Original Article

Chinese herbal injections plus Western Medicine on inflammatory factors for patients with acute exacerbation of chronic obstructive pulmonary disease: a systematic review and network meta-analysis

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Background: Chinese herbal injections (CHIs) are commonly prescribed in China as adjuvant therapy for acute exacerbation of chronic obstructive pulmonary disease (AECOPD). However, evidence supporting the effect of CHIs on inflammatory factors for patients with AECOPD is insufficient, posing a challenge for clinicians to choose the optimal CHIs for AECOPD. This network meta-analysis (NMA) aimed to compare the effectiveness of several CHIs combined with Western Medicine (WM) and WM alone on the inflammatory factors in AECOPD.

Methods: Randomized controlled trials (RCTs) on different CHIs for treating AECOPD were thoroughly searched from several electronic databases up to August 2022. The quality assessment of the included RCTs was conducted according to the Cochrane risk of bias tool. Bayesian network meta-analyses were designed to assess the effectiveness of different CHIs. Systematic Review Registration CRD42022323996.

Results: A total of 94 eligible RCTs involving 7,948 patients were enrolled in this study. The NMA results showed that using Xuebijing (XBJ), Reduning (RDN), Tanreqing (TRQ), and Xiyanping (XYP) injections combined with WM significantly improved treatment effects compared to using WM alone. XBJ + WM and TRQ + WM significantly changed the level of C-reactive protein (CRP), white blood cells, percentage of neutrophils, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). TRQ + WM showed the most significant effect in reducing the level of procalcitonin. XYP + WM and RDN + WM could reduce the level of white blood cells and the percentage of neutrophils. A total of 12 studies reported adverse reactions in detail, and 19 studies demonstrated no significant adverse reactions.

Conclusions: This NMA showed that using CHIs combined with WM could significantly reduce the level of inflammatory factors in AECOPD. A combination of TRQ and WM may be a relatively prior adjuvant therapy option for AECOPD treatment considering its effects in reducing the levels of the anti-inflammatory mediators.

Keywords: Chinese herbal injections (CHIs); inflammatory factors; acute exacerbation of chronic obstructive pulmonary disease (AECOPD); systematic review; network meta-analysis (NMA)

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow restriction. The disease is caused by abnormal airways and/or alveoli due to long-term exposure to harmful particles or gases (1). The global prevalence of COPD is about 11.7%, and the annual mortality rate is about 3.5 million. The World Health Organization (WHO) estimates that by 2030, more than 4.5 million people will die of COPD and related diseases worldwide every year (2). In China, the COPD prevalence in the population over 40 years old in China is 13.7%, and there are nearly 100 million COPD patients (3,4), ranking third among all the disease-related causes of death (5). The acute exacerbation of chronic obstructive pulmonary disease (AECOPD) follows the natural course of COPD, which is manifested by the aggravation of clinical symptoms, the decline of pulmonary function, and the reduction of quality of life. Most patients experience other diseases concurrently, resulting in an increase in mortality and economic burden (6). About 22–40% of patients with COPD experience at least 1 bout of moderate or severe exacerbation every year (7).

The Western Medicine (WM) of AECOPD, such as long-term use of bronchodilators and inhalation of corticosteroids, which can increase the incidence of adverse events (8,9). Chinese herbal injections (CHIs) are a new type of traditional Chinese medicine (TCM) preparation, which are made by extracting and purifying the effective and active compounds from herbs (or other decoctions) via modern scientific techniques and methods (10,11). During the acute exacerbation of COPD, the activation and accumulation of inflammatory factors in the lungs are internal factors that lead to symptom exacerbation. In recent years, the combination of CHIs and WM could significantly reduce the level of inflammatory factors in AECOPD (12); many previously conducted double-arm meta-analyses have evaluated the effectiveness of CHIs on serum inflammatory factors in AECOPD (13-16). However, the curative effects of various CHIs have not been horizontally compared and ranked. Network meta-analysis (NMA) can synthesize multiple correlation factors, and perform direct or indirect comparisons simultaneously by summarizing different interventions for the same disease. Moreover, NMA can provide evidence for identifying optimal therapies based on the rankings of different outcomes. The NMA method was used in this study to comprehensively evaluate the efficacy of 4 CHIs on serum inflammatory factors in AECOPD, the 4 CHIs included Reduning injection (RDN), Tanreqing injection (TRQ), Xuebijing injection (XBJ), and Xiyanping injection (XYP), and to explore the optimal CHI for reducing inflammatory factor levels in AECOPD. We present the following article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-402/rc).

Highlight box

Key findings

- CHIs combined with WM could improve treatment performance for patients with AECOPD, and TRQ + WM may be the best choice in AECOPD treatment.

What is known and what is new?

- CHIs combined with WM mainly improve the efficacy of AECOPD treatment by reducing the level of inflammatory factors in serum. Although many previously published double-arm meta-analyses had evaluated the effectiveness of CHIs on serum inflammatory factors in AECOPD, the curative effects of various CHIs were not horizontally compared and ranked.
- This study ranked the efficacy of CHIs treatment through NMA, and TRQ + WM showed a preferable improvement in all the outcomes of AECOPD.

What is the implication, and what should change now?

- In the treatment of AECOPD patients, clinicians can consider using TRQ + WM injections to reduce the levels of inflammatory factors in AECOPD patients, and then improving clinical efficacy.

Methods

NMA analysis was performed based on the following procedures: literature search, inclusion criteria data extraction, quality assessment, and statistical analysis. The protocol of this study was registered in the international prospective register of systematic reviews (PROSPERO) under the registration code of CRD42022354772.

Inclusion criteria

Types of studies

Randomized controlled trials (RCTs) investigating one of the CHIs (RDN, TRQ, XBJ, and XYP) combined with WM in the treatment of AECOPD were eligible.

Types of participants

Patients were diagnosed with AECOPD based on current or previous diagnostic criteria (1,17) with no limitation on gender and nationality.

Types of interventions

Patients in the control group only received WM, such as beta 2-agonists, anticholinergic drugs, theophylline drugs, and inhaled glucocorticoids ect. Patients in the treatment group received CHIs with WM therapy.

Types of outcome measures

The primary outcome measures included C-reactive protein (CRP) and procalcitonin (PCT). The secondary outcome measures included white blood cell (WBC), percentage of neutrophils (NE%), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor α (TNF-α), and adverse reactions.

Exclusion criteria

The exclusion criteria were as follows: (I) reviews, duplicate studies, pharmacological experiments, case reports, editorials, and letters; (II) use of TCM treatment methods other than CHIs regimen; (III) for similar articles, only the latest or more comprehensive one was included; (IV) research with incomplete data or obvious errors.

Search strategy

We performed the literature search using four English databases (PubMed, Cochrane Library, Web of Science, and Embase) and 4 Chinese databases [China National Knowledge Infrastructure (CNKI), Wanfang, Chinese Biological Medicine Database (CBM), and Chinese Scientific Journal Database (VIP)] from the establishment of the databases to August 2022. The search terms included "chronic obstructive pulmonary disease", "COPD", "Reduning injection", "Tanreqing injection", "Xuebijing injection", "Xiyanping injection", "randomized controlled trial", and "placebo". The details are presented in Appendix 1.

Data extraction and quality assessment

Data were independently extracted from the eligible RCTs by two researchers (XB Meng and N Lei) based on a custom-made form, and discrepancies were discussed with a third party and resolved by consensus.

The quality assessment was independently performed by two reviewers (XB Meng and N Lei) using the Cochrane Collaboration's tools (version 5.1.0; http://handbook-5-1.cochrane.org/). In the case of dissent, resolution was achieved via consensus or a third investigator (XY Zhu).

Statistical analysis

The software R 4.0.3 and Stata 15.1 were employed to analyze data (18). The mean difference (MD), with a 95% confidence interval (CI) (contain zero, the differences between the groups were not statistically significant), for outcomes were summarized. Surface under the cumulative ranking curve (SUCRA) used to determine the probability of a treatment being the most effective (100%: treatment is certain to be the best; 0%: treatment is certain to be the worst) (19,20). The node-splitting method was used to evaluate the local inconsistency of the outcome measures in a closed loop. Furthermore, a comparison funnel plot was used to test the publication bias.

Results

Study selection

A total of 2,595 articles were obtained from 8 databases. After removing duplicates, 1,725 studies were selected. After reviewing the titles and abstracts, the initially selected studies were further screened by the full texts to remove those that did not meet the inclusion criteria. Finally, 94 RCTs investigating the combination of CHIs and WM regimen for treating AECOPD were included. Additionally, this NMA included 4 types of CHIs, namely, RDN, TRQ, XBJ, and XYP. All trials were published in Chinese, and the flow diagram is shown in *Figure 1*.

Study characteristics

A total of 7,948 patients with AECOPD from 94 RCTs were included in this NMA analysis. Among them, 4,031 patients were treated with the combination of CHIs and WM, and 3,917 patients received WM treatment alone. Furthermore, approximately 62% patients were male. The study duration ranged from 3 to 14 days. The basic characteristics of each trial are listed in *Table 1*. The network graph of the effects of different interventions on the outcome measures is shown in *Figure 2*.

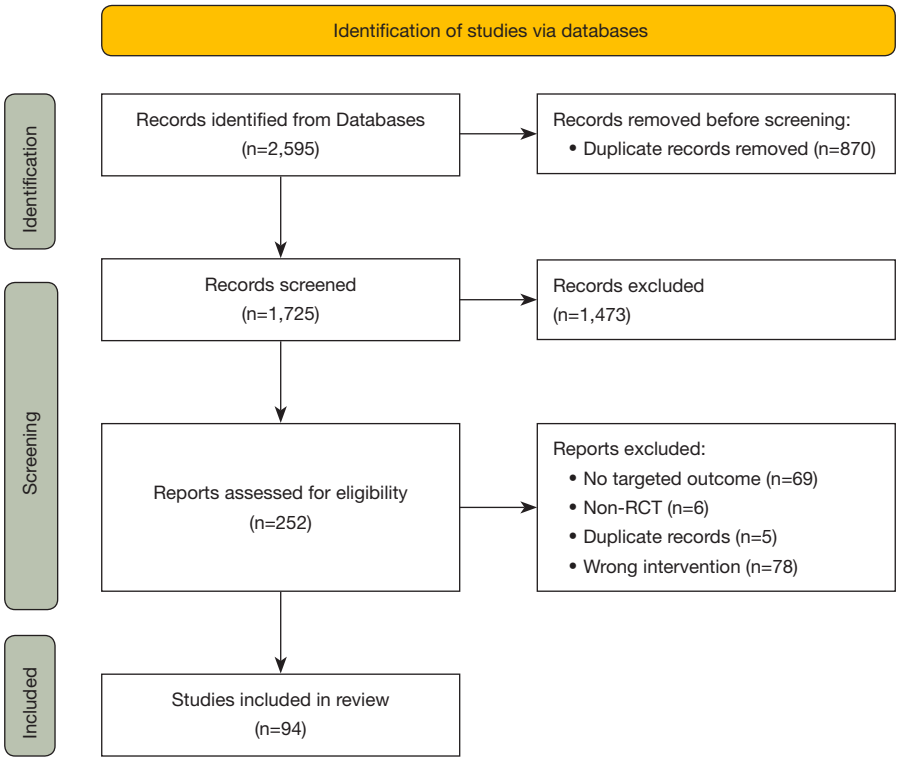

Figure 1 Flowchart of searching and screening for the studies. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; RCT, randomized controlled trial.

Quality evaluation

By using the Cochrane risk of bias tool, the methodological quality of the included RCTs was evaluated. Although all studies reported randomization, only 30 RCTs used a random number table to generate random sequences, which were rated as low risk. A total of 9 studies were classified as "high risk", because the participants were assigned into each group according to the time of admission in 4 RCTs, according to visiting sequence in 2 RCTs, and according to clinical examination results in 3 RCTs. The risk of the remaining studies was rated as "unclear", because they only mentioned "randomization" without detailed methods. Selection bias was rated as "unclear risk" since the allocation concealment was not reported in all the included RCTs. The studies did not report blinding, therefore the performance bias was rated as "unclear risk". Since the assessment of the associated findings from the included RCTs was not impacted by the blinding of outcome evaluators, the detection bias was rated as "low risk". None of the included RCTs had incomplete data, hence the attrition bias was rated as "low risk". The reporting bias was rated as "unclear risk" because the whole implementation plan could not be collected. Since no other overt bias was found in any of the included studies, it was rated as "low risk". A summary of the risk of bias for each included RCT is shown in *Figure 3*.

Outcome measures

The node-splitting method was used to evaluate the local inconsistency of the outcome measures in a closed loop. The results showed that there was no difference between local direct comparison and indirect comparison (Appendix 2).

CRP

The data on CRP were available in 65 RCTs involving 4 types of CHIs [2008–2011, 13 studies (21-33); 2012–2015, 24 studies (34-57); 2016–2019, 22 studies (58-79); 2000–2022, 6 studies (80-85)]. As shown in Table S1, patients receiving XBJ + WM and TRQ + WM had a significant improvement in CRP compared with those receiving a

Table 1 Characteristics of the included studies

Study ID	N (E/C)	Sex (M/F)	Age (years) (E/C)	I (E)	I (C)	Cs (day)	Outcome
Zhang *et al.*, 2011 (21)	45/42	67/20	66.2±5.5/65.7±5.6	RDN 20 mL + WM	WM	10	①
Ying, 2011 (22)	32/30	44/18	73.38±7.61/74.21±10.47	TRQ 20 mL + WM	WM	10	①③④⑧
Wang, 2011 (23)	29/26	29/26	60.25±11.23/58.12±10.58	XBJ 100 mL + WM	WM	7	①⑥
Wang *et al.*, 2011 (24)	39/39	46/32	62.7±4.8/58.8±6.1	TRQ 20 mL + WM	WM	14	
Chen *et al.*, 2011 (25)	30/30	39/21	68±9/71±7	XBJ 100 mL + WM	WM	7	①⑦
Chen, 2011 (26)	28/32	50/10	72.86±4.40/72.72±4.90	TRQ 20 mL + WM	WM	7	①③④⑧
Chen *et al.*, 2011 (27)	43/43	54/32	68.3±7.9/65.7±7.3	XBJ 100 mL + WM	WM	5	①③④
Hao *et al.*, 2010 (28)	30/30	42/18	66±6/67±5	XBJ 100 mL + WM	WM	10	①
Feng, 2010 (29)	54/52	67/39	65.49±9.25/67.13±10.20	TRQ 20 mL + WM	WM	14	①③⑥
Yin *et al.*, 2009 (30)	40/40	43/37	–	TRQ 20 mL + WM	WM	10	①
Luo *et al.*, 2009 (31)	35/32	53/14	68.2±6.5/67.3±6.7	TRQ 20 mL + WM	WM	14	①
Du *et al.*, 2009 (32)	50/50	82/18	46-75/48-76	TRQ 20 mL + WM	WM	14	①
Peng *et al.*, 2008 (33)	32/30	44/18	66.0±1.45/67.1±1.42	XBJ 80 mL + WM	WM	4	①③④
Wang, 2015 (34)	30/30	29/31	69.6/71	XBJ 100 mL + WM	WM	7	①③④⑧
Wang, 2015 (35)	46/46	53/39	–	TRQ 20 mL + WM	WM	7	①③④
Wang *et al.*, 2015 (36)	33/33	40/26	75±12/76±10	XBJ 100 mL + WM	WM	10	①②⑥⑦
Luo *et al.*, 2015 (37)	20/20	35/5	76.00±8.62/75.00±9.23	XBJ 200 mL + WM	WM	5	①②③
Li *et al.*, 2015 (38)	50/50	50/50	–	XBJ 100 mL + WM	WM	9	①③④
Zhou, 2014 (39)	30/30	32/28	72.6±5.4/73.1±5.8	RDN 20 mL + WM	WM	5-7	①⑧
Zhang *et al.*, 2014 (40)	46/46	62/30	67.84±7.4/67.64±7.2	XYP 250 mg + WM	WM	14	①
Zhang *et al.*, 2014 (41)	40/40	64/16	62.8±3.5/63.1±3.8	XYP 400 mg + WM	WM	10	①③④⑧
Yue, 2014 (42)	33/32	41/24	73±4.8/70±4.5	RDN 20 mL + WM	WM	7-14	①
Yan, 2014 (43)	55/55	81/29	60.7±8.4/63.4±8.8	TRQ 20 mL + WM	WM	7	①
Mu, 2014 (44)	36/36	43/29	–	XBJ 100 mL + WM	WM	7	①③④
Li *et al.*, 2014 (45)	38/38	42/34	64.3±3.2/66.3±3.8	TRQ 20 mL + WM	WM	7	①③⑧
Tang, 2013 (46)	30/30	39/21	68±5/63±9	XBJ 100 mL + WM	WM	7	①⑦
Nie *et al.*, 2013 (47)	50/50	44/56	70.4±11.7/70.2±12.1	RDN 20 mL + WM	WM	3	①②⑦
Ma *et al.*, 2013 (48)	60/60	84/36	61.10±7.21/61.12±12.35	TRQ 20 mL + WM	WM	10	①
Lu *et al.*, 2013 (49)	30/30	37/23	59.3±8.6/58.4±7.2	TRQ 20 mL + WM	WM	10	①③④
Li, 2013 (50)	40/40	51/29	70.6±5.95/69.5±5.92	TRQ 20 mL + WM	WM	7	①
Chen, 2013 (51)	53/53	56/50	–	RDN 20 mL + WM	WM	7	①⑦⑧
Zhang, 2012 (52)	40/40	58/22	69/66	XBJ 100 mL + WM	WM	7	①⑦
Sun *et al.*, 2012 (53)	52/50	58/44	–	RDN 20 mL + WM	WM	7-10	①②③⑤⑥⑦⑧
Shi, 2012 (54)	45/41	55/31	69.40±5.70/68.50±7.10	TRQ 20 mL + WM	WM	10	①⑧

Table 1 (*continued*)

Table 1 (*continued*)

Study ID	N (E/C)	Sex (M/F)	Age (years) (E/C)	I (E)	I (C)	Cs (day)	Outcome
Peng, 2012 (55)	26/26	33/19	–	TRQ 20 mL + WM	WM	14	①⑤⑦
Long, 2012 (56)	64/60	88/36	61.10±7.21/61.12±12.35	TRQ 20 mL + WM	WM	7	①
Li *et al.*, 2012 (57)	60/60	79/41	41–79/45–76	XBJ 100 mL + WM	WM	10	①
Xiu *et al.*, 2019 (58)	15/15	17/13	66.4±2.7/67.1±2.91	RDN 20 mL + WM	WM	7	①③④⑧
Fang, 2019 (59)	41/41	50/32	53.86±8.05/54.17±8.27	TRQ 20 mL + WM	WM	7	①③④
Zhang *et al.*, 2018 (60)	40/40/40	62/58	69.13±5.28/68.93±5.87/ 68.36±5.67	XBJ 50 mL + WM	WM	10	①②③⑤⑦
Yang *et al.*, 2018 (61)	30/30	45/15	64.5±11.6/64.2±11.5	RDN 20 mL + WM	WM	10	①②③④⑧
Mo *et al.*, 2018 (62)	100/100	–	–	TRQ 10 mL + WM	WM	10	①
Li, 2018 (63)	45/45	66/24	61.56±5.24/61.83±5.39	TRQ 20 mL + WM	WM	10	①②⑧
Li, 2018 (64)	54/54	60/48	68.42±9.17/68.29±9.13	TRQ 30 mL + WM	WM	14	①②
Chen *et al.*, 2018 (65)	28/28	48/8	55.6±15.9/57.3±15.1	XBJ 100 mL + WM	WM	10	①⑤⑦
Zhang *et al.*, 2017 (66)	68/68	91/45	68.5±7.2/70.3±6.3	TRQ 20 mL + WM	XYP 150 mL + WM	10	①⑤⑥⑦⑧
Xu, 2017 (67)	53/53	62/44	–	XBJ 100 mL + WM	WM	7	①③④
Xi *et al.*, 2017 (68)	39/39	27/51	65.44±1.44/65.48±1.89	XBJ 100 mL + WM	WM	10	①②③
Wang *et al.*, 2017 (69)	60/60	104/16	63.2±11.8/64.1±11.2	TRQ 20 mL + WM	WM	10	①③④
Wang, 2017 (70)	35/35	36/34	69.23±5.29/ 68.94±5.99	XBJ 60 mL + WM	WM	7	①②③⑤⑧
Liang, 2017 (71)	35/35	45/25	62.34±5.52/61.76±5.59	TRQ 20 mL + WM	WM	7	①⑤⑧
Li, 2017 (72)	55/55	66/44	62.4±9.2/63.8±10.2	TRQ 20 mL + WM	WM	10–14	①②⑦⑧
Dong, 2017 (73)	32/30	38/24	61.3±6.7/62.6±7.4	TRQ 20 mL + WM	WM	10	①
Wu *et al.*, 2016 (74)	56/64	80/40	67.5/66.9	TRQ 20 mL + WM	WM	10	①②③④⑧
Shen *et al.*, 2016 (75)	50/50	78/22	71±10/70±9	XBJ 100 mL + WM	WM	7	①②⑤
Ma *et al.*, 2016 (76)	60/60	80/40	64/60	XBJ 50 mL + WM	WM	10	①⑦
Li, 2016 (77)	41/41	43/39	69.3±7.2/70.3±6.8	XBJ 100 mL + WM	WM	14	①③④
Hu *et al.*, 2016 (78)	50/50/50	115/35	66.7±4.2/69.3±6.3/68.4±5.8	I1: TRQ 20 mL + WM; I2: XBJ 30 mL + WM	WM	7	①⑤⑥⑦⑧
Hou *et al.*, 2016 (79)	30/30	–	57.4±8.3/ 58.1±7.9	XYP 250 mg/ + WM	WM	10	①②③④
Liu *et al.*, 2022 (80)	40/40	41/39	54.00±4.68/54.10±3.22	TRQ 20 mL + WM	WM	10	①②⑥
Fan *et al.*, 2022 (81)	50/50	75/25	63.87±6.03/62.71±5.98	TRQ 20 mL + WM	WM	7	①②
Tang, 2021 (82)	45/45	48/42	63±6/63±7	RDN 20 mL + WM	WM	14	①②⑤
Huang *et al.*, 2021 (83)	25/25	27/23	64.49±6.29/64.35±6.21	TRQ 20 mL + WM	WM	14	①⑤⑦
Yu *et al.*, 2020 (84)	50/50	53/47	49.12±7.67/49.73±7.92	TRQ 20 mL + WM	WM	7	①②⑦
Wang *et al.*, 2020 (85)	50/50	61/39	53.49±12.27/3.13±13.85	TRQ 20 mL + WM	WM	10	①②⑦
Ren, 2021 (86)	90/90	98/82	58.76±5.29/57.46±4.41	TRQ 20 mL + WM	WM	7	②⑤

Table 1 (*continued*)

Table 1 (*continued*)

Study ID	N (E/C)	Sex (M/F)	Age (years) (E/C)	I (E)	I (C)	Cs (day)	Outcome
Qian *et al.*, 2020 (87)	24/24	35/13	62.5±4.0/63.4±5.1	TRQ 20 mL + WM	WM	7	②
Qiu, 2013 (88)	31/27	36/22	–	XBJ 200 mL + WM	WM	7	②
Qian *et al.*, 2013 (89)	30/30	32/28	52–65/55–70	XYP 250 mL + WM	WM	10	③④⑧
Bai, 2013 (90)	51/49	71/29	74.8±10.6/72.5±12.2	XBJ 100 mL + WM	WM	7	③
Xie, 2011 (91)	40/40	58/22	60–85/60–83	TRQ 20 mL + WM	WM	14	③④⑧
Ma *et al.*, 2011 (92)	30/30	53/7	79~88/77~87	XBJ 100 mL + WM	WM	10	③④⑧
Xu, 2010 (93)	35/25	36/24	67±7.2/65±8.3	TRQ 20 mL + WM	WM	14	③④
Zhang *et al.*, 2006 (94)	29/29	38/20	71.48±7.72/69.34±7.83	TRQ 20 mL + WM	WM	12	③④
Shi *et al.*, 2022 (95)	44/44	53/35	70.22±5.19/70.13±5.26	XBJ 100 mL + WM	WM	7	⑤⑦⑧
Ma, 2022 (96)	35/35	43/27	80.21±3.57/80.16±3.74	TRQ 20 mL + WM	WM	14	⑤⑦⑧
Peng *et al.*, 2021 (97)	36/36	39/33	65.83±8.23/63.92±10.32	RDN 20 mL + WM	WM	10	⑤⑥⑦
Chen *et al.*, 2019 (98)	79/79	113/45	67.29±9.48/67.34±10.23	TRQ 20 mL + WM	WM	14	⑤⑥⑦⑧
Wang *et al.*, 2009 (99)	43/43	60/26	64.73±5.44/ 65.25±5.34	XBJ 100 mL + WM	WM	14	⑤⑥⑦
Li, 2008 (100)	30/30	36/24	73.36/72.39	TRQ 20 mL + WM	WM	14	⑤⑦
Xu, 2006 (101)	27/25	33/19	60.0±6.5/59.0±7.8	TRQ 20 mL + WM	WM	12	⑤⑥⑦
Feng *et al.*, 2020 (102)	33/33	37/29	53.50±4.30/ 52.89±4.51	TRQ 20 mL + WM	WM	14	⑥⑦⑧
Xu *et al.*, 2019 (103)	32/36	44/24	73.60±10.60/75.10±8.30	TRQ 20 mL + WM	WM	10	⑥⑦⑧
Pan *et al.*, 2015 (104)	71/71	110/32	65.17±9.24/63.51±11.26	TRQ 20 mL + WM	WM	15	⑥⑦⑧
Yang *et al.*, 2014 (105)	60/60	78/42	–	TRQ 20 mL + WM	WM	7	⑥⑦⑧
Xu *et al.*, 2011 (106)	15/15	15/15	–	RDN 20 mL + WM	WM	7	⑥⑦⑧
Wei *et al.*, 2011 (107)	40/40	44/36	59.26±8.56/58.08±9.28	TRQ 20 mL + WM	WM	14	⑥⑦
Li *et al.*, 2011 (108)	28/28	48/8	58.25±8.85/57.42±9.27	TRQ 20 mL + WM	WM	5	⑥⑦
Chen *et al.*, 2011 (109)	52/52	66/38	62±8.2/63±9.1	TRQ 20 mL + WM	WM	14	⑥⑦
Xu, 2010 (110)	15/15	15/15	–	RDN 20 mL + WM	WM	7	⑥⑦⑧
Yang, 2008 (111)	30/30	53/7	63.2±4.8/ 65.2±8.4	TRQ 20 mL + WM	WM	10	⑥⑧
Li *et al.*, 2021 (112)	50/50	51/49	64.84±5.51/65.42±5.23	TRQ 20 mL + WM	WM	14	⑦
Li *et al.*, 2017 (113)	50/50	47/53	45.2±14.4/45.3±14.2	XBJ 100 mL + WM	WM	14	⑦
Fu *et al.*, 2014 (114)	40/40	41/39	70.2–86.2/69.4–86.3	XBJ 100 mL + WM	WM	10	⑦

The data in age are expressed as mean ± standard deviation or mean or minimum age to maximum age. ①, C-reactive protein; ②, procalcitonin; ③, white blood cell; ④, percentage of neutrophils; ⑤, interleukin-6; ⑥, interleukin-8; ⑦, tumor necrosis factor-α; ⑧, adverse reaction. C, control group; E, experimental group; Cs, course; F, female; M, male; I, intervention; XBJ, Xuebijing injection; RDN, Reduning injection; TRQ, Tanreqing injection; WM, Western Medicine; I^1, intervention 1; I^2, intervention 2; XYP, Xiyanping injection.

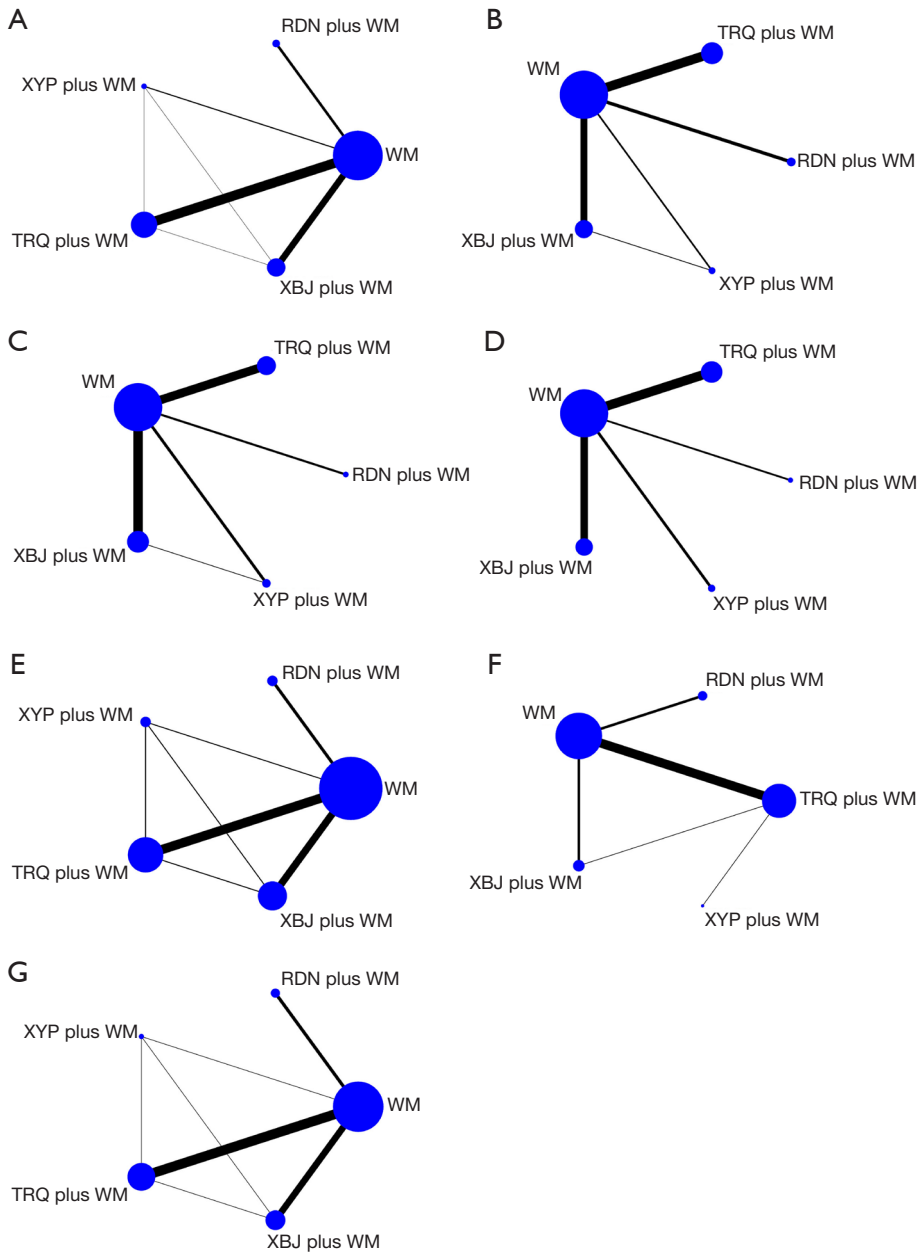

Figure 2 Network graph of the outcomes. (A) CRP; (B) PCT; (C) WBC; (D) NE%; (E) IL-6; (F) IL-8; (G) TNF-α. RDN, Reduning injection; WM, Western Medicine; XYP, Xiyanping injection; TRQ, Tanreqing injection; XBJ, Xuebijing injection; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cells; NE, neutrophils; IL-6, interleukin-6; IL-8, interleukin-8; TNF-α, tumor necrosis factor-α.

WM regimen alone [MD and 95% CIs were −4.84 (−9.07 to −0.62), 1.48 (0.74 to 2.23), respectively]. In contrast, compared with using a WM regimen alone, there was no significant change in CRP level in the XYP + WM and RDN + WM groups. In addition, there was no statistically significant difference between other interventions and the WM regimen.

PCT

In total, 23 RCTs (36,37,47,53,60,61,63,64,68,70,72,74,75,77,79-82,84-88) involving 4 CHIs were used to analyze the change in PCT. Patients receiving TRQ + WM showed significant improvement in PCT compared to those who received WM alone or XBJ + WM, with MD

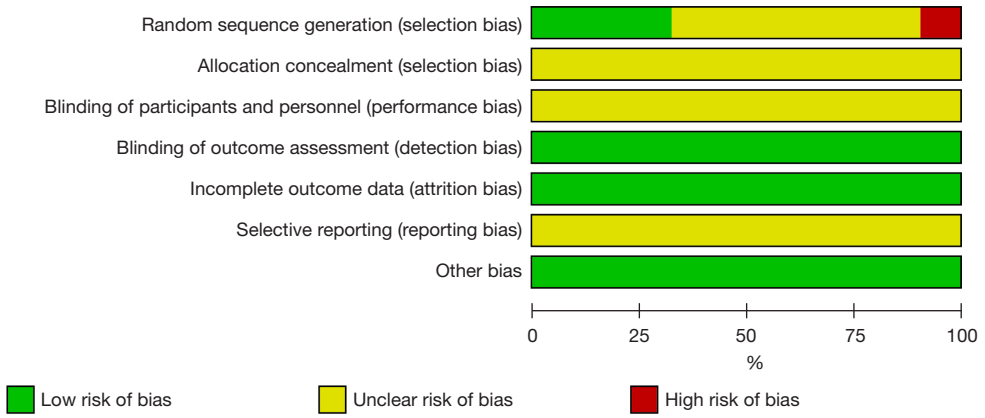

Figure 3 Risk of bias graph.

and 95% CIs of −2.40 (−3.48 to −1.32) and −1.74 (−3.46 to −0.01), respectively (Table S1). There was no statistically significant difference between other interventions and WM regimen.

WBC

A total of 31 RCTs involving 4 CHIs were used to analyze the change in the WBC [2015–2022, 15 studies (34,35,37,38,58-61,67-70,74,77,79); 2006–2014, 16 studies (22,25,26,29,33,41,44,45,49,53,89-94)]. XYP + WM, XBJ + WM, TRQ + WM, and RDN + WM had a significant effect on WBC compared to WM regimen alone, with MD and 95% CIs of −1.92 (−3.64 to −0.20), −1.50 (−1.89 to −1.12), 0.88 (0.47 to 1.29), and 1.95 (1.14 to 2.76), respectively (Table S2). Moreover, XBJ + WM and RDN + WM showed significantly better effects compared with TRQ + WM, with MD and 95% CIs of −0.62 (−1.18 to −0.07) and 1.07 (0.17 to 1.98), respectively.

NE%

A total of 23 RCTs (22,26,27,33-35,38,41,44,49,58,59,61, 67,69,74,77,79,89,91-94) involving 4 CHIs were used to analyze the change in the NE%. XYP + WM, XBJ + WM, TRQ + WM, and RDN + WM had a significant effect on NE% compared to the WM regimen alone, with MD and 95% CIs of 4.21 (0.85 to 7.57), 5.59 (3.45 to 7.73), −3.16 (−5.30 to −1.03), and −9.52 (−13.53 to −5.51), respectively (Table S2). Furthermore, RDN + WM showed significantly better effects compared with TRQ + WM and XYP + WM, with MD and 95% CIs of −6.36 (−10.90 to −1.82) and −5.31 (−10.54 to −0.08), respectively.

IL-6

In total, 19 RCTs (53,55,60,65,66,70,71,75,78,82,83,86,95-101) involving 4 CHIs were used to analyze the change in the IL-6. XBJ + WM and TRQ + WM had a significant effect on IL-6 compared to using WM alone, with MD and 95% CIs of −5.62 (−7.93 to −3.32) and 1.96 (1.16 to 2.76), respectively. XBJ + WM and RDN + WM showed significantly better effects compared with XYP + WM, with MD and 95% CIs of 3.92 (0.63 to 7.20) and 4.51 (2.00 to 7.02), respectively (Table S3). XBJ + WM showed significantly better effects compared with TRQ + WM, with MD and 95% CI of −3.66 (−6.10 to −1.22).

IL-8

In total, 22 RCTs (23,24,29,36,53,66,78,80,97-99,101-111) involving 4 CHIs were used to analyze the change in IL-8. Indirect comparisons demonstrated that RDN + WM had a significant effect on the levels of IL-8 compared with TRQ + WM, with MD and 95% CI of −3.01 (−5.23 to −0.79) (Table S3). There was no statistically significant difference between other interventions.

TNF-α

In total, 36 RCTs involving 4 CHIs were used to analyze the change in TNF-α [2015–2022, 19 studies (36,60,65,66,72,76,78,83-85,95-98,102-104,112,113); 2006–2014, 17 studies (25,46,47,51-53,55,99-101,105-

Table 2 SUCRA values of different groups for outcomes

Treatment	CRP	PCT	WBC	NE%	IL-6	IL-8	TNF-α
XYP plus WM	49.1%	73.9%*	75.8%*	49.0%	68.4%*	53.5%	64.7%*
XBJ plus WM	72.2%*	32.4%	61.6%	68.3%*	50.8%	79.7%*	60.8%
WM	9.0%	8.5%	0.4%	0.2%	4.7%	15.6%	2.0%
TRQ plus WM	65.1%*	82.6%*	28.8%	34.3%	85.5%*	64.3%*	82.2%*
RDN plus WM	54.7%	52.7%	83.4%*	98.2%*	40.6%	36.9%	40.3%

*, the values indicate the top 2 interventions with higher SUCRAs for different outcomes. SUCRA, surface under the cumulative ranking curve; XYP, Xiyanping injection; WM, Western Medicine; XBJ, Xuebijing injection; TRQ, Tanreqing injection; RDN, Reduning injection; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cells; NE, neutrophils; IL-6, interleukin-6; IL-8, interleukin-8; TNF-α, tumor necrosis factor-α.

110,114)]. XBJ + WM and TRQ + WM had a significant effect on TNF-α level compared with using WM alone, with MD and 95% CIs of −5.59 (−7.65 to −3.52) and 1.69 (1.21 to 2.18), respectively. Moreover, XBJ + WM and RDN + WM showed significantly better effects compared with XYP + WM, with MD and 95% CIs of 4.09 (1.21 to 6.98) and 4.21 (2.05 to 6.37), respectively (Table S4). XBJ + WM showed significantly better effects compared with TRQ + WM, with MD and 95% CI of −3.89 (−6.02 to −1.77). RDN + WM showed significantly better effects compared with XBJ + WM, with MD and 95% CI of 1.01 (0.19 to 1.83).

SUCRA values of CHIs groups for outcome measures

Based on the calculated probabilities (*Table 2*), XBJ + WM (72.2%) and TRQ + WM (65.1%) showed better outcomes in improving CRP level among all CHI groups. TRQ + WM (82.6%) and XYP + WM (73.9%) demonstrated the best effects on improving PCT. RDN + WM (83.4%) and XYP + WM (75.8%) demonstrated the best effects on improving WBC. RDN + WM (98.2%) and XBJ + WM (68.3%) seemed to be optimal choices for improving the area of NE%. TRQ + WM (85.5%) and XYP + WM (68.4%) presented higher probability in improving IL-6 level. XBJ + WM (79.7%) and TRQ + WM (64.3%) presented higher probability in improving IL-8 level. With regard to TNF-α, TRQ + WM (82.2%) and XYP + WM (64.7%) showed better performance in drug safety. The figures of the cumulative probabilities for outcome measures are listed in Appendix 3.

Safety

A total of 12 RCTs (39,45,58,63,66,74,78,95,96, 102,104,111) provided detailed information on the conditions, and 19 RCTs (22,26,34,41,51,53,54,61, 70-72,89,91,92,98,103,105,106,110) reported no adverse reaction. The rest of the included studies did not provide information on any adverse reactions. In addition, the majority of the adverse reactions were resolved after drug withdrawal according to the RCTs. The detailed conditions and cases are presented in *Table 3*.

Publication bias

Stata software was employed to assess publication bias by creating funnel plots. Comparisons between different interventions were demonstrated by different colors. In terms of the CRP, PCT, NE%, IL-6, IL-8, and TNF-α, the funnel plots of 4 outcomes were asymmetrical, suggesting the existence of bias (*Figure 4* and Appendix 4). However, the funnel plot of WBC was visually symmetrical, indicating that there was no bias.

Discussion

This NMA included 94 RCTs involving 4 CHIs that evaluated the levels of CRP, PCT, WBC, NE%, IL-6, IL-8, TNF-α, and adverse reactions after the application of CHIs combined with RT. According to this NMA, compared with using WM alone, using a combination of CHIs with WM could significantly reduce the level of inflammatory factors in AECOPD. TRQ and XBJ combined with WM could reduce the levels of CRP, WBC, NE%, IL-6, and TNF-α. TRQ combined with RT could decrease the levels of PCT. XYP and RDN combined with WM could reduce the level of WBC and NE%. Based on the SUCRA values, TRQ + WM had the most obvious advantages in decreasing the levels of PCT, IL-6, and TNF-α. XBJ + RT was shown to

Table 3 Details of adverse drug reactions

Adverse events	RDN + WM (%)	TRQ + WM (%)	XBJ + WM (%)	XYP + WM (%)	WM (%)	Total
Dizziness	1 (7.1)	1 (7.1)	2 (14.3)	0 (0.0)	10 (71.4)	14
Headache	0 (0.0)	2 (66.7)	0 (0.0)	0 (0.0)	1 (33.3)	3
Skin irritation	0 (0.0)	2 (66.7)	0 (0.0)	0 (0.0)	1 (33.3)	3
Gastrointestinal reaction	0 (0.0)	14 (41.2)	0 (0.0)	0 (0.0)	20 (58.8)	34
Phlebitis	0 (0.0)	1 (16.7)	3 (50.0)	2 (33.3)	0 (0.0)	6

XBJ, Xuebijing injection; RDN, Reduning injection; TRQ, Tanreqing injection; XYP, Xiyanping injection; WM, Western Medicine.

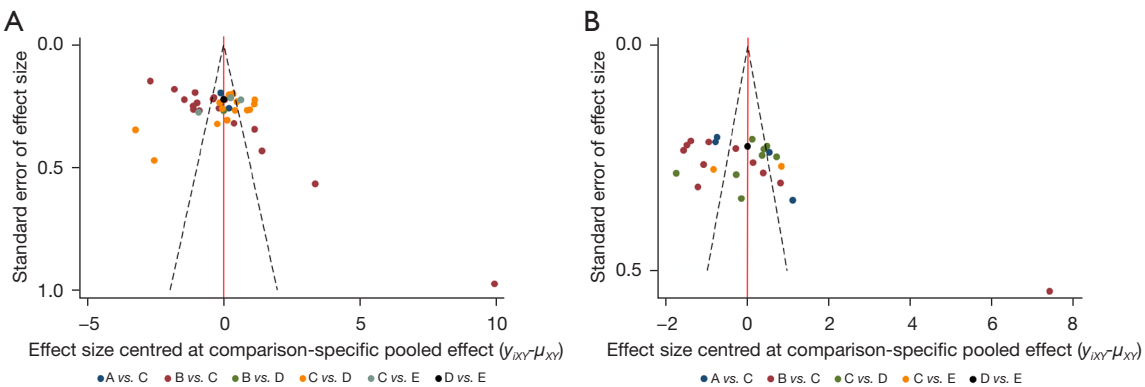

Figure 4 Funnel plots of outcomes: (A) CRP; (B) PCT. A, Reduning injection plus Western Medicine; B, Tanreqing injection plus Western Medicine; C, Western Medicine; D, Xuebijing injection plus Western Medicine; E, Xiyanping injection plus Western Medicine; CRP, C-reactive protein; PCT, procalcitonin.

be the most effective method in decreasing the levels of CRP and IL-8. RDN + WM showed the best effects on reducing the level of WBC and NE%. TRQ + WM showed more obvious therapeutic effects in patients with AECOPD if the improvement in CRP and all other above mentioned outcome measures was taken into account. Besides the efficacy, the safety of CHIs in the treatment of AECOPD warrants considerable attention. However, approximately 68% of included RCTs did not specifically report adverse reactions of using CHIs, leading to a lack of attention to drug safety among clinicians. Further studies are needed to determine the safety of using RDN, XYP, XBJ, and TRQ combined with WM.

Studies have shown that COPD is a systemic inflammatory syndrome, especially in the acute exacerbation stage, with the levels of inflammatory mediators (CRP, PCT, WBC, NE, IL-6, IL-8, and TNF-α) remarkably increased (115-119). These inflammatory mediators participate in the occurrence and development of systemic inflammation in COPD patients. The enhanced inflammatory response is the main pathogenesis of COPD (120). Treatment of AECOPD with the combination of TCM and WM can improve the treatment effect and reduce the level of these inflammatory mediators. As the currently preferred treatment, antibiotics can cause serious drug resistance and adverse reactions, making the alternative treatment of CHIs combined with WM more attractive. RDN consists of *Artemislae annuae herba*, *Lonicerae japonicae flos*, and *Gardenia fructus*. Xuebijing injection is composed of 5 TCM extracts including *Flos Carthami*, *Ligusticum striatum*, *Paeonia lactiflora*, *Angelica sinensis*, and *Salvia miltiorriza*. The components of TRQ are *Scutellariae radix*, bear bile powder, *Saigae tataricae cornu*, *Lonicerae japonicae flos*, and *Forsythiae fructus*. XYP is mainly constituted by andrographolide sulfonate. Modern studies have shown that these 4 CHIs have anti-inflammatory effects (121-124). These results indicate that clinicians can consider using WM + CHI to reduce the levels of inflammatory factors in AECOPD patients, and then improving clinical efficacy.

This NMA compared the efficacy of using different

CHIs combined with WM and using WM alone, and indirectly evaluated the efficacy of various CHIs + WM in the treatment of AECOPD. The objective evaluation in this study provides new insight for choosing optimal CHIs in AECOPD treatment. However, this NMA had several limitations. First, the quality of the included RCTs was general. Only 30 RCTs described the method of generating random sequences such as using a random number table, which led to an overstated therapeutic effect and poor reliability of the data. Second, because all the included RCTs were carried out among a Chinese population, our findings might not be applicable to other races and regions. Third, the funnel plots of 4 outcomes (CRP, PCT, NE%, IL-6, IL-8, and TNF-α) were asymmetrical, suggesting the existence of bias. This may be because the WM treatment was not sufficiently elaborated in original literatures, including information on drug dosage and delivery. This prevents us from conducting subgroup analyses for various WM treatment strategies. Therefore, the specific medication and dosage of WM should be recorded in detail, to increase the credibility of the evidence-based evidence when conducting RCTs on using CHI combined with WM in treating AECOPD. It is recommended that clinical trials must focus more on raising the level of methodological quality. Despite the above limitations, our NMA offered a comprehensive assessment of the therapeutic effects on inflammatory factors of several CHI for AECOPD.

Conclusions

In conclusion, this NMA showed that using CHIs combined with WM could significantly reduce the level of inflammatory factors in AECOPD. A combination of TRQ and WM may be a relatively prior adjuvant therapy option for AECOPD treatment considering its effects in reducing the levels of the anti-inflammatory mediators.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-402/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-402/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Mean difference (95% CIs) of CRP and PCT

PCT (Right upper part)					
CRP (Left lower part)	**XYP plus WM**	1.76 (–2.05, 5.58)	2.42 (–1.15, 5.99)	0.03 (–3.70, 3.75)	–0.65 (–2.89, 1.58)
	3.80 (–2.20, 9.79)	**XBJ plus WM**	0.66 (–0.69, 2.01)	**–1.74 (–3.46, –0.01)**	1.99 (–1.83, 5.80)
	–1.05 (–5.30, 3.20)	**–4.84 (–9.07, –0.62)**	**WM**	**–2.40 (–3.48, –1.32)**	–1.31 (–3.09, 0.47)
	0.44 (–3.75, 4.62)	–3.36 (–7.65, 0.93)	**1.48 (0.74, 2.23)**	**TRQ plus WM**	1.09 (–1.00, 3.17)
	3.21 (–1.12, 7.54)	1.24 (–0.17, 2.64)	–0.25 (–1.84, 1.34)	–0.27 (–4.54, 3.99)	**RDN plus WM**

The numbers in bold in the table indicate that there are statistically significant differences between this group and the RT group. CIs, confidence intervals; CRP, C-reactive protein; PCT, procalcitonin; WM, Western Medicine; XBJ, Xuebijing injection; RDN, injection; TRQ, Tanreqing injection; XYP, Xiyanping injection.

Table S2 Mean difference (95% CIs) of WBC and NE%

NE% (Right upper part)					
WBC (Left lower part)	**XYP plus WM**	–1.38 (–5.37, 2.61)	**4.21 (0.85, 7.57)**	1.05 (–2.93, 5.02)	**–5.31(–10.54, –0.08)**
	–0.42 (–2.17, 1.34)	**XBJ plus WM**	**5.59 (3.45, 7.73)**	2.43 (–0.60, 5.46)	–3.93 (–8.48, 0.62)
	–1.92 (–3.64, –0.20)	**–1.50 (–1.89, –1.12)**	**WM**	**–3.16 (–5.30, –1.03)**	**–9.52 (–13.53, –5.51)**
	–1.04 (–2.80, 0.73)	**–0.62 (–1.18, –0.07)**	**0.88 (0.47, 1.29)**	**TRQ plus WM**	**–6.36 (–10.90, –1.82)**
	0.45 (–0.45, 1.35)	–0.21 (–2.05, 1.64)	**1.95 (1.14, 2.76)**	**1.07 (0.17, 1.98)**	**RDN plus WM**

The numbers in bold in the table indicate that there are statistically significant differences between this group and the WM group. CIs, confidence intervals; WBC, white blood cells; NE, neutrophils; WM, Western Medicine; XBJ, Xuebijing injection; RDN, injection; TRQ, Tanreqing injection; XYP, Xiyanping injection.

Table S3 Mean difference (95% CIs) of IL-6 and IL-8

IL-8 (Right upper part)					
IL-6 (Left lower part)	**XYP plus WM**	4.49 (–4.72, 13.70)	1.16 (–2.83, 5.14)	–1.85 (–6.41, 2.70)	0.30 (–7.96, 8.56)
	3.92 (0.63, 7.20)	**XBJ plus WM**	–2.88 (–14.36, 8.60)	2.80 (–5.46, 11.05)	–0.21 (–8.16, 7.74)
	–1.71 (–4.05, 0.64)	**–5.62 (–7.93, –3.32)**	**WM**	5.67 (–2.31, 13.65)	–2.66 (–5.62, 10.95)
	0.25 (–1.95, 2.46)	**–3.66 (–6.10, –1.22)**	**1.96 (1.16, 2.76)**	**TRQ plus WM**	**–3.01 (–5.23, –0.79)**
	4.51 (2.00, 7.02)	0.86 (–0.42, 2.15)	–1.10 (–2.61, 0.41)	**–0.69 (–3.06, 1.68)**	**RDN plus WM**

The numbers in bold in the table indicate that there are statistically significant differences between this group and the WM group. CIs, confidence intervals; IL-6, interleukin-6; IL-8, interleukin-8; WM, Western Medicine; XBJ, Xuebijing injection; RDN, injection; TRQ, Tanreqing injection; XYP, Xiyanping injection.

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Table S4 Mean difference (95% CIs) of TNF-α

TNF-α				
XYP plus WM				
4.09 (1.21, 6.98)	**XBJ plus WM**			
–1.50 (–3.51, 0.52)	**–5.59 (–7.65, –3.52)**	**WM**		
0.20 (–1.75, 2.15)	**–3.89 (–6.02, –1.77)**	**1.69 (1.21, 2.18)**	**TRQ plus WM**	
4.21 (2.05, 6.37)	**1.01 (0.19, 1.83)**	–0.68 (–1.64, 0.27)	–1.47 (–3.52, 0.59)	**RDN plus WM**

The numbers in bold in the table indicate that there are statistically significant differences between this group and the WM group. CIs, confidence intervals; TNF-α, tumor necrosis factor-α; XYP, Xiyanping injection; WM, Western Medicine; XBJ, Xuebijing injection; RDN, injection; TRQ, Tanreqing injection.

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Appendix 1: Search strategy of EMBASE.

#1 'pulmonary disease, chronic obstructive': ab, ti
#2 'bronchitis, chronic': ab, ti OR emphysema: ab, ti
#3 copd: ab, ti
#4 'chronic obstructive pulmonary': ab, ti
#5 coad: ab, ti
#6 'chronic obstructive airway': ab, ti
#7 'chronic obstructive lung': ab, ti
#8 'chronic obstructive bronchopulmonary': ab, ti
#9 'chronic obstructive respiratory': ab, ti
#10 'chronic airflow obstruction': ab, ti
#11 'chronic airflow obstructive': ab, ti
#12 'chronic bronchitis': ab, ti
#13 'pulmonary emphysema': ab, ti
#14 'lung emphysema': ab, ti
#15 'chronic airflow limitation': ab, ti
#16 'reduning injection': ab, ti
#17 'tanreqing injection': ab, ti
#18 'xuebijing injection': ab, ti
#19 'xiyanping injection': ab, ti
#20 'randomized controlled trial': ab, ti
#21 'controlled clinical trial': ab, ti
#22 randomized: ab, ti
#23 randomly: ab, ti
#24 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#25 #16 OR #17 OR #18 OR #19
#26 #20 OR #21 OR #22 OR #23
#27 #24 AND #25 AND #26

Appendix 2: Node-splitting for Outcomes

	P value (CRP)	P value (PCT)	P value (WBC)	P value (IL-6)	P value (IL-8)	P value (TNF-α)
A C	0.991	0.995	0.986	0.997	0.996	0.999
B C	0.458	0.999	0.993	0.156	0.263	0.155
B D	0.173	/	/	0.143	0.341	0.116
B E	0.878	/	/	0.807	0.996	0.953
C D	0.547	0.746	0.618	0.558	0.603	0.850
C E	0.891	0.386	0.907	0.202	/	0.056
D E	0.813	0.673	0.732	0.070	/	0.064

Note: A: Reduning injection plus WM; B: Tanreqing injection plus WM; C: WM; D: Xuebijing injection plus WM; E: Xiyanping injection plus WM. WM: Western Medicine.

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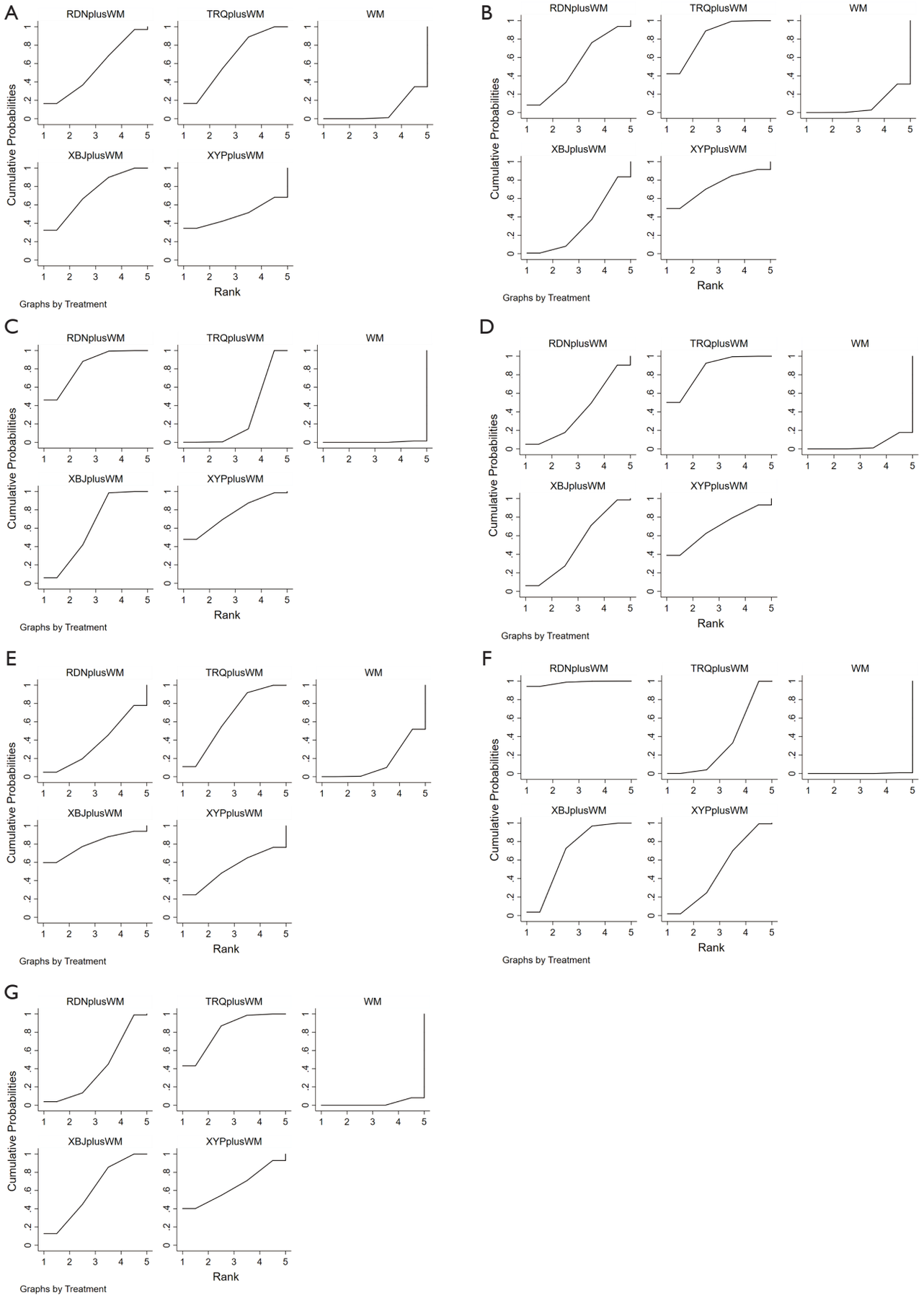
Appendix 3: The figure of the cumulative probabilities for outcomes



Note: A, CRP; B, PCT; C, WBC; D, NE%; E, IL-6; F, IL-8. G, TNF-α. RDN, Reduning injection; WM, Western Medicine; XYP, Xiyanping injection; TRQ, Tanreqing injection; XBJ, Xuebijing injection; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cells; NE, neutrophils; IL-6, interleukin-6; IL-8, interleukin-8; TNF-α, tumor necrosis factor-α.

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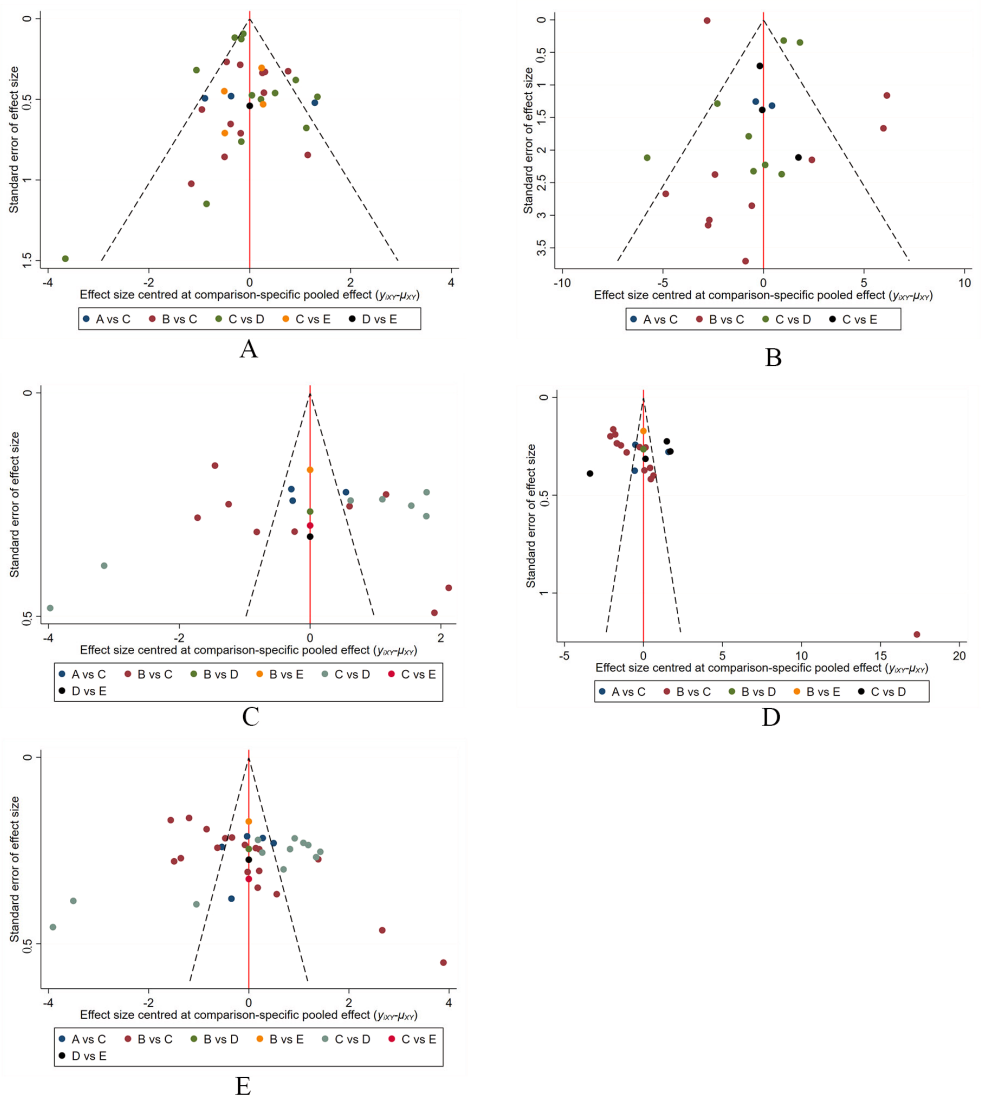
Appendix 4: Funnel plots of outcomes.



Note: A, WBC; B, NE%; C, IL-6; D, IL-8. E, TNF-α. A, Reduning injection plus Western Medicine; B, Tanreqing injection plus Western Medicine; C, Western Medicine; D, Xuebijing injection plus Western Medicine; E, Xiyanping injection plus Western Medicine; WBC, white blood cells; NE, neutrophils; IL-6, interleukin-6; IL-8, interleukin-8; TNF-α, tumor necrosis factor-α.

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