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REVIEW

Chinese Medical Injections for Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Network Meta-analysis

Haiyin Hu[1,*]
Zhaochen Ji[1,*]
Xiaoyu Qiang[1]
Shigang Liu[2]
Xiaodi Sheng[1]
Zhe Chen[1]
Fanqi Liu[3]
Hui Wang[1]
Junhua Zhang[1]

[1]Evidence-Based Medicine Center, Tianjin University of Traditional Chinese Medicine, Tianjin, People's Republic of China; [2]Department of Respiratory Diseases, Guang'anmen Hospital, Beijing, People's Republic of China; [3]Department of Cardiovascular Disease, The Second Affiliated Hospital of Tianjin University of Chinese Medicine, Tianjin, People's Republic of China

*These authors contributed equally to this work

Background: The World Health Organization has indicated that chronic obstructive pulmonary disease (COPD) may become the third leading cause of death by 2030. Acute exacerbation of COPD (AECOPD) is an important process in clinical treatment. Recent studies have shown that Chinese medical injections (CMI) are effective against AECOPD, but the effective difference among different CMIs remains unclear. The aim of this network meta-analysis (NMA) is to compare the therapeutic effect of various CMIs.

Methods: We conducted an overall, systematic literature search in the China National Knowledge Infrastructure, Wanfang, VIP, SinoMed, PubMed, Embase, Cochrane Library, and Web of Science databases to retrieve randomized controlled trials (RCTs) of CMIs for AECOPD published up to January 2021. The Cochrane risk of bias tool was used to assess the risk of bias. Stata 13.1 and WinBUGS 14.3 were used for data analyses.

Results: In total, 103 RCTs involving 8767 participants and 23 CMIs were included. The results indicated that among all treatments conventional Western medical therapy (WM) plus Dengzhanxixin injection (DZXX) led to the best improvement in the clinical efficacy and the ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) (FEV_1/FVC), with surface under the cumulative ranking curve (SUCRA)=80.47% and 98.55%, respectively. Moreover, Shenmai injection (SM) plus WM and Reduning injection (RDN) plus WM led to the best improvement in the FEV_1 (SUCRA=80.18%) and the ratio of forced expiratory volume in one second to the predicted value (FEV_1%, SUCRA=87.28%). Shengmai injection (SGM) plus WM led to the most considerable shortening in the length of hospital stay (SUCRA=94.70%). Cluster analysis revealed that WM+DZXX had the most favorable response for clinical efficacy and FEV_1, as well as clinical efficacy and FEV_1/FVC, WM+RDN had the most favorable response for clinical efficacy and FEV_1%, WM+SGM had the most favorable response for clinical efficacy and length of hospital stay.

Conclusion: WM+DZXX, WM+RDN, and WM+SGM were noted to be the optimum treatment regimens for improving in clinical efficacy, FEV_1, FEV_1/FVC, FEV_1% and reducing the hospital stay length of AECOPD patients. Considering the limitations this NMA may have, the current results warrant further verification via additional high-quality studies.

Keywords: traditional Chinese medicine, TCM, Chinese medical injection, CMI, acute exacerbation of chronic obstructive pulmonary disease, AECOPD, COPD, network meta-analysis, NMA

Correspondence: Hui Wang, Junhua Zhang
Email wanghui1983@foxmail.com; zjhtcm@foxmail.com

Introduction

Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by progressive, persistent airflow restriction and abnormal airway inflammation. When

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the related respiratory symptoms worsen continually, warranting conventional medication changes, the condition is defined as acute exacerbation of COPD (AECOPD).[1–3] AECOPD can severely impact the patient's daily life and impair their lung function.[4] According to the World Health Organization, the COPD is expected to be the third leading cause of death by 2030 globally.[5–8] In the Asia-Pacific region, COPD incidence is estimated to be as high as 6.2% and rising.[9] In 2019 an expert consensus on anti-infective therapy for AECOPD in China showed that COPD prevalence in Chinese residents aged >40 and >60 years was 13.7% and >27.0%.[10–12] Mortality risk increases significantly in patients with AECOPD.[13]

Corticosteroids and long-acting bronchodilators are recommended as the first-line therapies for AECOPD along with the additional use of antibiotics if required.[14] However, long-term treatment with systemic corticosteroids is immunosuppressive, which increases the risk and severity of viral infections.[15] Moreover, the wide application of antibiotics has led to bacterial resistance .[16] These factors can reduce treatment efficacy further.[17]

Chinese medical injections (CMIs) are widely used in clinical practices.[16] Some clinical trials have evaluated the efficacy of CMIs for patients with AECOPD and reported their effectiveness in inhibiting inflammation, regulating immune function, and alleviating symptoms.[18–20]

Recent systematic reviews have also shown that CMIs are effective for treating AECOPD,[21–25] but the effective difference among different CMIs remains unclear. Therefore, in this study, we performed a network meta-analysis (NMA) of all published RCTs on CMIs for treating of AECOPD to compare the therapeutic effect of the different CMIs used.

Methods

Protocol and Registration

The study protocol was registered on PROSPERO (Registration No. CRD42021236247; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021236247).

Eligibility Criteria

Inclusion Criteria

We included RCTs with participants diagnosed with AECOPD (based on diagnosis and treatment guidance of chronic obstructive pulmonary disease).[26] The experimental group received a CMI plus conventional Western medical therapy (WM) (including oxygen inhalation, spasmolysis, anti-asthmatic and nutritional support, and antibiotic treatment), whereas the control group received WM alone or another CMI plus WM. No restrictions on language, sex, age, and disease course were imposed.

The main outcome was clinical efficacy and the evaluation criteria were as follows:

- Significantly effective: clinical symptoms and signs such as cough and dyspnea disappeared or improved significantly, the pulmonary rales disappeared or decreased, and laboratory examinations showed normal results at the end of the treatment.
- Effective: clinical symptoms, signs, and laboratory examinations, all improved at the end of the treatment.
- Invalid: the condition neither improved nor worsened by the end of the treatment.

Next, clinical efficacy rate was calculated as [(significantly effective cases+effective cases)/total cases]×100%.

The secondary outcomes were as follows:

- Lung function: this included forced expiratory volume in one second (FEV_1), the ratio of FEV_1 to the predicted value (FEV_1%), and the ratio of FEV_1 to forced vital capacity (FEV_1/FVC), as recommended by the Global Strategy for Prevention, Diagnosis and Management of COPD.[14]
- Length of hospital stay: this is closely related to the cost of hospitalization and the economic burden of patients.[27]

The improvements in the lung function and length of hospital stay were expressed as means ± standard deviations.

Exclusion Criteria

We excluded studies including AECOPD patients with other comorbidities such as gastroesophageal reflux disease, depression, and osteoporosis—all of which are associated with COPD exacerbation and COPD development acceleration.[28] We also excluded studies where a combination of multiple TCM injections was used, or where TCM injections were combined with other therapies (decoction, acupuncture, moxibustion, etc). Finally, conference articles, duplicated literature, unavailable studies, and studies with missing data were all excluded.

Data Sources and Search Strategy

Eight databases including the China National Knowledge Infrastructure, Wanfang, VIP, SinoMed, PubMed, Embase, Cochrane Library, and Web of Science were searched for eligible studies published from database inception until January 27, 2021. We used search terms including Chinese medicine, injection, COPD, and chronic obstructive pulmonary disease, etc. The complete search strategy is provided in Supplementary File.1. For example, we used the following search strategy on PubMed:

#1((((((((Pulmonary Disease; Chronic Obstructive [MeSH Terms]) OR (Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome[MeSH Terms])) OR (COPD; Severe Early-Onset[Supplementary Concept])) OR (pulmonary disease; chronic obstructive [Title/Abstract])) OR (chronic obstructive pulmonary disease[Title/Abstract])) OR (chronic airflow obstruction [Title/Abstract])) OR (COPD[Title/Abstract])) OR (chronic obstructive lung disease[Title/Abstract])) OR (chronic obstructive airway disease[Title/Abstract])

#2(((((Traditional Chinese medicine[MeSH Terms]) OR (Traditional Chinese medicine[Text Word])) OR (Chinese medicine[Text Word])) OR (injection[Text Word])) OR (zhongyi[Text Word])) OR (zhongyao[Text Word])

#3((randomized trials[MeSH Terms]) OR (randomized trials[Text Word])) OR (randomized[Text Word])

#4#1 AND #2 AND #3

Literature Selection and Data Extraction

Two researchers independently conducted literature screening and data extraction. Eligible studies were reviewed and the following data were abstracted using a pre-established data extraction table: age, sex, sample size, intervention/control measures, treatment course, outcomes, and adverse reactions. The selected studies and extracted data were cross-checked by two authors and if there were any disagreements they were resolved through consulting with a third party.

Quality Assessment

The quality of the included studies was evaluated using the Cochrane risk of bias tool recommended by the Cochrane Handbook for Systematic Reviews Version 5.3. Study quality was evaluated on the basis of seven aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases.[29] For each item the use of the right method was rated as low risk of bias, unclear description was rated as unknown risk of bias, and the use of an incorrect method was rated as high risk of bias. All results were cross-checked by two authors and if there were any disagreements they were resolved through consulting with a third party.

Statistical Analysis

Dichotomous outcomes were measured as odds ratios (ORs), whereas continuous outcomes were measured as mean differences (MDs). When 95% confidence interval (CI) of the ORs and MDs did not contain 1 and 0, respectively, the differences were considered statistically significant.

Stata 13.1 was used to draw a network plot—where thicker lines indicated a higher number of the RCTs and a larger dot indicated a larger sample size. An inconsistency test was specifically needed when a closed loop formed in network plot. An inconsistency test was used to mainly evaluate the degree of consistency between the direct comparison results and indirect comparison results. Here $P \geq 0.05$ indicated low inconsistency in the closed loop, whereas $P < 0.05$ indicated significant inconsistency.

We used the Markov Chain Monte Carlo method with a random-effect model on WinBUGS 14.3 to perform Bayesian NMA. The iterations were set to 400,000. The first 100,000 times were used for annealing to eliminate the influence of the initial value and the last 300,000 times were used for sampling. The results are reported as the ORs and MDs with their respective 95%CIs. Surface under the cumulative ranking curve (SUCRA) was used to rank the efficacy of each intervention. The publication bias was assessed by comparison-adjusted funnel plot with Begg's test. Cluster analysis was conducted using STATA 13.1 to determine the dependency between outcomes and thus to the best interventions. This study was reported in accordance with PRISMA extension for network meta-analysis.[30]

Results

Literature Search and Characteristics of the Included Studies

After our preliminary literature search 2430 studies were obtained of which 345 duplicates were removed. A total of 1653 articles were excluded after reading titles and abstracts because they were non-RCTs, non-AECOPD studies, concomitant use of other therapies, included patients with other diseases, animal studies, or systematic reviews. Furthermore, 329 studies were excluded after reading full texts because they reported unrelated outcomes, incomplete data, or lack of full text. Finally, 103 RCTs were included. PRISMA flow diagram for study selection is shown in Figure 1.

The characteristics of included studies are shown in Table 1. One hundred and three RCTs comprised a total of

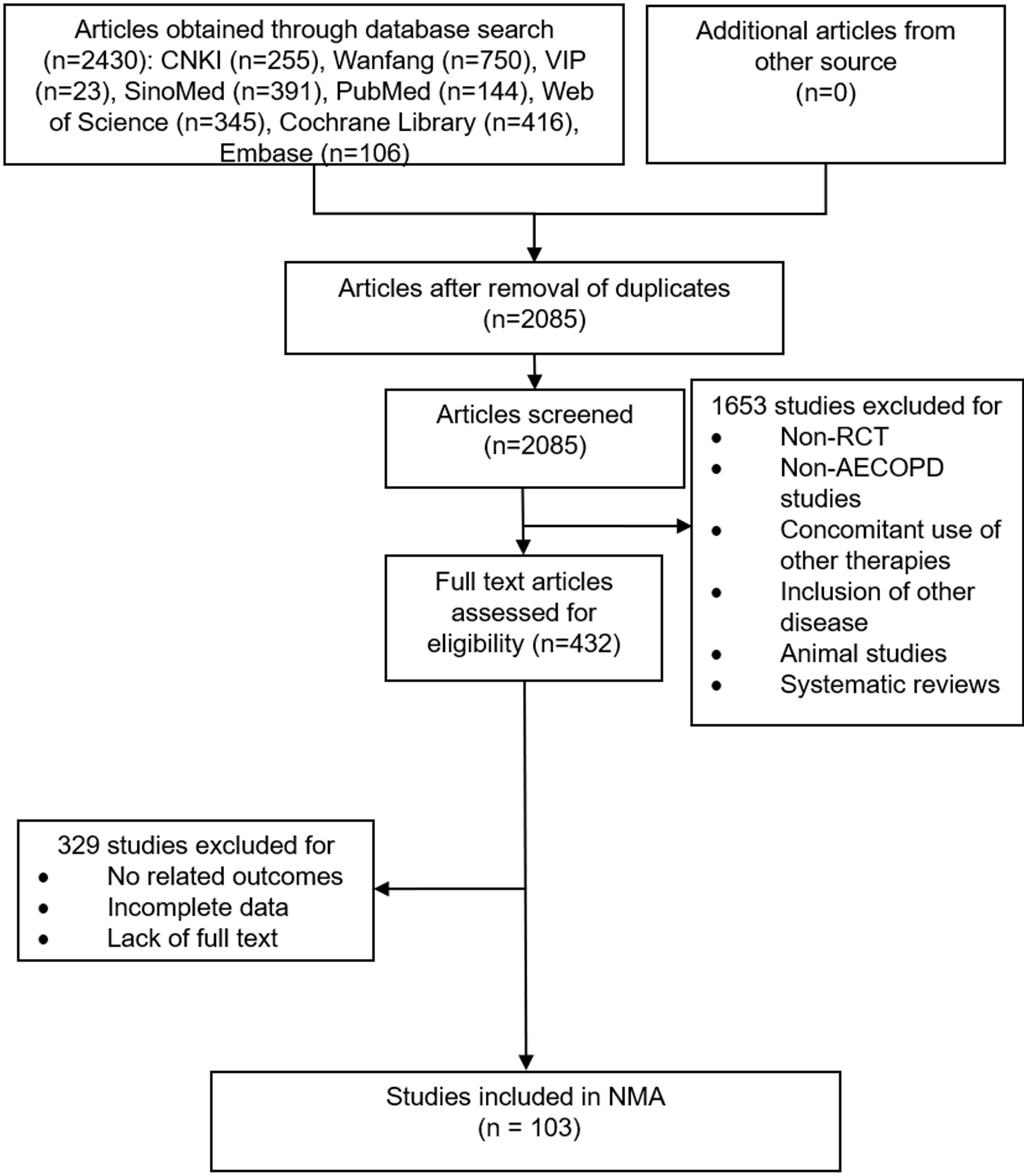

Figure 1 PRISMA flow diagram.

Notes: PRISMA figure adapted from Hutton B, Salanti G, Caldwell DM, et al.The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777–784. Creative Commons.[30]

Table 1 The Characteristics of Included Studies

Study	Sample size		Gender		Age (years)		Interventions		Courses (days)	Outcomes
	T1 (T2)	C	Male	Female	T1 (T2)	C	T1(T2)	C		
Cai Lili 2014[57]	55	55	69	41	75±4.8	74±5.4	WM+KA	WM	14	②⑤⑪⑫
Chen Weizhong 2014[58]	77	77	89	65	64.7±12.2	65.8±11.8	WM+RDN	WM	7	②③⑤⑪⑫
Chen Zhuo 2013[59]	52	48	60	40	66.6±7.4	63.8±7.8	WM+DH	WM	14	②
Chi Yongsheng 2015[60]	48	48	42	54	76.45±5.66	77.68±6.21	WM+SF	WM	14	②⑤
Cui Yandong 2010[61]	24	24	31	17	50–74	51–76	WM+CKZ	WM	14	②
Dong Hongzhen 2015[62]	30	30	39	21	62.3±1.9	61.3±2.1	WM+RDN	WM	7	②
Du Jin 2014[63]	30	30	34	26	65±8.4	62±9.8	WM+DH	WM	14	②⑧
Du Yong 2015[64]	60	60	82	38	67.54±10.66	66.38±11.34	WM+TRQ	WM	10	②
Duan Limin 2015[65]	46	46	63	29	70.3±5.8	70.3±5.8	WM+XBJ	WM	7	②
Fan Yongxia 2011[66]	25	25	29	21	58	57	WM+DH	WM	14	②
Feng Qing 2015[67]	33	32	38	27	62±5.0	64±6.0	WM+TRQ	WM	7	②
Feng Zhijun 2010[68]	54	52	67	39	64.5±6.8	64.5±6.8	WM+TRQ	WM	–	②
Fu Dongwei 2012[69]	35	35	41	29	61.45±5.23	59.57±5.84	WM+TRQ	WM	15	②
Fu Qin 2009[70]	50	50	92	8	80~93	81~94	WM+TRQ	WM	7~10	②
Fu Yongwang 2009[71]	65	63	68	60	61.2±1.2	61.8±2.8	WM+TRQ	WM	10	②⑤
Ge Zhongkai 2015[72]	30	30	39	21	53.1±8.5	52.6±8.2	WM+TRQ	WM	10	②③⑪
Ge Zhongkai 2016[73]	32	32	41	23	54.9±4.4	55.7±4.6	WM+DH	WM	14	②
Guo Xia 2009[74]	35	35	40	30	67	66	WM+SM	WM	15	②
Han Fang 2015[75]	62	60	70	52	56	61	WM+XYP	WM	14	③⑤⑫
Hao Tianpao 2010[76]	30	30	42	18	66±6	67±5	WM+XBJ	WM	10	②
He Shaoling 2019[77]	44	44	60	28	57.97±7.56	58.31±6.86	WM+XBJ	WM	14	②⑪⑫
He Xiang 2016[78]	35	35	56	14	69.39±7.56	70.24±6.89	WM+TRQ	WM	7	②⑤
He Yongliang 2012[79]	40	42	58	24	63.4±10.3	62.8±10.5	WM+DS	WM	10~14	②
Hu Xiaolin 2016[80]	50(50)	50	115	35	69.3±6.3(66.7±4.2)	68.4±5.8	WM+XBJ(WM+TRQ)	WM	7	②③⑥
Hua Wenshan 2014[81]	20	20	21	19	55~80	50~75	WM+TRQ	WM	–	②
Huang Bin 2006[82]	30	30	45	15	64.21±8.21	64.21±8.21	WM+TRQ	WM	14	②③⑤
Kang Jin 2016[83]	60	60	69	51	44.37±13.25	45.36±14.85	WM+TRQ	WM	7	②
Li Daxiang 2015[84]	33	33	33	33	53.1±1.3	55.8±7.7	WM+XBJ	WM	3	②⑤
Li Guoling 2009[85]	36	36	53	19	72.25±9.340	71.50±9.637	WM+TRQ	WM	–	②④
Li Linlin2014[86]	38	38	42	34	64.3±3.2	66.3±3.8	WM+TRQ	WM	7	②④
Li Wen 2010[87]	28	26	35	19	67.1±7.1	67.8±8.2	WM+TRQ	WM	10	①②
Liang Gang 2009[88]	30	30	41	19	81.2±6.8	80.1±6.5	WM+DS	WM	14	②⑤
Liang Wei 2017[89]	35	35	45	25	62.34±5.52	61.76±5.59	WM+TRQ	WM	7	②
Liao Wensheng 2008[90]	30	28	39	19	68.3±7.4	65.2±5.9	WM+SF	WM	14	②⑪⑫

(*Continued*)

Table 1 (Continued).

Study	Sample size		Gender		Age (years)		Interventions		Courses (days)	Outcomes
	T1 (T2)	C	Male	Female	T1 (T2)	C	T1(T2)	C		
Ling Daobo 2009[91]	30	30	44	16	71.5	70.8	WM+XBJ	WM	7	②⑧
Liu Hongbo 2008[92]	60	60	79	41	64.24±12.35	63.55±11.35	WM+TRQ	WM	14	②③⑤⑦⑫
Liu Honghong 2016[93]	30	30	33	27	69.00±5.73	68.10±5.94	WM+XYP	WM	–	②④⑪⑫
Liu Yan 2019[94]	30	30	32	28	60.53±8.42	63.71±9.52	WM+SXT	WM	14	②③⑤⑪⑫
Liu Zhanxiang 2007[95]	100	98	103	95	61.2±1.2	61.8±2.8	WM+TRQ	WM	7	②
Liu Zhonggui 2014[96]	56	54	65	45	63.1±2.5	63.1±2.5	WM+TRQ	WM	10	②③⑪
Long Hai 2012[97]	64	60	88	36	61.10±7.21	61.12±12.35	WM+TRQ	WM	7	②③⑤⑪
Lu Na 2013[98]	49	49	71	27	72.2	71.5	WM+TRQ	WM	14	②⑦
Mu Lin 2014[99]	36	36	43	29	51~82	51~82	WM+XBJ	WM	7	②⑤
Pang Lijian 2015[100]	55	55	51	59	55±4.25	54±3.65	WM+RDN	WM	14	②⑤
Peng Bo 2007[101]	30	30	35	25	60.3±6.6	59.3±8.18	WM+TRQ	WM	12	②⑫
Qiu Qin 2013[102]	35	35	48	22	72.4±11.3	72.4±11.3	WM+XBJ	WM	10	②⑧⑪⑫
Qu Qiu2014[103]	30	30	44	16	78±5.7	78±5.7	WM+HJT	WM	10	②⑤
Ren Yuejuan 2013[104]	35	35	41	29	62.5±5.4	62.8±5.01	WM+SF	WM	14	②⑤
Shi Ce 2009[105]	25	25	37	13	45~75	46~77	WM+TRQ	WM	7~14	②
Shi Daihui 2013[106]	42	42	54	30	55~84	56~82	WM+TRQ	WM	10	②⑤
Shi Yiying 2009[107]	23	23	27	19	58	57	WM+DH	WM	14	②⑪⑫
Song Liang 2012[108]	40	40	58	22	52–82	54–84	WM+CKZ	WM	7	②
Sun Jin 2008[109]	75	63	–	–	–	–	WM+TRQ	WM	14	②⑦
Tang Na 2016[110]	60	60	87	33	62.8±9.6	63.1±9.5	WM+TRQ	WM	–	②③④⑪
Tang Wei 2012[111]	56	56	65	47	72.5±5.0	71.0±4.2	WM+HQ	WM	21	②
Tian Rukang 2009[112]	38	34	40	32	68	66	WM+SM	WM	15	②⑤
Tian Tulie 2015[113]	37	37	42	32	60.8	59.7	WM+RDN	WM	10	②⑪⑫
Wang Aidong 2011[114]	72	70	100	42	61.8±6.3	64.7±8.6	WM+TRQ	WM	10~14	②⑤⑪⑫
Wang Haiyan 2010[115]	30	30	41	19	64	62	WM+DZXX	WM	10	②③⑪
Wang Lixia 2008[116]	50	46	59	37	68.5	67.2	WM+TRQ	WM	7~14	②
Wang Qiu 2013[117]	47	47	67	27	60.4	60.4	WM+TRQ	WM	10	②⑦
Wang Tiejun 2012[118]	39	40	50	29	55.76±8.23	56.36±7.69	WM+SXN	WM	14	③⑥
Wang Tongbing 2015[119]	46	46	53	39	59.26±2.68	59.26±2.68	WM+TRQ	WM	14	②③⑤⑪
Wang Xianghua 2011[120]	39	39	46	32	62.7±4.8	58.8±6.1	WM+TRQ	WM	14	②③⑤⑪
Wang Xueqin 2015[121]	30	30	29	31	69.6	71.0	WM+XBJ	WM	7	②
Wang Yong 2007[122]	32	28	51	9	69.5±7.8	69.3±8.0	WM+SGM	WM	14	②④⑤⑥⑦
Wei Sizun 2011[123]	40	40	44	36	59.28±8.56	58.08±9.28	WM+TRQ	WM	–	②③⑪
Wei Yaomin 2014[124]	37	33	39	31	61.3±2.5	61.3±2.5	WM+RDN	WM	10	②③⑪
Wnag Yuanjun 2012[125]	50	50	69	31	40~65	40~65	WM+XBJ	WM	7	②

Wu Beishou 2015[126]	38	38	39	37	50.7±9.3	53.6±6.8	WM+Salvianolate	WM	14	②
Wu Dengxiang 2015[127]	50	50	56	44	52.5±5.7	53.4±6.7	WM+TRQ	WM	15	②⑤
Wu Yi 2017[128]	40	40	52	28	66±6	67±5	WM+CKZ	WM	7	②
Xia Chunxia 2010[129]	40	40	58	22	69.9±11.3	69.1±10.9	WM+KDZ	WM	14	②⑤
Xiang Wei 2012[130]	44	42	43	43	32.5±2.3	39.85±1.73	WM+CKZ	WM	7	②
Xiang Zhi 2020[131]	60	60	68	52	68.01±10.28	67.25±9.4	WM+TRQ	WM	10	④⑤⑫
Xiao Chenxi 2018[132]	45	44	53	36	68.14±9.41	67.15±8.62	WM+HQ	WM	14	②④⑨⑩
Xie Yonghong 2005[133]	52	30	49	33	63.67±8.21	63.41±9.35	WM+TRQ	WM	15	②⑤⑦
Xiong Suqiong 2013[134]	56	56	63	49	66.7	66.5	WM+HQ	WM	14	②
Xu Weijun 2017[135]	32	36	44	24	73.60±10.60	75.00±8.30	WM+TRQ	WM	14	②⑤⑪⑫
Yang Jiewu 2012[136]	110	110	149	71	56.60±6.20	56.60±6.20	WM+DH	WM	14	②⑪⑫
Yang Ruifang 2010[137]	42	40	63	19	66.5±5.8	67.2±4.6	WM+DH	WM	14	②
Yang Weizhong 2014[138]	60	60	78	42	70.0±6.4	70.0±6.4	WM+TRQ	WM	7	②④
Yang Xiuhong 2006[139]	14	12	16	10	62.8±11.2	62.8±11.2	WM+TRQ	WM	10	②
Ye Ling 2010[140]	30	27	50	7	–	–	WM+XBJ	WM	10	②⑤⑧⑪⑫
YE Shihua 2016[141]	40	40	45	35	62.8±3.4	62.4±3.9	WM+RDN	WM	35	②⑪⑫
Yin Libo 2009[142]	32	30	44	18	73.38±7.61	74±10.47	WM+TRQ	WM	10	②⑤
YU Changxiu 2020[143]	42	42	56	28	56.5±2.3	57.5±2.1	WM+SM	WM	14	②③
Zhang Chimei 2014[144]	30	28	35	23	65.1±5.4	63.8±5.1	WM+HQ	WM	14	②
Zhang Li 2013[145]	60	60	56	64	70.6±3.3	70.6±3.3	WM+DH	WM	14	②
Zhang Liyun 2017[146]	30	30	51	9	64.51±11.31	65.04±12.42	WM+ZCL	WM	7	②
Zhang Qiang 2015[147]	30	30	42	18	66.5±8	64.8±10	WM+QKL	WM	14	②⑪
Zhang Qiong 2014[148]	64	64	71	57	64.45±9.46	64.41±9.45	WM+DH	WM	14	②
Zhang Wenqian 2010[149]	36	36	49	23	60.4	61.5	WM+QKL	WM	7	②⑤
Zhang Xiaohua 2016[150]	47	47	75	19	50–82	53–75	WM+HH	WM	15	②
Zhang Xin 2014[151]	46	46	62	30	67.8±7.4	67.6±7.2	WM+XYP	WM	14	②③⑪
Zhang Ying 2004[152]	29	29	38	20	71.48±7.72	69.34±7.83	WM+TRQ	WM	12	①②⑥⑦
Zhang Yuanhua 2015[153]	35	35	45	25	65	66	WM+KDZ	WM	10	②
Zhao Zhenhuan 2016[154]	50	50	74	26	64.8±6.9	68.3±7.8	WM+SHL	WM	10	②
Zhang Yali 2017[155]	45	44	57	32	65.9±13.4	66.4±12.8	WM+SF	WM	14	②⑤⑪⑫
Zhou Aizhu 2013[156]	20	20	35	5	62±4.5	62±4.5	WM+XST	WM	14	②⑤⑪⑫
Zhou Jianguo 2014[157]	30	30	32	28	72.6±5.4	73.1±5.8	WM+RDN	WM	7	①②
Zhou Zhong 2009[158]	72	50	83	39	63.67±7.25	65.27±9.35	WM+TRQ	WM	10~14	②⑤
Zuo Xiqing 2010[159]	30	30	48	12	70.35±5.12	70.85±4.04	WM+DH	WM	14	②⑤

Notes: ① Chinese Medical Symptom Scores; ② Clinical efficacy; ③ FEV_1; ④ Length of hospital stay; ⑤ Blood gas analysis; ⑥ Blood routine examination; ⑦ Sign; ⑧ Blood coagulation function; ⑨ Immunologic function; ⑩ Mechanical ventilation index; ⑪ FEV_1/FVC; ⑫ FEV_1 %.

Abbreviations: T1, treatment group 1; T2, treatment group 2; C, control group; WM, conventional Western medical therapy; CKZ, Chuankezhi injection; DH, Danhong injection; DS, Danshen injection; DZXX, Dengzhanxixin injection; HH, Honghua injection; HJT, Hongjingtian injection; HQ, Huangqi injection; KA, Kangai injection; KDZ, Kudiezi injection; QKL, Qingkailing injection; RDN, Reduning injection; SF, Shenfu injection; SGM, Shengmai injection; SM, Shenmai injection; SHL, Shuanghuanglian injection; SXN, Shuxuening injection; SXT, Shuxuetong injection; TRQ, Tanreqing injection; XYP, Xiyanping injection; XBJ, Xuebijing injection; XST, Xuesaitong injection; ZCL, Zhichuanling injection; Salvianolate, Salvianolate injection.

8767 patients, including 4461 and 4306 participants in the treatment group and control group, respectively. The sample size of these studies ranged from 26 to 220. The number of male and female patients was 5502 and 3127, respectively. However, one study did not report the sex ratio. The participant's ages ranged from 30 to 94 years. All included studies were conducted in China and among them one was a three-arm RCT and 102 were two-arm RCTs.

In total 23 CMIs were included: Chuankezhi injection (CKZ), Danhong injection (DH), Danshen injection (DS), Dengzhanxixin injection (DZXX), Honghua injection (HH), Hongjingtian injection (HJT), Huangqi injection (HQ), Kangai injection (KA), Kudiezi injection (KDZ), Qingkailing injection (QKL), Reduning injection (RDN), Shenfu injection (SF), Shengmai injection (SGM), Shenmai injection (SM), Shuanghuanglian injection (SHL), Shuxuening injection (SXN), Shuxuetong injection (SXT), Tanreqing injection (TRQ), Xiyanping injection (XYP), Xuebijing injection (XBJ), Xuesaitong injection (XST), Zhichuanling injection (ZCL), and Salvianolate injection (Salvianolate). Details about the included CMIs are given in Supplementary Table S1. The treatment duration ranged from 3 to 35 days.

Risk of Bias

The assessment of risk of bias for all the included studies is illustrated in Figure 2 and Supplementary Table S2.

Regarding random sequence generation, 32 studies used the correct stochastic grouping method and thus were assessed to have low risk, whereas two studies grouped with registration order and thus were assessed to have high risk. The remaining 69 studies reported "random allocation" without specific methods and were assessed to have unclear risk.

Regarding allocation concealment, 102 studies were assessed to have unclear risk because they did not describe their allocation methods. Moreover, one study allotted drugs with a specially assigned person and was assessed to have low risk.

Regarding blinding of participants and personnel, only three studies concealed the used interventions from patients, and thus, these studies were assessed to have low risk. The other 100 studies were assessed to have unclear risk.

Regarding blinding of outcome assessment, 42 studies did not describe the blinding of outcome assessment, but all results assessed using objective indicators, thus, these studies were assessed to have low risk. However, 16 studies used subjective indicators alone to assess result and thus were assessed to have high risk. The remaining studies were deemed to have unclear risk.

Regarding incomplete outcome data, the outcome data of all the included studies were complete, and thus, these studies were assessed to have low risk.

Regarding selective reporting, one study was assessed to have high risk due to the inconformity between its methods and results. The other studies did not report selectively and were assessed to have low risk.

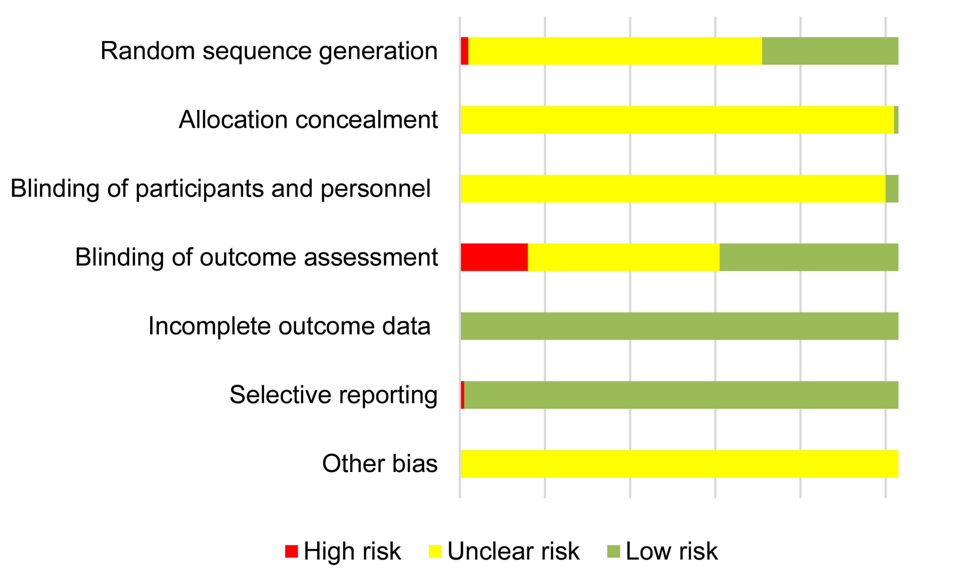

Figure 2 Assessment of the risk of bias.

All the included studies were deemed to have unclear risk of other bias because some details in these studies (eg, conflict of interest and registration scheme) were unclear.

Bayesian NMA Results

Clinical Efficacy

In total, 99 studies evaluated clinical efficacy, included 22 CMIs and 8326 patients. There are 98 two-arm and one three-arm RCTs, included 23 direct and 230 indirect comparisons. The network plot is presented in Figure 3A.

One closed loop formed in the network plot, and it required an inconsistency test of the direct and indirect comparisons in this closed loop. The results indicated that the inconsistent probability between direct and indirect comparisons in the closed loop WM–(WM+TRQ)–(WM+XBJ) was low (ROR=2.261, 95%CI: 1.00,6.65, *P*=0.139, Supplementary Figure S1 and Figure S2).

The clinical efficacy of WM+CKZ (OR=5.37, 95%CI: 1.93, 12.25), WM+DH (OR=6.34, 95%CI: 3.02, 11.96), WM+DS (OR=6.89, 95%CI: 1.33, 22.74), WM+DZXX (OR=115.4, 95%CI: 1.42, 514), WM+KDZ (OR=6.88, 95%CI: 1.18, 24.15), WM+QKL (OR=5.86, 95%CI: 1.04, 20.03), WM+RDN (OR=4.65, 95%CI: 2.11, 9.08), WM+SF (OR=4.87, 95%CI: 1.59,11.89), WM+SM (OR=4.51, 95%CI: 1.14, 12.99), WM+TRQ (OR=4.48, 95%CI: 3.28,6.02), and WM+XBJ (OR=3.52, 95%CI: 1.91, 6.1) was significantly higher than that of WM alone. Other comparisons did not show significant differences. The detailed results are shown in Table 2.

WM+DZXX was ranked the best in clinical efficacy (SUCRA=80.47%), followed by WM+DH (SUCRA=66.78%) and WM+HJT (SUCRA=65.66%). All SUCRA rankings for clinical efficacy are presented in Supplementary Table S3.

FEV_1

In total, 18 RCTs using eight of the CMIs reported FEV_1 improvements in AECOPD patients. The 18 RCTs (one three-arm and 17 two-arm) included 1715 patients. In total, 9 direct and 27 indirect comparisons formed. The network plot is presented in Figure 3B.

In the network plot of the included comparisons that reported FEV_1, one closed loop needed an inconsistency test. The direct and indirect comparisons of closed loop WM–(WM+TRQ)–(WM+XBJ) were consistent (ROR=1.004, 95%CI: 1.00, 2.38, *P*=0.993, Supplementary Figure S3 and Figure S4).

Of the eight CMIs, only WM+TRQ revealed significant differences in FEV_1 compared with WM alone (MD=0.42, 95%CI: 0.22, 0.62, Table 3). The network

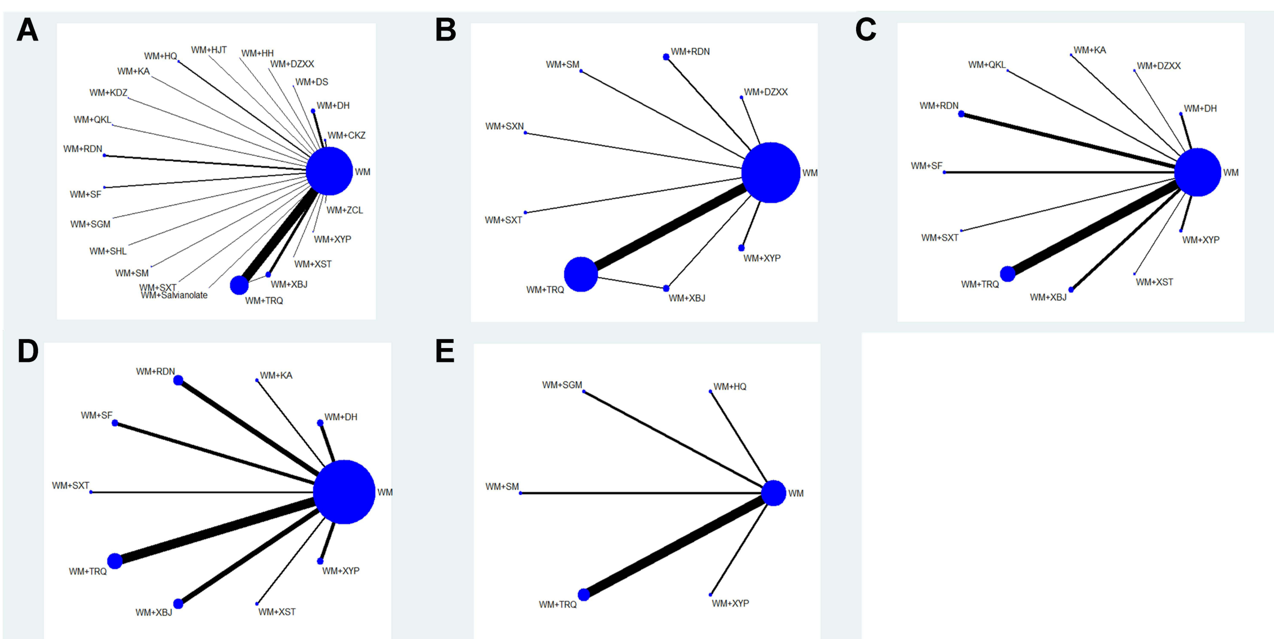

Figure 3 Network plot. (**A**) Clinical efficacy (**B**) FEV_1, (**C**) FEV_1/FVC, (**D**) FEV_1%, (**E**) Length of hospital stay.

Abbreviations: WM, conventional Western medical therapy; CKZ, Chuankezhi injection; DH, Danhong injection; DS, Danshen injection; DZXX, Dengzhanxixin injection; HH, Honghua injection; HJT, Hongjingtian injection; HQ, Huangqi injection; KA, Kangai injection; KDZ, Kudiezi injection; QKL, Qingkailing injection; RDN, Reduning injection; SF, Shenfu injection; SGM, Shengmai injection; SM, Shenmai injection; SHL, Shuanghuanglian injection; SXN, Shuxuening injection; SXT, Shuxuetong injection; TRQ, Tanreqing injection; XYP, Xiyanping injection; XBJ, Xuebijing injection; XST, Xuesaitong injection; ZCL, Zhichuanling injection; Salvianolate, Salvianolate injection.

Table 2 The Results of Network Meta-analysis of Clinical Efficacy

OR (95% CI)	WM	WM+CKZ	WM+DH	WM+DS	WM +DZXX	WM+HH	WM+HJT	WM+HQ	WM+KA	WM+KDZ	WM +QKL
WM	1										
WM+CKZ	5.37 (1.93, 12.25)[a]	1									
WM+DH	6.34 (3.02,11.96)[a]	1.47 (0.39,3.91)	1								
WM+DS	6.89 (1.33,22.74)[a]	1.6 (0.21,6.11)	1.23 (0.19,4.44)	1							
WM+DZXX	115.4 (1.42,514)[a]	27.03 (0.25,116.9)	20.44 (0.21,92.44)	27.07 (0.18,126.2)	1						
WM+HH	5.25 (0.75,19.02)	1.22 (0.12,5.01)	0.94 (0.11,3.66)	1.29 (0.08,6.02)	0.72 (0.01,4.43)	1					
WM+HJT	15.36 (0.95,77.41)	3.59 (0.16,18.94)	2.75 (0.14,14.33)	3.79 (0.11,21.22)	2.15 (0.01,13.97)	5.82 (0.14,33.05)	1				
WM+HQ	2.21 (0.86,4.74)	0.51 (0.12,1.46)	0.39 (0.11,1.02)	0.54 (0.07,1.95)	0.3 (0,1.65)	0.83 (0.09,3.35)	0.53 (0.02,2.55)	1			
WM+KA	14.96 (0.99,73.39)	3.5 (0.17,17.86)	2.67 (0.15,13.46)	3.6 (0.12,20.09)	2.02 (0.01,12.95)	5.61 (0.15,32.05)	3.52 (0.05,21.2)	8.16 (0.41,41.85)	1		
WM+KDZ	6.88 (1.18,24.15)[a]	1.6 (0.19,6.45)	1.23 (0.17,4.67)	1.69 (0.12,7.76)	0.95 (0.01,5.77)	2.59 (0.15,12.57)	1.65 (0.04,9.18)	3.76 (0.46,14.88)	1.63 (0.05,8.9)	1	
WM+QKL	5.86 (1.04,20.03)[a]	1.36 (0.16,5.33)	1.05 (0.15,3.9)	1.44 (0.11,6.5)	0.81 (0.01,4.85)	2.21 (0.13,10.72)	1.4 (0.04,7.71)	3.2 (0.41,12.34)	1.39 (0.04,7.5)	1.55 (0.1,7.1)	1
WM+RDN	4.65 (2.11,9.08)[a]	1.08 (0.28,2.92)	0.83 (0.27,1.99)	1.14 (0.16,3.95)	0.64 (0.01,3.42)	1.75 (0.2,6.88)	1.11 (0.05,5.26)	2.53 (0.71,6.57)	1.1 (0.05,5.04)	1.22 (0.15,4.42)	1.41 (0.18,4.98)
WM+SF	4.87 (1.59,11.89)[a]	1.13 (0.23,3.49)	0.87 (0.21,2.46)	1.2 (0.14,4.52)	0.67 (0.01,3.78)	1.83 (0.17,7.66)	1.16 (0.05,5.71)	2.66 (0.57,7.99)	1.16 (0.05,5.61)	1.29 (0.13,5.07)	1.47 (0.16,5.7)
WM+SGM	12.96 (0.76,65.29)	3 (0.13,16)	2.3 (0.11,12.04)	3.19 (0.09,17.75)	1.76 (0.01,11.57)	4.92 (0.11,28.38)	3.15 (0.04,19.09)	7.01 (0.32,37.55)	3.15 (0.04,18.65)	3.37 (0.09,19.29)	3.88 (0.11,22.07)
WM+SM	4.51 (1.14,12.99)[a]	1.05 (0.17,3.64)	0.81 (0.16,2.58)	1.11 (0.11,4.54)	0.62 (0.01,3.58)	1.71 (0.13,7.64)	1.08 (0.04,5.59)	2.46 (0.43,8.31)	1.07 (0.04,5.42)	1.19 (0.1,5.01)	1.37 (0.12,5.73)
WM+SHL	12.92 (0.85,64.72)	3 (0.14,15.91)	2.3 (0.13,11.9)	3.17 (0.1,17.66)	1.78 (0.01,11.62)	4.87 (0.13,28.5)	3.1 (0.04,18.82)	7.05 (0.35,36.75)	3.11 (0.04,18.92)	3.42 (0.1,19.23)	3.91 (0.12,22.12)
WM+SXT	8.69 (0.5,44.36)	2.04 (0.08,10.84)	1.55 (0.07,8.18)	2.15 (0.06,12.23)	1.21 (0,7.84)	3.33 (0.08,19.25)	2.09 (0.02,12.94)	4.73 (0.21,25.34)	2.08 (0.03,12.69)	2.3 (0.06,13.14)	2.63 (0.07,15.04)
WM+TRQ	4.48 (3.28,6.02)[a]	1.04 (0.34,2.41)	0.8 (0.35,1.56)	1.1 (0.19,3.46)	0.62 (0.01,3.19)	1.69 (0.23,6.1)	1.07 (0.06,4.8)	2.45 (0.89,5.39)	1.06 (0.06,4.59)	1.18 (0.18,3.9)	1.35 (0.21,4.4)
WM+XYP	2.93 (0.64,8.76)	0.68 (0.1,2.42)	0.52 (0.09,1.73)	0.72 (0.06,3)	0.4 (0,2.38)	1.1 (0.08,5.04)	0.7 (0.02,3.7)	1.6 (0.25,5.49)	0.69 (0.02,3.53)	0.77 (0.06,3.34)	0.88 (0.07,3.77)
WM+XBJ	3.52 (1.91,6.1)[a]	0.82 (0.24,2.08)	0.63 (0.23,1.4)	0.86 (0.13,2.88)	0.48 (0.01,2.56)	1.33 (0.16,5.04)	0.84 (0.04,3.9)	1.92 (0.6,4.69)	0.83 (0.04,3.74)	0.93 (0.13,3.22)	1.06 (0.15,3.64)
WM+XST	82.43 (0.5228.6)	17.99 (0.09,53.05)	15.58 (0.08,40.28)	17.17 (0.06,55.81)	6.33 (0.01,30.04)	59.16 (0.08,85.58)	21.27 (0.03,52.97)	41.88 (0.22,125.1)	17.74 (0.03,52.69)	22.32 (0.06,59.95)	22.45 (0.08,69.31)
WM+ZCL	7.36 (0.38,37.47)	1.71 (0.06,9.09)	1.31 (0.06,6.91)	1.8 (0.05,10.11)	1.01 (0,6.51)	2.77 (0.06,15.95)	1.74 (0.02,10.62)	4 (0.16,21.4)	1.76 (0.02,10.63)	1.95 (0.05,11.19)	2.24 (0.05,12.62)

WM +RDN	WM+SF	WM+SGM	WM+SM	WM+SHL	WM+SXT	WM +TRQ	WM+XYP	WM+XBJ	WM+XST	WM +ZCL	WM +Salvianolate
1											
1.2 (0.29,3.42)	1										
3.2 (0.15,16.77)	3.47 (0.14,18.65)	1									
1.12 (0.21,3.6)	1.21 (0.18,4.28)	1.33 (0.04,6.94)	1								
3.22 (0.17,16.58)	3.44 (0.16,18.34)	3.82 (0.05,23.59)	4.19 (0.16,22.9)	1							
2.14 (0.1,11.31)	2.32 (0.09,12.57)	2.54 (0.03,15.88)	2.83 (0.09,15.53)	2.36 (0.03,14.39)	1						
1.11 (0.46,2.24)	1.2 (0.36,2.91)	1.32 (0.07,5.99)	1.46 (0.33,4.03)	1.21 (0.07,5.31)	1.98 (0.1,9.17)	1					
0.72 (0.12,2.43)	0.78 (0.11,2.84)	0.86 (0.03,4.53)	0.95 (0.11,3.69)	0.79 (0.03,4.08)	1.28 (0.04,6.84)	0.67 (0.14,2.04)	1				
0.87 (0.31,1.99)	0.94 (0.25,2.51)	1.03 (0.05,4.84)	1.14 (0.23,3.39)	0.95 (0.05,4.34)	1.55 (0.07,7.4)	0.8 (0.4,1.46)	1.87 (0.34,5.99)	1			
19.3 (0.1,56.43)	22.14 (0.1,61.29)	21.12 (0.03,65.18)	25.91 (0.1,74.21)	15.18 (0.03,59.7)	44.7 (0.05,97.04)	18.3 (0.11,52.22)	40.23 (0.16,122.1)	22.91 (0.14,71.32)	1		
1.82 (0.08,9.53)	1.98 (0.07,10.56)	2.15 (0.02,13.25)	2.42 (0.07,13.38)	1.96 (0.02,11.99)	3.2 (0.03,19.75)	1.68 (0.08,8.62)	3.93 (0.11,21.65)	2.29 (0.1,11.82)	2.59 (0.01,17.35)	1	

(*Continued*)

Table 2 (Continued).

OR (95% CI)	WM	WM+CKZ	WM+DH	WM+DS	WM +DZXX	WM+HH	WM+HJT	WM+HQ	WM+KA	WM+KDZ	WM +QKL
WM +Salvianolate	2.69 (0.36,10.05)	0.63 (0.06,2.64)	0.48 (0.05,1.93)	0.66 (0.04,3.14)	0.37 (0,2.28)	1.02 (0.05,5.14)	0.65 (0.01,3.63)	1.47 (0.14,6.06)	0.63 (0.02,3.51)	0.71 (0.04,3.45)	0.82 (0.04,3.95)

Note: [a]The 95%CIs of the ORs did not contain 1.
Abbreviations: OR, odds ratio; CI, confidence interval; WM, conventional Western medical therapy; CKZ, Chuankezhi injection; DH, Danhong injection; DS, Danshen injection; DZXX, Dengzhanxixin injection; HH, Honghua injection; HJT, Hongjingtian injection; HQ, Huangqi injection; KA, Kangai injection; KDZ, Kudiezi injection; QKL, Qingkailing injection; RDN, Reduning injection; SF, Shenfu injection; SGM, Shengmai injection; SM, Shenmai injection; SHL, Shuanghuanglian injection; SXT, Shuxuetong injection; TRQ, Tanreqing injection; XYP, Xiyanping injection; XBJ, Xuebijing injection; XST, Xuesaitong injection; ZCL, Zhichuanling injection; Salvianolate, Salvianolate injection.

Table 3 The Results of Network Meta-analysis of FEV_1

MD (95%CI)	WM	WM +DZXX	WM+RDN	WM+SM	WM+SXN	WM+SXT	WM+TRQ	WM+XYP	WM +XBJ
WM	0								
WM +DZXX	0.33 (−0.34, 1)	0							
WM +RDN	0.31 (−0.12, 0.75)	−0.02 (−0.82, 0.78)	0						
WM+SM	0.59 (0, 1.18)	0.26 (−0.63, 1.15)	0.28 (−0.46, 1.01)	0					
WM +SXN	0.38 (−0.21, 0.97)	0.05 (−0.84, 0.94)	0.07 (−0.67, 0.8)	−0.21 (−1.05, 0.63)	0				
WM +SXT	0.21 (−0.39, 0.81)	−0.12 (−1.02, 0.78)	−0.1 (−0.84, 0.64)	−0.38 (−1.22, 0.46)	−0.17 (−1.01, 0.67)	0			
WM +TRQ	0.42 (0.22, 0.62)[a]	0.09 (−0.61, 0.79)	0.11 (−0.37, 0.58)	−0.17 (−0.8, 0.45)	0.04 (−0.59, 0.66)	0.21 (−0.42, 0.84)	0		
WM +XYP	0.25 (−0.17, 0.67)	−0.08 (−0.87, 0.71)	−0.06 (−0.67, 0.54)	−0.34 (−1.07, 0.39)	−0.13 (−0.86, 0.6)	0.04 (−0.69, 0.77)	−0.17 (−0.64, 0.3)	0	
WM+XBJ	0.3 (−0.25, 0.85)	−0.03 (−0.9, 0.83)	−0.01 (−0.71, 0.69)	−0.29 (−1.1, 0.52)	−0.08 (−0.89, 0.73)	0.09 (−0.72, 0.9)	−0.12 (−0.67, 0.44)	0.05 (−0.65, 0.75)	0

Note: [a]The 95%CIs of the MDs did not contain 0.
Abbreviations: MD, mean difference; CI, confidence interval; WM, conventional Western medical therapy; DZXX, Dengzhanxixin injection; RDN, Reduning injection; SM, Shenmai injection; SXN, Shuxuening injection; SXT, Shuxuetong injection; TRQ, Tanreqing injection; XYP, Xiyanping injection; XBJ, Xuebijing injection.

analysis showed no significant differences between other comparisons.

In the probability rankings, WM+SM (SUCRA=80.18%) was the most likely to improve FEV_1 in the patients with AECOPD, followed by WM+TRQ (SUCRA=66.73%), WM +SXN (SUCRA=58.81%). SUCRA rankings for FEV_1 are presented in Supplementary Table S3.

FEV_1/FVC

In 27 two-arm RCTs, the changes in FEV_1/FVC before and after treatment with 11 CMIs plus WM in 2362 patients with AECOPD were examined. This led to 11 direct and 55 indirect comparisons forming. The network plot for FEV_1/FVC is shown in Figure 3C.

Of the 11 CMIs, WM+DZXX (MD=19.25, 95%CI: 9.15, 29.32), WM+KA (MD=8.14, 95%CI: 0.24, 16.05), WM +RDN (MD=8.8, 95%CI: 4.41, 13.28), and WM+TRQ (MD=6.54, 95%CI: 3.84, 9.27) were more effective than WM alone in improving the FEV_1/FVC in patients with AECOPD. Moreover, WM+DH was inferior to WM+DZXX (MD=17.96, 95%CI: 6.52, 29.43) and WM+RDN (MD=7.52, 95%CI: 0.52, 14.57), whereas WM+DZXX was superior to

WM +RDN	WM+SF	WM+SGM	WM+SM	WM+SHL	WM+SXT	WM +TRQ	WM+XYP	WM+XBJ	WM+XST	WM +ZCL	WM +Salvianolate
0.66 (0.07,2.69)	0.72 (0.06,3.1)	0.8 (0.02,4.54)	0.88 (0.06,3.94)	0.73 (0.02,4.07)	1.19 (0.03,6.74)	0.61 (0.08,2.32)	1.44 (0.09,6.7)	0.83 (0.09,3.26)	0.99 (0.01,6.26)	1.53 (0.03,8.85)	1

WM+QKL (MD = −16.17, 95%CI: −29.36,−2.95), WM+SF (MD = −15.35, 95%CI: −27, −3.7), WM+SXT (MD = −16.51, 95%CI: −29.45, −3.55), WM+TRQ (MD = −12.71, 95%CI: −23.11, −2.25), WM+XYP (MD = −16.39, 95%CI: −28.05, −4.71), and WM+XBJ (MD = −14.8, 95%CI: −26.04, −3.52). The detailed results are shown in Table 4. Other comparisons did not reach statistical significance.

WM+DZXX was ranked the best in FEV_1/FVC (SUCRA=98.55%), followed by WM+RDN (SUCRA=77.15%) and WM+KA (SUCRA=69.47%). SUCRA rankings for FEV_1/FVC are presented in Supplementary Table S3.

FEV_1 %

FEV_1% was reported in 20 two-arm RCTs, including nine CMIs and 1838 patients—forming 9 direct and 36 indirect comparisons. The network plot for FEV_1% is shown in Figure 3D.

WM+RDN (MD=11.5, 95%CI: 6.57, 16.41), WM +TRQ (MD=6.64, 95%CI: 2.58, 10.64), WM+XYP (MD=9.12, 95%CI: 2.57, 15.56), WM+XBJ (MD=8.39, 95%CI: 2.91, 13.79) were significantly superior to WM alone in increasing FEV_1%. Other comparisons did not show significant results. The detailed results are shown in Table 5.

For FEV_1%, WM+RDN (SUCRA=87.28%) was ranked the best, followed by WM+XYP (SUCRA=69.75%), WM +XBJ (SUCRA=64.86%). SUCRA rankings for FEV_1% are presented in Supplementary Table S3.

Length of Hospital Stay

Eight two-arm RCTs including five CMIs and 717 patients recorded the length of hospital stay and formed 5 direct and 10 indirect comparisons. The network plot for length of hospital stay is shown in Figure 3E.

WM+SGM (MD = −6.9, 95%CI: −10.89, −2.9) and WM+TRQ (MD = −3.07, 95%CI: −4.97, −1.15) led to a shorter length of hospital stay than did WM alone (Table 6). There was no significant difference in other comparisons.

In terms of shortening the length of hospital stay, WM+SGM (SUCRA=94.70%) was ranked the best, followed by WM+SM (SUCRA=57.49%) and WM+XYP (SUCRA=55.85%). SUCRA rankings for length of hospital stay are presented in Supplementary Table S3.

Cluster Analysis Plot for Outcomes

Cluster analysis was performed on clinical efficacy and FEV_1, clinical efficacy and FEV_1/FVC, clinical efficacy and FEV_1%, clinical efficacy and length of hospital stay so as to find the best interventions. The results showed that the most favorable response by WM+DZXX were for clinical efficacy and FEV_1 as well as for clinical efficacy and FEV_1/FVC, by WM+RDN were for clinical efficacy and FEV_1%, and by WM+SGM were for clinical efficacy and length of hospital stay (Figure 4).

Publication Bias

Begg's test was used to identify the possible publication bias related to the different interventions and the impact of small sample studies. The results demonstrated potential publication bias in the funnel plot of clinical efficacy (P=0.000), suggesting that the publication bias was small in the funnel plot for FEV_1 (P=0.347), FEV_1/FVC (P=0.359), and FEV_1% (P=0.381, Supplementary Figure S5). Because the number of included studies that reported the length of hospital stay was <10, we did not assess the publication bias for length of hospital stay.

Safety

Of the 103 included RCTs, 49 reported regarding adverse reactions, of these 49 studies, 29 reported that no adverse reactions appeared. The remaining 20 studies included 1539 patients and 12 TCM injections. Of the 742 patients who received WM, 50 (6.74%) had the following adverse

Table 4 The Results of Network Meta-analysis of FEV_1/FVC

MD (95% CI)	WM	WM+DH	WM+DZXX	WM+KA	WM+QKL	WM+RDN	WM+SF	WM+SXT	WM+TRQ	WM +XYP	WM+XBJ	WM +XST
WM	0											
WM+DH	1.28 (−4.17, 6.75)	0										
WM +DZXX	19.25 (9.15, 29.32)[a]	17.96 (6.52, 29.43)[a]	0									
WM+KA	8.14 (0.24, 16.05)[a]	6.86 (−2.74, 16.47)	−11.11 (−23.9, 1.71)	0								
WM +QKL	3.07 (−5.44, 11.6)	1.79 (−8.33, 11.9)	−16.17 (−29.36, −2.95)[a]	−5.07 (−16.68, 6.55)	0							
WM +RDN	8.8 (4.41, 13.28)[a]	7.52 (0.52, 14.57)[a]	−10.44 (−21.4, 0.59)	0.66 (−8.36, 9.77)	5.73 (−3.82, 15.38)	0						
WM+SF	3.89 (−1.93, 9.72)	2.61 (−5.36, 10.59)	−15.35 (−27, −3.7)[a]	−4.25 (−14.05, 5.59)	0.82 (−9.49, 11.16)	−4.91 (−12.29, 2.36)	0					
WM +SXT	2.74 (−5.37, 10.83)	1.46 (−8.31, 11.21)	−16.51 (−29.45, −3.55)[a]	−5.4 (−16.74, 5.91)	−0.34 (−12.1, 11.4)	−6.07 (−15.36, 3.12)	−1.16 (−11.14, 8.82)	0				
WM +TRQ	6.54 (3.84, 9.27)[a]	5.26 (−0.82, 11.37)	−12.71 (−23.11, −2.25)[a]	−1.6 (−9.94, 6.78)	3.47 (−5.44, 12.41)	−2.26 (−7.49, 2.92)	2.65 (−3.76, 9.1)	3.8 (−4.71, 12.38)	0			
WM +XYP	2.86 (−3.04, 8.76)	1.58 (−6.44, 9.61)	−16.39 (−28.05, −4.71)[a]	−5.28 (−15.14, 4.57)	−0.21 (−10.59, 10.13)	−5.94 (−13.37, 1.39)	−1.03 (−9.35, 7.28)	0.12 (−9.89, 10.14)	−3.68 (−10.19, 2.78)	0		
WM+XBJ	4.44 (−0.56, 9.5)	3.16 (−4.22, 10.61)	−14.8 (−26.04, −3.52)[a]	−3.7 (−13.03, 5.71)	1.37 (−8.49, 11.28)	−4.36 (−11.08, 2.32)	0.55 (−7.11, 8.27)	1.71 (−7.79, 11.26)	−2.1 (−7.8, 3.62)	1.59 (−6.12, 9.37)	0	
WM +XST	8.1 (0, 16.2)	6.82 (−2.97, 16.59)	−11.15 (−24.05, 1.74)	−0.04 (−11.36, 11.25)	5.03 (−6.76, 16.76)	−0.7 (−9.99, 8.48)	4.21 (−5.79, 14.18)	5.36 (−6.1, 16.83)	1.56 (−7, 10.09)	5.24 (−4.8, 15.22)	3.66 (−5.93, 13.17)	0

Note: [a]The 95%CIs of the MDs did not contain 0.

Abbreviations: MD, mean difference; CI, confidence interval; WM, conventional Western medical therapy; DH, Danhong injection; DZXX, Dengzhanxixin injection; KA, Kangai injection; QKL, Qingkailing injection; RDN, Reduning injection; SF, Shenfu injection; SXT, Shuxuetong injection; TRQ, Tanreqing injection; XYP, Xiyanping injection; XBJ, Xuebijing injection; XST, Xuesaitong injection.

Table 5 The Results of Network Meta-analysis of FEV_1%

MD (95% CI)	WM	WM+DH	WM+KA	WM+RDN	WM+SF	WM+SXT	WM+TRQ	WM+XYP	WM+XBJ	WM +XST
WM	0									
WM+DH	3.8 (−2.16, 9.78)	0								
WM+KA	5.58 (−2.87, 14.02)	1.78 (−8.57, 12.11)	0							
WM+RDN	11.5 (6.57, 16.41)[a]	7.7 (−0.06, 15.43)	5.92 (−3.85, 15.68)	0						
WM+SF	5.74 (−0.57, 12.07)	1.94 (−6.75, 10.63)	0.17 (−10.38, 10.72)	−5.76 (−13.75, 2.26)	0					
WM+SXT	6.8 (−2.08, 15.66)	3 (−7.71, 13.68)	1.22 (−11, 13.45)	−4.7 (−14.84, 5.43)	1.06 (−9.85, 11.94)	0				
WM+TRQ	6.64 (2.58, 10.64)[a]	2.84 (−4.4, 10.01)	1.07 (−8.32, 10.37)	−4.86 (−11.23, 1.47)	0.9 (−6.63, 8.36)	−0.15 (−9.92, 9.56)	0			
WM+XYP	9.12 (2.57, 15.56)[a]	5.32 (−3.57, 14.08)	3.55 (−7.18, 14.13)	−2.38 (−10.57, 5.72)	3.38 (−5.74, 12.39)	2.33 (−8.72, 13.25)	2.48 (−5.19, 10.09)	0		
WM+XBJ	8.39 (2.91, 13.79)[a]	4.59 (−3.55, 12.61)	2.82 (−7.29, 12.82)	−3.11 (−10.47, 4.18)	2.65 (−5.73, 10.94)	1.59 (−8.86, 11.95)	1.75 (−5.02, 8.51)	−0.73 (−9.19, 7.75)	0	
WM+XST	7.59 (−1.01, 16.19)	3.78 (−6.69, 14.24)	2.01 (−10.03, 14.06)	−3.92 (−13.82, 6.02)	1.84 (−8.83, 12.52)	0.79 (−11.56, 13.16)	0.94 (−8.51, 10.48)	−1.54 (−12.25, 9.32)	−0.81 (−10.92, 9.42)	0

Note: [a]The 95%CIs of the MDs did not contain 0.

Abbreviations: MD, mean difference; CI, confidence interval; WM, conventional Western medical therapy; DH, Danhong injection; KA, Kangai injection; RDN, Reduning injection; SF, Shenfu injection; SXT, Shuxuetong injection; TRQ, Tanreqing injection; XYP, Xiyanping injection; XBJ, Xuebijing injection; XST, Xuesaitong injection.

Table 6 The Results of Network Meta-analysis of Length of Hospital Stay

MD (95%CI)	WM	WM+HQ	WM+SGM	WM+SM	WM+TRQ	WM+XYP
WM	0					
WM+HQ	−2.08 (−5.83, 1.67)	0				
WM+SGM	−6.9 (−10.89, −2.9)[a]	−4.82 (−10.28, 0.68)	0			
WM+SM	−3.44 (−7.42, 0.55)	−1.36 (−6.82, 4.11)	3.46 (−2.21, 9.09)	0		
WM+TRQ	−3.07 (−4.97, −1.15)[a]	−0.99 (−5.18, 3.24)	3.83 (−0.61, 8.27)	0.37 (−4.03, 4.79)	0	
WM+XYP	−3.4 (−8.03, 1.22)	−1.32 (−7.25, 4.61)	3.5 (−2.61, 9.59)	0.04 (−6.05, 6.13)	−0.33 (−5.35, 4.67)	0

Note: [a]The 95%CIs of the MDs did not contain 0.
Abbreviations: MD, mean difference; CI, confidence interval; WM, conventional Western medical therapy; HQ, Huangqi injection; SGM, Shengmai injection; SM, Shenmai injection; TRQ, Tanreqing injection; XYP, Xiyanping injection.

reactions: nausea and vomiting (n=16), fever (n=12), gastrointestinal reactions (n=6), rash (n=6), sweating (n=5), xerostomia (n=4), and chest distress (n=1). In contrast, of the 797 patients who received TCM injections plus WM, 55 patients (6.90%) had the following adverse reactions: nausea and vomiting (n=11), fever (n=8), dizziness (n=4), xerostomia (n=4), gastrointestinal reaction (n=6), phlebitis (n=4), chest distress (n=1), epigastric discomfort (n=2), bellyache (n=2), itchy skin (n=2), rash (n=2), allergy (n=2), local pain during intravenous infusion (n=2),

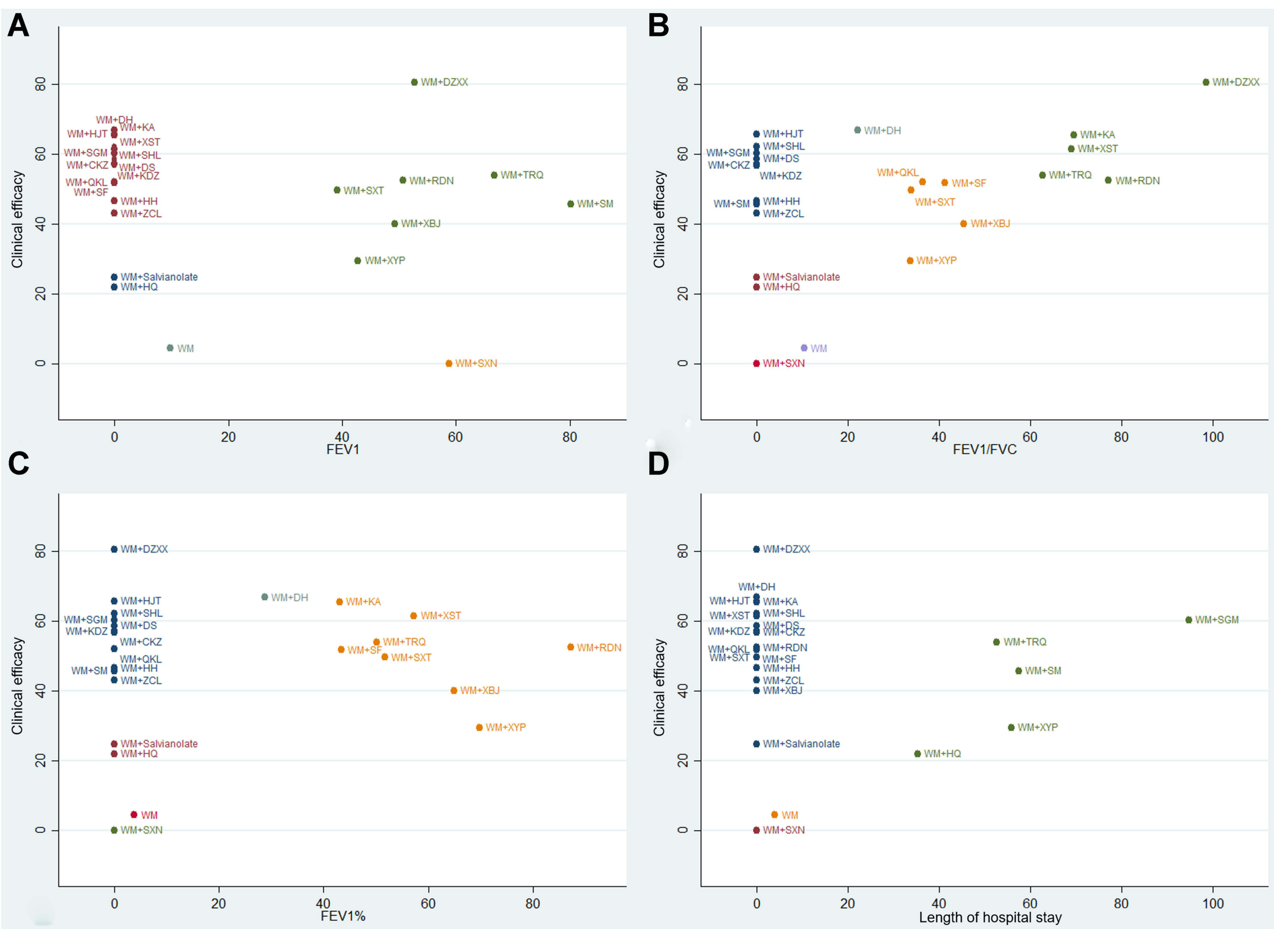

Figure 4 Cluster analysis plot for outcomes ((**A**) Clinical efficacy and FEV_1 (**B**) Clinical efficacy and FEV_1/FVC (**C**) Clinical efficacy and FEV_1% (**D**) Clinical efficacy and length of hospital stay)).
Abbreviations: WM; conventional Western medical therapy; CKZ; Chuankezhi injection; DH; Danhong injection; DS; Danshen injection; DZXX; Dengzhanxixin injection; HH; Honghua injection; HJT; Hongjingtian injection; HQ; Huangqi injection; KA; Kangai injection; KDZ; Kudiezi injection; QKL; Qingkailing injection; RDN; Reduning injection; SF; Shenfu injection; SGM; Shengmai injection; SM; Shenmai injection; SHL; Shuanghuanglian injection; SXN; Shuxuening injection; SXT; Shuxuetong injection; TRQ; Tanreqing injection; XYP; Xiyanping injection; XBJ; Xuebijing injection; XST; Xuesaitong injection; ZCL; Zhichuanling injection; Salvianolate; Salvianolate injection.

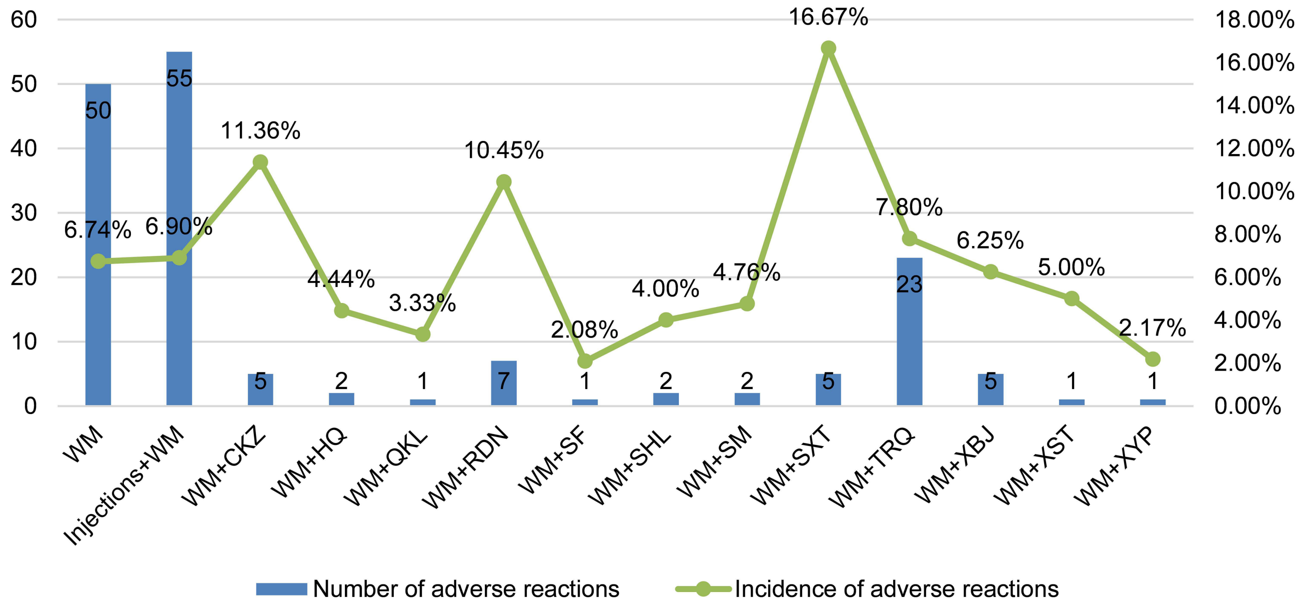

Figure 5 Number and incidence of adverse reactions of the included interventions.
Abbreviations: WM; conventional Western medical therapy; CKZ; Chuankezhi injection; HQ; Huangqi injection; QKL; Qingkailing injection; RDN; Reduning injection; SF; Shenfu injection; SM; Shenmai injection; SHL; Shuanghuanglian injection; SXT; Shuxuetong injection; TRQ; Tanreqing injection; XYP; Xiyanping injection; XBJ; Xuebijing injection; XST; Xuesaitong injection.

palpitation (n=1), headache (n=1), diarrhea (n=1), and dizziness+chest distress+xerostomia (n=2). Of the 12 TCM injections, the highest incidence of adverse reactions was noted after WM+SXT (16.67%), followed by WM+CKZ (11.36%) and WM+RDN (10.45%). Adverse reactions were shown in Figure 5 and Supplementary Table S4. WM alone and TCM injections plus WM both had the following common adverse reactions: fever, nausea and vomiting, xerostomia, gastrointestinal reaction, and rash (Figure 6).

Discussion

This study included 103 RCTs, with 8767 patients and 23 CMIs including CKZ, DH, DS, DZXX, HH, HJT, HQ, KA, KDZ, QKL, RDN, SF, SGM, SM, SHL, SXN, SXT, TRQ, XYP, XBJ, XST, ZCL, and Salvianolate.

In patients with AECOPD, WM+DZXX had the highest likelihood of being the best treatment for improving both the clinical efficacy and FEV_1/FVC, WM+SM, WM+RDN and WM+SGM had the highest likelihood of being the best treatment for improving FEV_1, FEV_1%, and length of hospital stay, respectively.

The cluster analysis revealed that WM+DZXX had the most favorable response for clinical efficacy and FEV_1, as well as clinical efficacy and FEV_1/FVC, WM+RDN had the most favorable response for clinical efficacy and FEV_1%, WM+SGM had the most favorable response for clinical efficacy and length of hospital stay.

DZXX is a sterile aqueous solution composed of Erigerontis Herba extract, has been used in China for many years. Its main active components include flavonoids and phenolic acids.[31] Flavonoids can activate blood and dissolve stasis as well as inhibit the inflammatory reaction in the lung and the synthesis of collagen fiber to prevent pulmonary fibrosis.[32] Clinical studies have shown that compared with WM alone, DZXX achieved better efficacy when administered to patients with moderately severe COPD, it could not only reduce inflammation, but also improve hemorheological indicators and lung function.[33] Experimental studies show that DZXX can decrease transforming growth factor β1 activity to inhibit fibroblast proliferation, collagen fiber and extracellular matrix synthesis, delaying or improving the process of airway remodeling and irreversible obstruction in COPD.[34–36]

RDN is composed of Artemisiae Annuae Herba, Lonicerae Japonicae Flos, and Gardeniae Fructus, is generally administered as an intravenous injection to treat cold, cough, upper respiratory infections, and acute bronchitis, and it has a good curative effect in clinics.[37,38] Previous studies have shown that cryptochlorogenic acid, neochlorogenic acid, and geniposide—the main active substances of RDN[39–44]—can increase superoxide dismutase (SOD) activity, suppress myeloperoxidase (MPO)

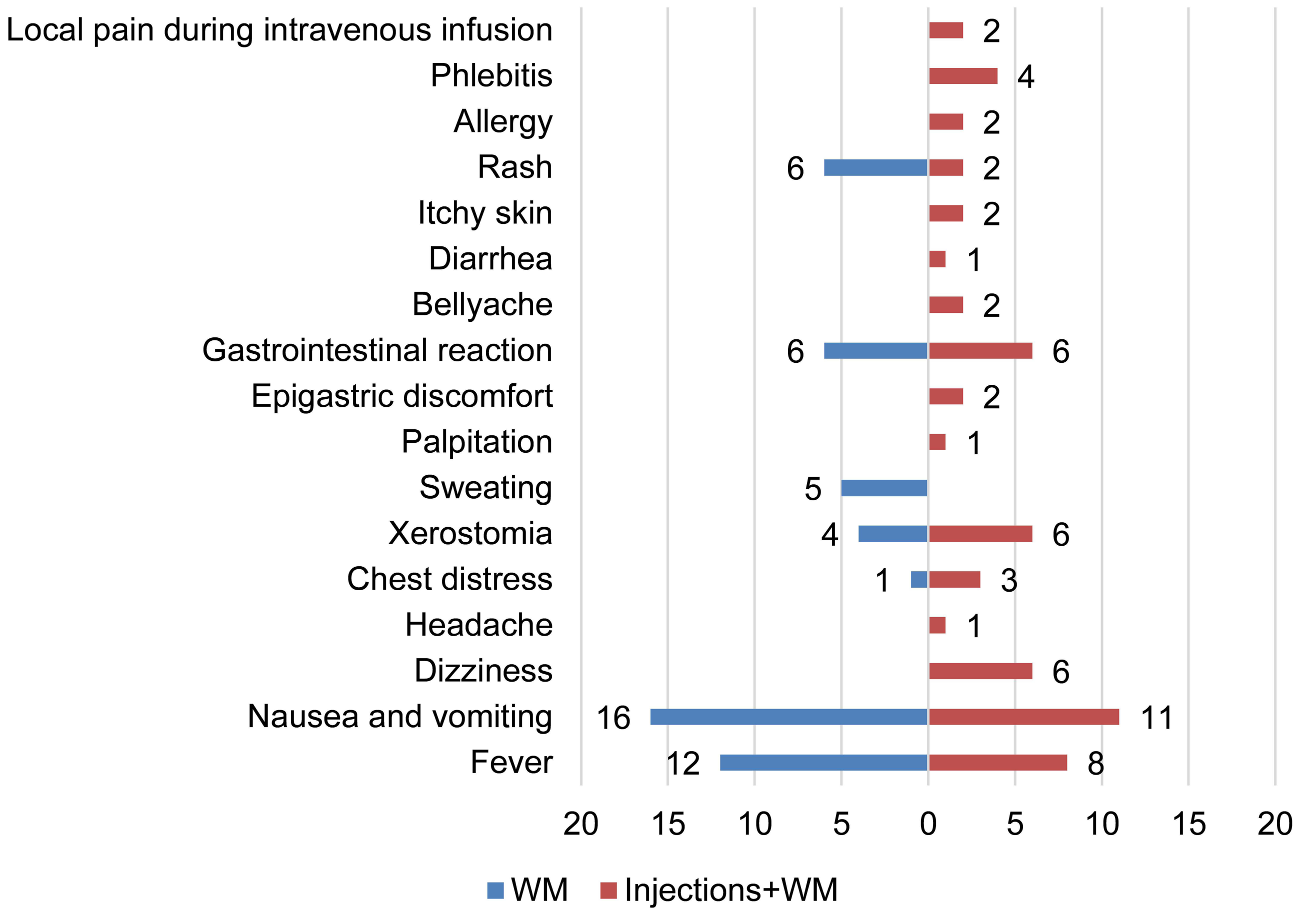

Figure 6 Adverse reactions after WM alone and TCM injections plus WM.
Abbreviation: WM; conventional Western medical therapy.

activity, and reduce the wet/dry (W/D) ratio and total leukocyte and neutrophil numbers,[38] it can thus be anti-inflammatory, improve immunity, and alleviate damage caused by the diseases.[45,46] In addition, a network analysis identified two key compounds (CFA and ferulic acid), five key targets (Bcl-2, eNOS, PTGS2, PPARA, and MMPs), and four key pathways (estrogen signaling pathway, PI3K-AKT signaling pathway, cGMP-PKG signaling pathway, and calcium signaling pathway) for RDN—all of which play critical roles in the treatment of inflammatory diseases.[47]

The normal respiratory movement of the human body involves the joint participation of nerve cells that produces the respiratory rhythm and those that regulate the respiratory movement in the central nervous system.[48] Studies have shown that the irreversible airflow limitation of COPD may be related to the abnormal excitability of the respiratory center.[48] SGM is composed of Red Ginseng, Ophiopogonis Radix, and Schisandrae Chinensis Fructus. Here, Ophiopogonis Radix nourishes the yin (nutrition and fluid in the human body, which nourishes various organs[49]), Schisandrae Chinensis Fructus astringents the qi (vital energy, regarded as a driving force of biological activities in the human body, including both nutrient substances and organ functions[50]) and has antitussive effects, and Red Ginseng tonifies qi and enhances immunity.[51] The combination of these herbs affects the respiratory center and then relieves dyspnea in COPD patients.[52,53] Modern studies have also indicated that SGM can improve pulmonary ventilation function, thus increasing the alveolar diffuse area, adjusting the airflow ratio, reducing myocardial oxygen consumption and glucose metabolism, and enhancing gland and endocrine function, as a result, the whole body function is adjusted, qi becomes tonified and blood is activated.[54] A meta-analysis reported that SGM+WM has significant efficacy in COPD treatment, where it improves clinical efficacy and lung function, regulates immune function, and shortens disappearance time of lung rales.[55,56]

Adverse reactions appeared in both treatment group and control group of included studies. However, the specific correlation between the TCM injections used and adverse reactions could not be determined. The incidence of adverse reactions was high in WM+SXT (16.67%), WM+CKZ (11.36%), and WM+RDN (10.45%), compared with WM alone. Thus, the safety of CMIs still needs further evaluation.

Limitations

The number of original studies on this research topic met the basic requirements for this NMA, but the quality of these studies were not high. In particular, the limitations of our study were as follows:

(1) Only 31.07% of the studies used the correct random method, which may have resulted in selective biases.

(2) Most of the studies did not mention the blinding of participants or personnel and allocation concealment, which may have resulted in implementation biases.

(3) Of all the included studies, 15.53% merely used subjective indicators as the outcome evaluation index, which may have resulted in measurement bias.

(4) The 103 included studies did not mention protocol registration and conflict of interests, therefore, the sources of other bias could not be determined.

(5) The funnel plot for clinical efficacy indicated the possibility of publication bias. The missing contents from ongoing studies and gray literature may result in publication bias.[55]

(6) None of the included studies restricted the TCM syndromes of AECOPD patients. However, patients with different TCM syndromes who were treated with the same intervention may not represent the real effect of the TCM drugs.

(7) The participant age and treatment duration varied in the included studies, which may have affected the stability of results.

(8) All included studies were conducted in China, this might weaken the generalization of the results.

Conclusion

In conclusion, WM+DZXX had the highest likelihood of being the best treatment for improving both the clinical efficacy and FEV_1/FVC, WM+SM, WM+RDN and WM +SGM had the highest likelihood of being the best treatment for improving FEV_1, FEV_1% and length of hospital stay, respectively. Combined with cluster analysis results, DZXX, RDN or SGM plus WM were noted to be the optimum treatment regimens for improving the condition of patients with AECOPD. However, the quality of studies evaluating the efficacy of various CMIs is not good. Therefore, additional high-quality studies are warranted.

Abbreviations

COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; TCM, traditional Chinese medicine; CMI, Chinese medical injection; RCT, randomized controlled trial; CKZ, Chuankezhi injection; DH, Danhong injection; DS, Danshen injection; DZXX, Dengzhanxixin injection; HH, Honghua injection; HJT, Hongjingtian injection; HQ, Huangqi injection; KA, Kangai injection; KDZ, Kudiezi injection; QKL, Qingkailing injection; RDN, Reduning injection; SF, Shenfu injection; SGM, Shengmai injection; SM, Shenmai injection; SHL, Shuanghuanglian injection; SXN, Shuxuening injection; SXT, Shuxuetong injection; TRQ, Tanreqing injection; XYP, Xiyanping injection; XBJ, Xuebijing injection; XST, Xuesaitong injection; ZCL, Zhichuanling injection; Salvianolate, Salvianolate injection; WM, conventional Western medical therapy; ADR, adverse reaction; FEV_1, forced expiratory volume in one second; FEV_1/FVC, ratio of forced expiratory volume in one second to forced vital capacity; FEV_1%, ratio of forced expiratory volume in one second to the predicted value.

Data Sharing Statement

The raw data supporting the conclusion of this article will be made available by the corresponding author (Hui Wang) without undue reservation.

Ethics Approval and Consent to Participate

This study is an overview of the literature thus ethics approval was not needed.

Consent to Publish

The study group consented to publish.

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Disclosure

The authors report no conflicts of interest in this work.

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