

Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-402>

Reviewer A

(1) Aspects related to the PRISMA checklist:

- Include the registration number of the systematic review in the abstract.

Reply: The registration number of the systematic review had added in the abstract.

Changes in the text: see Page 2, line 42-43.

(2) Was there an attempt to contact the authors to obtain articles that were not available in full text in the databases?

Reply: We contacted the authors to obtain articles that were not available in full text in the databases.

(3) Are all articles selected in the review in Chinese? None in English? Chinese herbal injections are probably more used in the origin country? Can this be considered a risk of bias?

Reply: All the included RCTs were carried out among a Chinese population, this be considered a risk of bias, and we discussed it in discussion.

(4) Why not perform subgroup analysis?

Reply: The western medicine in some RCTs were not sufficiently elaborated, including information on drug dosage and delivery. This prevents us from conducting subgroup analyses for various routine treatment strategies.

(5) Are the reported effects really expected? Are the data from the systematic review corroborated with other data in the literature?

Reply: The data from the systematic review corroborated with other data in the literature.

Reviewer B

This is not a methodological and technically sound network meta-analysis.

First of all, the authors ignored the significant differences across western medicines and considered them as one intervention as a whole. This is not correct and wrong because

of the different effects of western medicines on the inflammatory factors.

Reply: We did not ignore the significant differences across western medicines. 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 were 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. It has been added in page 12-13, line 378-386.

The second concern is the authors focused on the combined effects of CHIs + WM on the inflammatory factors, but the title did not indicate such and is misleading.

Reply: The title has been changed: 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. (page 1, line 3-5)

The third concern is the pooling of different combination of CHIs + WMs is also problematic, because of the heterogeneity caused by WMs.

Reply: The heterogeneity caused by WMs has been discussed in page 12-13, line 378-386.

Fourth, in the introduction the authors described “it is warranted to explore the comparative effectiveness and safety between different CHIs plus WM against AECOPD” as the purpose but in the analysis the analyzed the inflammatory factors. Please explain why inflammatory factors can denote efficacy and safety. The current data are not suitable to do network meta-analysis. The authors should reconsider the research focus appropriate for the data and completely rewrite this paper.

Reply: The introduction has been rewritten. 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 western medicine could significantly reduce the level of inflammatory factors in AECOPD; many previously conducted double-arm meta-analyses have evaluated the effectiveness of CHIs on serum inflammatory factors in AECOPD. 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.

Reviewer C

This systematic review and network meta-analysis investigated the effect of Chinese herbal injections (CHIs) on inflammatory factors for patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). The topic is of high clinical relevance. The study design is generally correct. I have some comments.

1. Table 1: The number of sex in some studies (references 37, 65, 92) is incorrect; please check it.

Reply: The number format is incorrect and has been modified in Table 1.

2. Line 363: because this study only investigated the effect of CHI on serum inflammatory markers, it cannot conclude that CHI provides therapeutic benefits.

Reply: It has been revised: According to this NMA, compared with using RT alone, using a combination of CHIs with RT could significantly reduce the level of inflammatory factors in AECOPD.

3. Line 385: Therefore, the results of this NMA have great clinical significance. This sentence should be removed.

Reply: The sentence has been deleted.

4. Lines 388 to 394: The components of CHI were introduced. However, the possible mechanisms of the anti-inflammation effects of these components were not introduced.

Reply: Modern research has only found that CHIs can reduce levels of inflammatory factors, but the specific anti-inflammatory mechanisms still need to be studied.

5. The clinical implications of this study should be discussed in the discussion section.

Reply: It has been added in page 13, line 390-392.

6. Exclusion criteria: full text unavailable should not be listed as an exclusion criterion.

Reply: It has been revised in Figure 1.

7. Were all searched literature screened by two reviewers independently?

Reply: All searched literature screened by two reviewers independently.

8. Table 1 has a large size, and I suggest submitting it as a supplementary table.

Reply: This table is usually included in the text. If there are any formatting issues, it can be submitted as a supplementary table.

9. Please report the methods to resolve the disagreement in data extraction and quality assessment.

Reply: Discrepancies were discussed with a third party and resolved by consensus.
(Page 6, line 161-162)

10. The results of publication bias should be discussed.

Reply: It has been added in page 12-13, line 378-386.