non-specific ulcerative colitis"[Title/Abstract] OR "ulcerative colitis"[Title/Abstract]
#3 #1 OR #2
#4 "Banxia xiexin decoction"[Title/Abstract]
#5 #3 AND #4
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Figure 1: PubMed search strategy

### 2.2 Inclusion criteria

① Randomized controlled clinical trials (RCTs) of Banxia Xiexin Decoction in the treatment of ulcerative colitis. ② UC patients met the diagnostic criteria, no race, gender, age, regional restrictions. ③ The experimental group was treated with Banxia Xiexin Decoction and its modified or Banxia Xiexin Decoction combined with conventional western medicine. The control group was given routine western medicine. Dosage, administration times, administration methods and course of treatment are not limited. ④ The methodological quality of the included literature was evaluated according to the Cochrane bias risk assessment tool. The types of bias and evaluation criteria are: 1) whether the random distribution sequence is generated correctly; 2) Whether the allocation hiding method is complete; 3) Whether the blind method is complete (both experimental recipients and experimental implementers); 4) Whether the result data are complete; 5) Results of selective research reports; 6) Whether there are other biases. ⑤ The main outcome index is the total effective rate of clinical efficacy. The total effective rate standard refers to *the guiding principle of clinical research on new drugs in China (trial)* [7]. The secondary outcome indexes include the cure rate, the incidence of adverse reactions, the disappearance time of symptoms (abdominal pain disappearance time, diarrhea disappearance time, purulent stool disappearance time), the levels of inflammatory factors in serum (tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) level in serum), interleukin-1 (IL-1) and colonoscopy score.

### 2.3 Exclusion criteria

① Non-RCT literature, such as case reports, animal experiments, cell experiments, conference papers, etc.; ② Non-ulcerative colitis or other serious organic diseases, such as intestinal perforation, massive hemorrhage and toxic megacolon; ③ incorrect random method ( including pseudo-random method and no random method ); ④ Research on repeated publication, incomplete literature information and data information fraud; ⑤ The experimental group was treated with Chinese medicine except Banxia Xiexin Decoction, or the control group was treated with non-western medicine; ⑥ not meeting the outcome indicators.

### 2.4 Diagnostic criteria

Western diagnostic criteria refer to the digestive system disease *ulcerative colitis integrated traditional Chinese and western medicine diagnosis and treatment plan (draft)* of Chongqing Chinese Society of Integrated Traditional Chinese and Western Medicine in 2003; the diagnostic criteria of traditional Chinese medicine refer to the *Guidelines for Integrated Traditional Chinese and Western Medicine Diagnosis and Treatment of Ulcerative Colitis (draft)*.

## 2.5 Data extraction

Two researchers independently completed the retrieval, data extraction and bias evaluation of each database. According to the inclusion and exclusion criteria, the required content was extracted from the selected literature by reviewing the topic, summary and reading the full text, and cross-checking was conducted. Preparation and development of the required information and data, establish Excel tables, improve the form information, including 1 ) the basic information of the literature, including research topics, the first author and publication time; 2 ) Research types and elements of bias risk assessment, including research design, random allocation methods and lost to follow-up, exit, the implementation of blind method, baseline situation; 3 ) The basic information of the research object, including the number of cases included, age, course of disease, etc. 4 ) Key elements of intervention measures, including specific medication, course of treatment, adverse reactions; 5 ) Measurement data of main outcome indicators and related results. If opinions are not unified, they are solved through discussion or assisted by the third researcher.

## 2.6 Statistical analysis

Statistical analysis was performed using Review Manager 5.3 software provided by Cochrane. Firstly, the heterogeneity of the included studies is tested, and if there is no heterogeneity, the fixed effect model is used for analysis. If there is heterogeneity, the random effect model is used to analyze and explore the size and source of heterogeneity. The heterogeneity was judged by  $I^2$ ,  $I^2 < 25\%$  indicates low heterogeneity;  $I^2 = 50\%$  indicates moderate heterogeneity;  $I^2 > 75\%$  indicates high heterogeneity and is not suitable for meta-analysis. The test results are listed in the forest map. The statistical data of this study were expressed by relative risk (RR), and the effect size of each study was expressed by 95% confidence interval (CI). The potential publication bias was evaluated by an inverted funnel plot.

## 3. Results

### 3.1 Literature retrieval

A total of 911 articles were retrieved, including the Cochrane Library (n=0), PubMed (n=86), Embase (n=2), CBM (n=0), CNKI (n=122), VIP (n=82), Wan Fang Data (n=617). Firstly, the endnote software was used and the topics and abstracts were deleted by reading. and finally included 16 RCT studies. The flow chart of literature screening is shown in **Figure 2**.

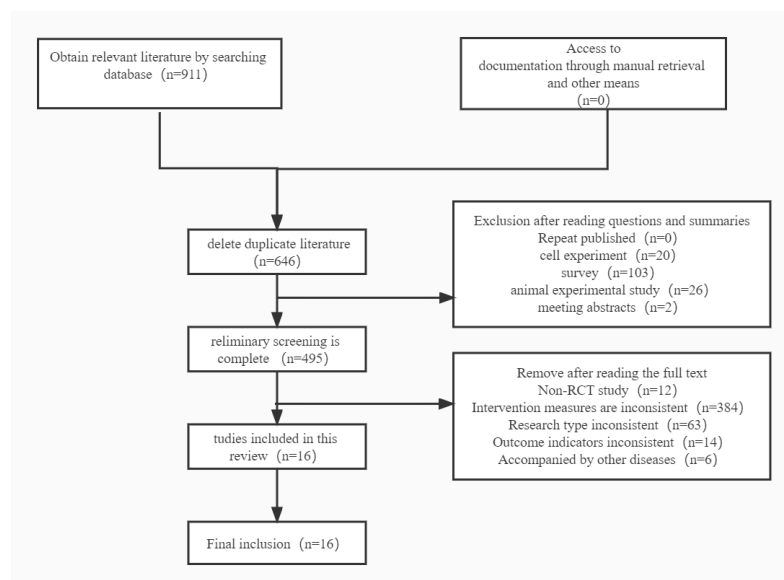


Figure 2: Flow chart of literature screening

### 3.2 Included in the research table

A total of 16 studies were included [8-23]. The total number of cases was 1332, and the number of cases

in the experimental group and the control group was 668 and 664, respectively. All studies reported the total effective rate of clinical efficacy, [8,11,14,17-19,22,23] reported adverse reactions, and [9,12,13,15,16,17,19,20,21] reported the cure rate. All studies showed the average age of patients in the experimental group and the control group; eight articles [8-9,11,14,18-19,21,23] did not describe the range and course of disease of patients; all studies did not specify the race, recurrence and follow-up of the case. In the 16 studies, the experimental group was mainly treated with Banxia Xiexin Decoction, and the control group was treated with conventional western medicine. In the 16 studies, the whole course of treatment was between 4w and 8w, the sample size was more than 10, and the age range was 18~60 years old. The main outcome indicators of 16 studies were the total effective rate, and the secondary outcome indicators were the incidence of adverse reactions, the cure rate, the disappearance time of symptoms and the level of serum inflammatory factors. 16 studies  $P>0.05$ , were comparable. The basic characteristics of the study are shown in **Table 1**.

Table 1: Basic information of included literature

research	sample size(T/C)	baseline	Intervention measures		Basic treatment	Outcome indicators
			T	C		
Cai Lingzhi 2018 <sup>[8]</sup>	45/45	comparable	Banxia Xiexin Decoction+Control Group	olsalazine sodium capsule	4W	ABD
He CaiDong 2020 <sup>[9]</sup>	46/46	comparable	Banxia Xiexin Decoction+Control Group	mesalazine enteric-coated tablets	1M	ACDE
Huang Guolin 2013 <sup>[10]</sup>	32/32	comparable	Banxia Xiexin Decoction+Control Group	olsalazine sodium	8W	A
Huang Liang 2019 <sup>[11]</sup>	50/50	comparable	Banxia Xiexin Decoction+Control Group	sulfasalazine	8W	ABE
Huang Weiqing 2016 <sup>[12]</sup>	38/40	comparable	Banxia Xiexin Decoction+Control Group	sulfasalazine	8W	AC
Peng Hongqiong 2010 <sup>[13]</sup>	31/33	comparable	Banxia Xiexin Decoction+Control Group	sulfasalazine	60D	AC
Ren Haifeng 2019 <sup>[14]</sup>	40/40	comparable	Banxia Xiexin Decoction	sulfasalazine	8W	ABD
Shi Yuanlong 2017 <sup>[15]</sup>	31/31	comparable	Banxia Xiexin Decoction+Control Group	Sulfasalazine+0.5% Metronidazole 100 mL Enema Therapy	1M	AC
Si Mayan 2020 <sup>[16]</sup>	50/50	comparable	Banxia Xiexin Decoction+Control Group	sulfasalazine	8W	ACDE
Xiao Zhongying 2020 <sup>[17]</sup>	60/60	comparable	Banxia Xiexin Decoction+Control Group	Sulfasalazine tablets+self-made Chinese medicine prescription for retention enema	4W	ABCD
Xin Jiwei 2020 <sup>[18]</sup>	30/30	comparable	Banxia Xiexin Decoction+Control Group	Sulfasalazine	2M	AB
Xu Lixiang 2018 <sup>[19]</sup>	50/50	comparable	Banxia Xiexin Decoction+Control Group	olsalazine	30D	ABC
Yang Lang 2004 <sup>[20]</sup>	63/58	comparable	Banxia Xiexin Decoction	salazosulfapyridine	60D	AC
Zhang Baofang 2018 <sup>[21]</sup>	28/25	comparable	Banxia Xiexin Decoction+Control Group	sulfasalazine	30D	ACDE
Zhang Haiyan 2016 <sup>[22]</sup>	40/40	comparable	Banxia Xiexin Decoction	sulfasalazine	8W	AB
Zhang Qiang 2018 <sup>[23]</sup>	34/34	comparable	Banxia Xiexin Decoction	olsalazine sodium capsule	1M	AB

Note: T is the observation group; C is the control group. Outcome indicators: A for clinical efficacy; B Rate of adverse reactions; C is cure rate; D was the level of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in serum. E is C-reactive protein (CRP) level.

### 3.3 Bias risk assessment of included studies

Of the 16 included studies, 1) random sequence generation: [9,11,15,17-18,21-22] were grouped by random number table method; the nine items [8,10,12-13,16,19-20,23] only describe the word "random"

without specifying the specific grouping method; 1) using computer random method. 2) Blind outcome assessment: The outcome indicators of 13 studies were objective indicators, so there was no measurement bias. Among the 3 outcome indicators, [9,11,19] were assessed by quality of life questionnaire and quality of life scale, including physiological function and physiological function. The outcome may be biased and high risk. 3) Data integrity: None of the studies reported the number of cases withdrew or shed. 4) Outcome report: The indicators set in 16 research programs were reported in the results. 5) All studies did not mention allocation concealment method, blind method of patients and researchers and other biases. The specific results are shown in **Figure 3**.

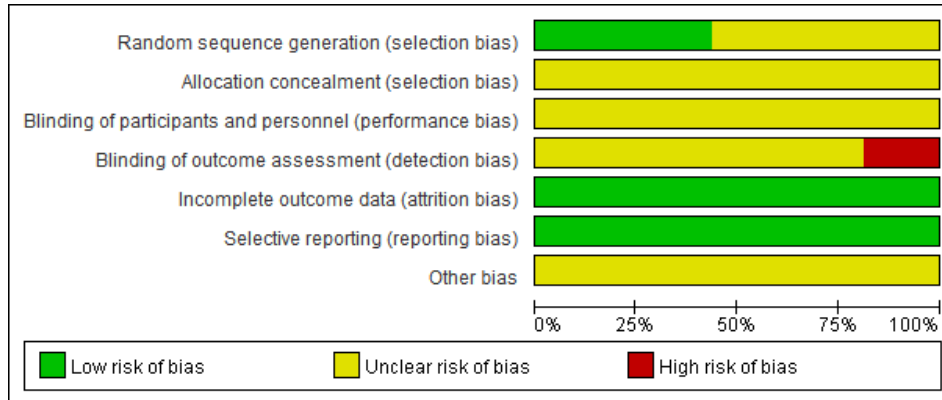


Figure 3: Proportion of bias risk: the author’s judgment on the percentage of all included projects with bias risk.

### 3.4 Meta analysis results

#### 3.4.1 Total effective rate

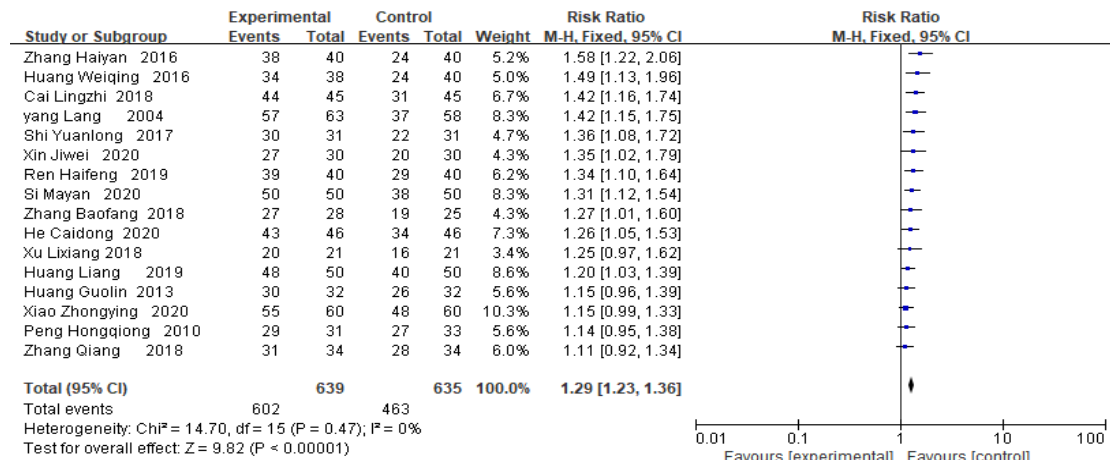


Figure 4: Forest map of total effective rate of Banxia Xiexin decoction in treating UC

A total of 16 references [8-23] were included, and the total clinical effective rate of Banxia Xiexin Decoction in the treatment of UC was reported, with heterogeneity (I<sup>2</sup>=0%, P=0.47). The results showed that RR=1.29, 95 % CI:1.23-1.36, Z = 9.82 (P<0.00001), indicating that the total clinical effective rate of Banxia Xiexin Decoction alone or combined with other drugs in the treatment of UC was significantly higher than that of the control group, and the difference was statistically significant. **Figure4**.

#### 3.4.2 Cure rate

Nine references [9,12,13,15,16,17,19,20,21] were included to report the comparison of the cure rates between the modified Banxia Xiexin Decoction combined with western medicine experimental group and the conventional UC western medicine control group. The heterogeneity (I<sup>2</sup>=0%, P=0.87), the results showed that: RR=1.72,95%CI: 1.43-2.06, Z=5.79 (P<0.00001), indicating that Banxia Xiexin Decoction combined with western medicine treatment of UC cure rate was significantly better than that of UC conventional western medicine control group, the difference was statistically significant. See **Figure 5**.

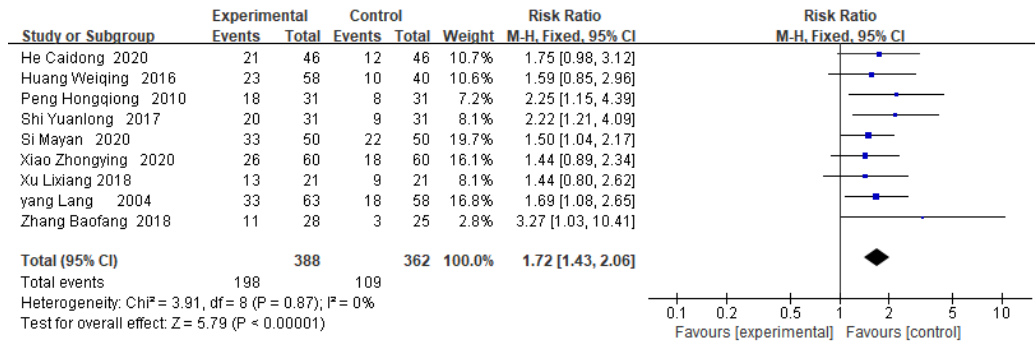


Figure 5: Forest map of the cure rate of Banxia Xiexin Decoction+Western medicine VS Western medicine group in the treatment of UC

### 3.4.3 Incidence of adverse reactions

Nine references [8,11,14,16-19,22,23] were included to report the incidence of adverse reactions of Banxia Xiexin Decoction in the treatment of UC. The adverse reactions included nausea and vomiting [8,9,11,14,17,18,19,22,23], sore throat [8,22,23], diarrhea [11,17,18], constipation [11,18], dizziness, headache, fever [22,23], rash and other abnormal symptoms. However, there was no adverse reaction in the experimental group and the control group after treatment in one literature, and the difference was not statistically significant. 8 studies [8,11,14,17-19,22,23], heterogeneity (I<sup>2</sup>=8%, P=0.37), the results showed: RR=1.29, 95% CI: 0.27-0.65, Z=3.88 (P=0.0001), indicating that Banxia Xiexin Decoction alone or combined with other drugs in the treatment of UC, the incidence of adverse reactions was significantly lower than the control group, the difference was statistically significant. See **Figure 6**.

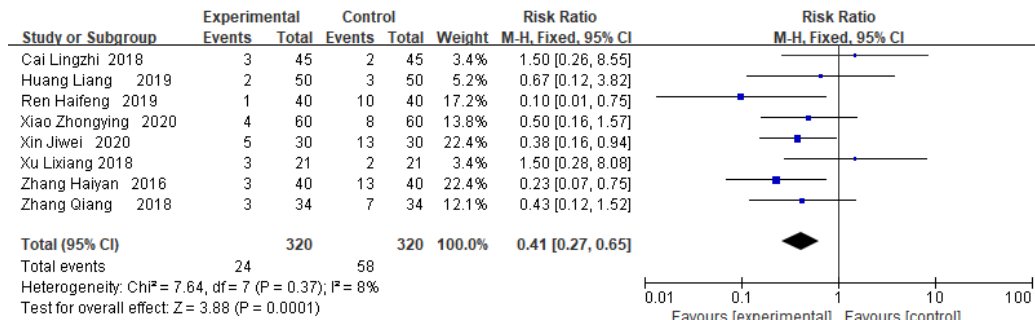


Figure 6: Forest plot of the incidence of adverse reactions of Banxia Xiexin Decoction in the treatment of UC

### 3.4.4 Asymptomatic time

Three articles [8,14,16] were included to report the disappearance time of symptoms in the treatment of UC with Banxia Xiexin Decoction, including the disappearance time of abdominal pain, diarrhea and purulent blood. The results showed that the heterogeneity I<sup>2</sup> of the three articles was more than 50%, suggesting that there was moderate heterogeneity among the literatures. Analysis of the source of heterogeneity may be due to only three studies, so there may be greater bias. See **figure 7**.

### 3.4.5 Inflammatory factors

The levels of TNF- $\alpha$  and IL-1 were included in nine literature, the inflammatory factor TNF- $\alpha$  index was included in six literature [8,9,14,16,17,21], and the IL-1 index was included in three literature [8,14,21]. The effects of Banxia Xiexin Decoction on inflammatory factors in UC serum were reported. The results showed that the heterogeneity of I<sup>2</sup> in nine literature was >75%. 1) Six literature on TNF- $\alpha$  level showed heterogeneity (I<sup>2</sup>=98%, P<0.00001) and high heterogeneity, MD = -5.36, 95% CI: -7.70~-3.02, Z = 4.49 (P<0.00001), indicating that Banxia Xiexin Decoction in the treatment of UC had better effect on reducing serum TNF- $\alpha$  than the control group, and the difference was statistically significant. 2) Three studies of IL-1 level literature, the heterogeneity (I<sup>2</sup>=93%, P<0.00001), high heterogeneity, MD = -0.41, 95% CI: -0.77~-0.06, Z=6.50 (P=0.02), indicating that Banxia Xiexin Decoction in the treatment of UC, to reduce serum IL-1 compared with the control group, the difference was not statistically significant. See **Figure 8**.

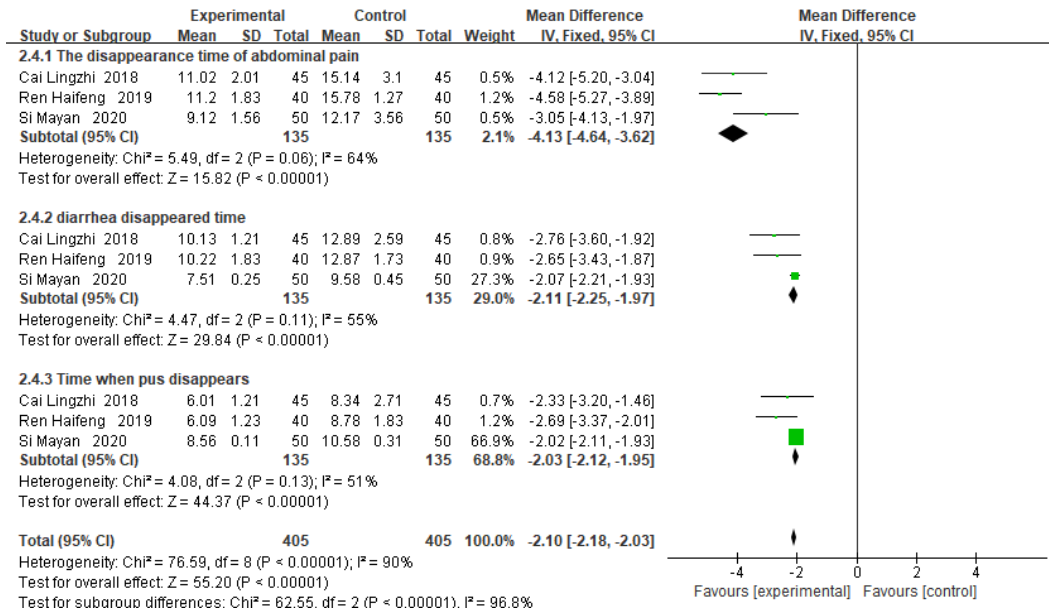


Figure 7: Forest map of disappearance time of UC symptoms treated with Banxia Xiexin decoction

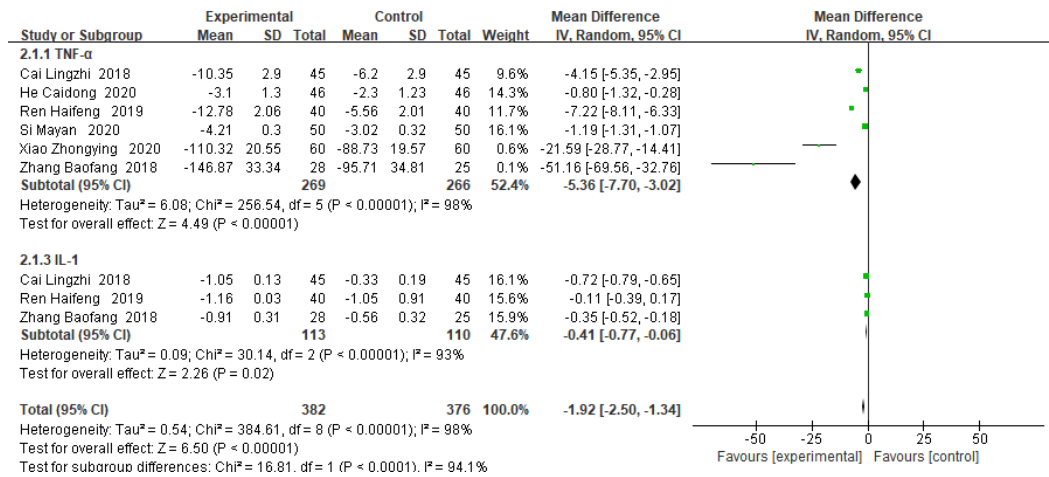


Figure 8: Forest plot of the effect of Banxia Xiexin Decoction on inflammatory factors TNF-α and IL-1 in UC serum

### 3.4.6 Colonoscopy score

Included in two studies [8,14] were reported Banxia Xiexin Decoction treatment group and western medicine control group UC, colonoscopy score comparison, the heterogeneity (I<sup>2</sup>=75 %,P=0.05), high heterogeneity, MD =-1.00,95% CI: -1.42~-0.59, Z=4.70 (P<0.00001), analysis of Banxia Xiexin Decoction in the treatment of UC, colonoscopy score effect is better than that of western medicine group, the difference was statistically significant. See figure 9.

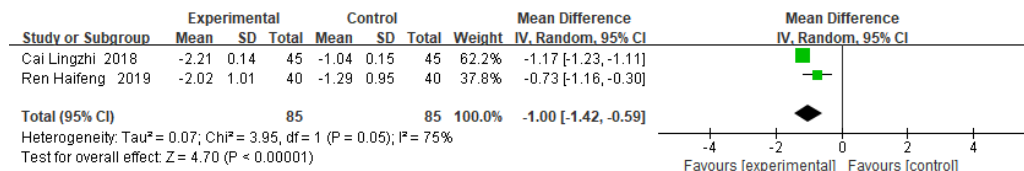


Figure 9: Forest map of the effect of Banxia Xiexin Decoction on UC colonoscopy score

### 3.5 Publishing deviation

The publication bias of the total effective rate was analyzed by funnel plot. The left and right asymmetry of the funnel plot of the total effective rate was obvious, which can be considered to have publication bias. See Figure 10.

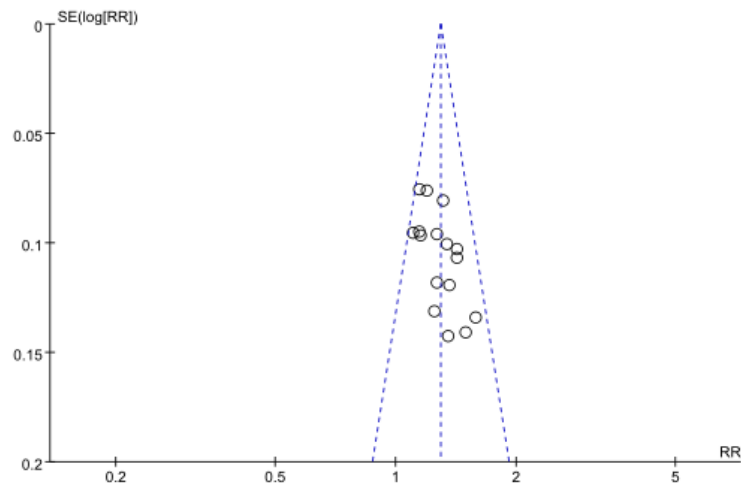


Figure 10: Funnel plot of total efficiency

#### 4. Discussion

Ulcerative colitis (UC) is a common inflammatory bowel disease. The symptoms of recurrent abdominal pain, diarrhea and hematochezia, greatly reduce the quality of life of patients [24]. In addition to the main disease prone to serious complications, a small number of UC patients with colorectal cancer increased risk [25]. Zhang et al [26-28] showed that Banxia Xiexin Decoction can reduce the levels of inflammatory factors (IL-1, TNF- $\alpha$ ) in serum and improve clinical symptoms. According to the clinical symptoms of Chinese medicine, it can be classified into the categories of dysentery and diarrhea [29]. The pathogenesis of UC in traditional Chinese medicine is that the damp-heat in the active stage is contained in the bowels, and the spleen deficiency and dampness are abundant in the remission stage [30]. The pathogenesis of UC is characterized by mixed cold and heat. The Banxia Xiexin Decoction, the classical prescription of *Treatise on Febrile Diseases*, conforms to the pathogenesis of mixed cold and heat and the inclusion of deficiency and excess [31].

There are 16 studies reported the total effective rate, and 9 reported the cure rate and the incidence of adverse reactions. These three indicators were included in more literature, and there was no heterogeneity between the literature, and the differences were statistically significant, suggesting that Banxia Xiexin Decoction in the treatment of UC can improve the clinical efficacy, reduce the incidence of adverse reactions, and provide certain reference for clinical medication. Other indicators of symptoms disappeared time, inflammatory factors (IL-1, TNF- $\alpha$ ), colonoscopy score showed high heterogeneity. reasons were as follows. First of all, the high risk of bias may be due to the small sample size. Secondly, because the diagnosis and treatment of traditional Chinese medicine diseases are complex and diverse, so the heterogeneity of this study may come from clinical heterogeneity. Finally, the sample size of the whole subject is small. Therefore, this systematic evaluation needs a large number of objective and scientific RCT studies to confirm.

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