



The efficacy and safety of combined traditional Chinese and western medicine in the treatment of chronic obstructive pulmonary disease complicated with respiratory failure: a systematic review and meta-analysis study

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Background: The conventional drugs to treat chronic obstructive pulmonary disease (COPD) complicated with respiratory failure (RF) (COPD + RF) in western medicine include antibiotics, etc., but the patients have serious adverse reactions and are prone to drug resistance. This study aims to analyze the curative effect of traditional Chinese medicine (TCM) combined with Western medicine (WM) in treating COPD + RF.

Methods: Randomized controlled studies on the treatment of COPD with RF were searched in PubMed, Web of Science, Embase, and The Cochrane Library. Outcome measures were treatment efficiency, oxygen partial pressure (PO₂), partial pressure of carbon dioxide (PCO₂), and pulmonary function [forced expiratory volume in 1 second (FEV1)%]. The Cochrane Reviewer's Handbook 4.2.5 was adopted for quality assessment of studies, and the data was analyzed using RevMan 5.3.

Results: Seven suitable articles were selected, including 490 patients. The literature quality met the requirements of this article, and there was no obvious publication bias. The effective rate of patients in the combined TCM and WM treatment group and control group (WM treatment) was analyzed as odds ratio (OR) [95% confidence interval (CI): 5.40 (3.14 to 9.29)], and statistically tested as $Z=6.09$ ($P<0.00001$). The analysis structure of PO₂ after treatment was mean difference (MD) (95% CI): 5.92 (2.27 to 9.56), and the statistical analysis suggested $Z=3.18$, $P=0.001$. The analysis of PCO₂ after treatment was MD (95% CI): -4.53 (-7.14 to -1.92), and $Z=3.40$, $P=0.0007$. The analysis structure of lung function index data was MD (95% CI): 8.16 (2.57 to 13.75), and $Z=2.86$ ($P=0.004$).

Discussion: The TCM combined with WM can effectively treat the symptoms related to COPD; the treatment efficiency is significantly improved compared with traditional WM; and the PO₂, PCO₂, and lung function (FEV1%) are improved for sure after treatment. Data of this study show that the combined treatment of TCM and WM has a good therapeutic effect on the acute exacerbation of COPD complicated with RF, which is worthy of clinical application. However, the included outcome indexes in this study were not sufficient, and the sample size and outcome indexes should be further expanded in the future.

Keywords: Traditional Chinese medicine (TCM); Western medicine; chronic obstructive pulmonary disease (COPD); respiratory failure

Submitted Feb 16, 2022. Accepted for publication Mar 18, 2022.

doi: 10.21037/apm-22-272

View this article at: <https://dx.doi.org/10.21037/apm-22-272>

Introduction

Chronic obstructive pulmonary disease (COPD) is featured with progressive airflow restriction that is not completely reversible, and it is more frequent in people aged over 40. It can have adverse effects on extra-pulmonary tissues and organs. Acute exacerbation caused by COPD (AECOPD) commonly leads to type II respiratory failure (RF), which is associated with a very high mortality rate (1-3). Treatments for COPD include infection control, airway relief, correcting water, electrolyte, and acid-base imbalances. In addition, it is important to actively improve oxygenation and combat RF. The ideal living environment for patients with COPD tends to be high altitude. Long-term oxygen therapy, inhaled corticosteroids, and bronchial pipette can effectively relieve the symptoms of patients with COPD. These treatments reduce hypoxemia and airway obstruction to some extent and significantly benefit the patient's subsequent treatment (4-6). However, respiratory muscle fatigue, poor nighttime respiratory center response, and carbon dioxide retention may contribute to further disease progression for patients with RF.

However, traditional treatment alone is not sufficient. Ko *et al.* [2016] (7) pointed out that excessive oxygen delivery may lead to increased carbon dioxide retention, which may worsen the disease, seriously affect lung function and quality of life, and even endanger patients' lives. Sudden deterioration is a common reason for emergency department visits and hospitalizations in patients with COPD. In the United States, from 1993 to 2005, acute exacerbation of chronic obstructive pulmonary disease (AECOPD) resulted in an average of 600,000 emergency department visits per year (8). Research has shown that current health treatment for AECOPD includes smoking cessation, inhaled bronchodilators, systemic corticosteroids, intravenous aminophylline, antibiotics, controlled oxygen supply, and mechanical ventilation when necessary (9). Treatment for AECOPD is progressive based on the severity of the clinical presentation. Outside of China, traditional Chinese medicine (TCM) is a complementary medicine, which is alternative and unique theoretical in disease treatment. TCM regards COPD as a syndrome of dyspnea and cough (10,11). Traditional Chinese medicine believes that COPD combined with respiratory failure belongs to the deficiency of the essence and the yin-deficiency, mainly due to deficiency of vital energy (12). Therefore, modern medical methods combined with TCM dialectical treatment methods can be used in clinical

practice to improve the clinical symptoms of patients. To improve the survival rate of patients with COPD + RF, clinical application of TCM dialectical treatment, combined with conventional western medicine (WM) treatment (such as chemical drugs), can significantly improve the patient's pulmonary ventilation function and ensure the patient's smooth breathing (13,14). Phlegm-heat blocking the lung is the main etiology and pathogenesis of COPD complicated with RF (15). Therefore, clearing heat and removing blood stasis, dispersing the lung and dredging collaterals are the main points of TCM treatment of the disease. The heat-clearing and phlegm-resolving formula is often used in the treatment of COPD complicated with RF diseases (16). This work aimed to evaluate the efficacy and safety of combined TCM and WM (pure chemical) and conventional WM alone in the treatment of AECOPD by collecting randomized controlled clinical trials (RCTs) of heat-clearing and phlegm-resolving formula or injection.

At present, a large number of studies at home and abroad have confirmed that traditional Chinese medicine combined with western medicine can achieve excellent results in the treatment of COPD complicated with RF disease (17,18). The research scope of the existing meta-analysis is too broad, and there are many TCM treatment methods, and there is no unified method at present. However, whether the traditional Chinese medicine "clearing heat and resolving phlegm" category combined with western medicine can achieve excellent results in the treatment of this disease has not yet been systematically evaluated. In order to increase the systematic analysis of TCM in treating COPD complicated with RF and reduce the economic burden of COPD patients, this study retrieved many clinical RCTs of integrated TCM and WM in treating COPD complicated with RF, and carried out meta-analysis, with the aim of gathering reliable evidence to verify its efficacy and safety. We have provided a reference for the future clinical treatment of COPD combined with RF in the integrative medicine. We present the following article in accordance with the PRISMA reporting checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-22-272/rc>).

Methods

Literature retrieval

Databases including PubMed, Web of Science, Embase, The Cochrane Library and Wanfang data were searched

by computer, and the search time range was set from the first month in 2000 to the ninth month in 2020. The key words for search were set as “Chinese medicine”, “Western medicine”, “chronic obstructive pulmonary disease”, and “respiratory failure”. A random combination of keywords was used to search the literature.

How to include and exclude the articles

The articles were included and excluded according to the participants, interventions, comparisons, outcomes (PICOS) principle. Patients in the treatment group were treated with TCM combined with chemotherapy, and those in the control group were treated with chemotherapy alone.

Articles meeting below criteria could be included: (I) Chinese and international articles about the efficacy of combined TCM and WM in treating COPD complicated with RF. (II) Direct or indirect evaluation of the indicators of curative effect of combined TCM and WM in treating COPD complicated with RF. (III) At least 15 samples were included in the study.

Articles had to be excluded if they met any of following items: (I) articles with repeated data. (II) Articles which were review, conference report, empirical lecture, case report, and commentary. (III) Research which was not related to the specific topic. (IV) Control group was not set, or the samples were different greatly so that they were comparable. (V) Studies with unclear or incomplete outcome indicators.

How to assess the literature quality

It was requested of 2 researchers that they read the full texts and extract relevant materials in the literature. Disagreements were addressed through mutual discussion or arbitration by a third party. The Cochrane Reviewer's Handbook 4.2.5 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) was used for literature quality assessment.

The evaluation included whether the article contained: (I) generation of random sequences. Describe in sufficient detail the method used to generate assignment sequences and assess whether the generated groupings are comparable. (II) Allocate hidden. Describe in sufficient detail the method to conceal the assignment sequence and decide whether the intervention assignment is visible during the included studies. (III) Double-blind of implementers and participants. For each primary outcome, assessments

were made whether relevant information on blinding was provided. (IV) Blinding of outcome assessment. Whether outcome recipients were blinded to avoid all measures of their receiving intervention information. (V) Incomplete outcome data. Mainly describe the completeness of outcome data, including natural deletion and exclusion. Whether the literature reports missing data and reason. (VI) Select Report. Review the possibility of selectively reporting outcomes, and review the results. (VII) Other offsets. Description of other important biases.

Data to be extracted

(I) The first author, publication year, and evaluation results needed to be extracted. (II) The evaluation results included the number of participants, experimental design, specific measures, research time, and outcome indicators. (III) Baseline data of patients. (IV) Indicators of feedback research quality.

Statistical analysis

Data were analyzed statistically using Review Manager 5.3 (RevMan 5.3; The Nordic Cochrane Center, Denmark, 2014). Peto was selected to analyze the literature heterogeneity. When $I^2 < 50\%$, no heterogeneity was indicated, and the meta-analysis was done by using fixed effects model (FEM). When $I^2 > 50\%$, the heterogeneity was obvious, and random effects model (REM) was selected. The measurement data were analyzed by using weighted mean difference (WMD), or otherwise the standard deviation (SD) was adopted. The counting data were indicated by relative risk (RR) and 95% confidence intervals (CI). The funnel plots were made to assess the publication bias. In addition, the reliability and stability of the outcomes were analyzed. When $P < 0.05$, the difference was considered to be statistically significant.

Results

Retrieval results and overview analysis

618 records were obtained initially, and 226 abstracts related to the topic specified in this work were obtained after deletion of duplicates. Two researchers read the abstract and title of the articles, 26 articles meeting the requirements were obtained through preliminary screening. After further reading the full text of the literature, non-random,

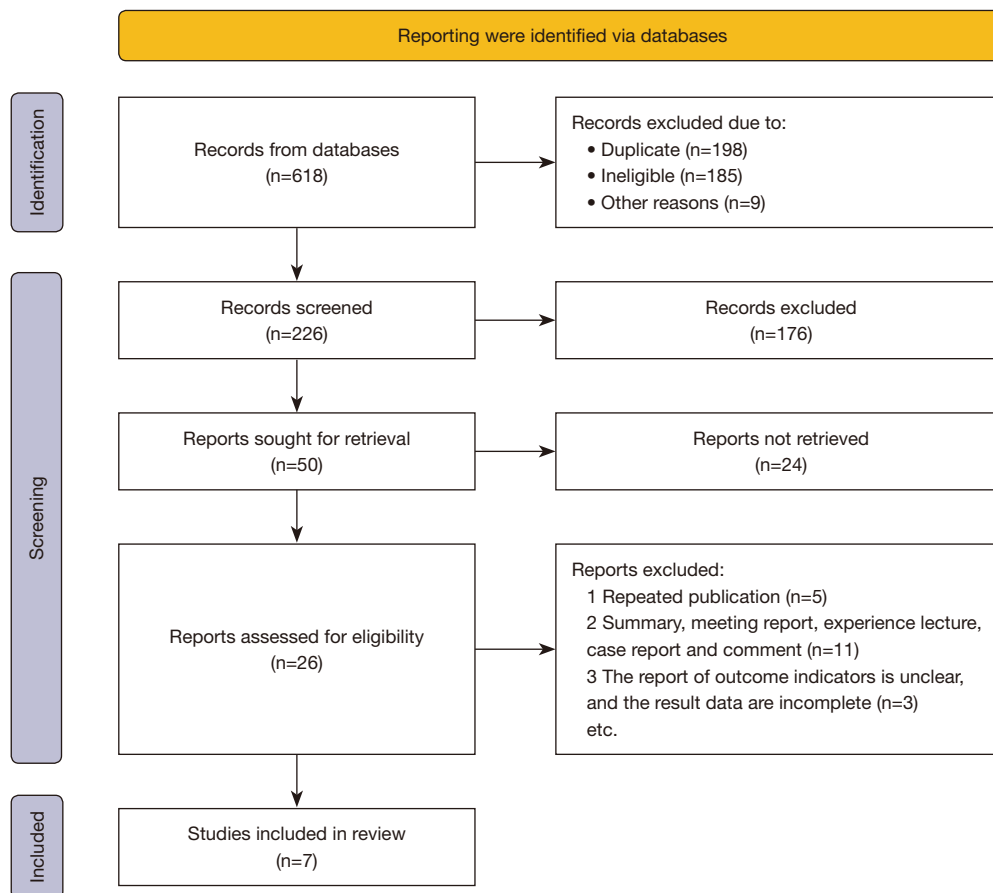


Figure 1 Literature retrieval process.

repeatable, and unavailable literatures were excluded, and 7 articles (*Figure 1*) meeting the requirements (*Table 1*) were obtained and included in this study (19-25).

Bias risk

The bias risk was assessed using Cochrane Systematic Review Manual (*Figures 2,3*). Random sequence generation, incomplete outcome data, and selective reporting did not exist in all the 7 studies. The bias risk was thus relatively low.

Meta-analysis on efficacy of combined TCM and WM in treating COPD + RF

Among the included articles, 6 articles carried out a detailed evaluation of the therapeutic efficiency of combined TCM and WM in treating COPD complicated with RF, and compared the therapeutic efficiency between combined

TCM and WM and the traditional WM in patients with COPD. The results are shown in *Figure 4*. The heterogeneity was not obvious in the treatment effective rate between the combined Chinese and WM treatment group and the control group ($I^2=0\%$, $P=0.85$). The FEM analysis results showed that the effective rate of the 2 groups was mean difference (MD) (95% CI): 5.40 (3.14 to 9.29), and $Z=6.09$ ($P<0.00001$). The results revealed greatly different effective rate of COPD combined with RF between the 2 groups.

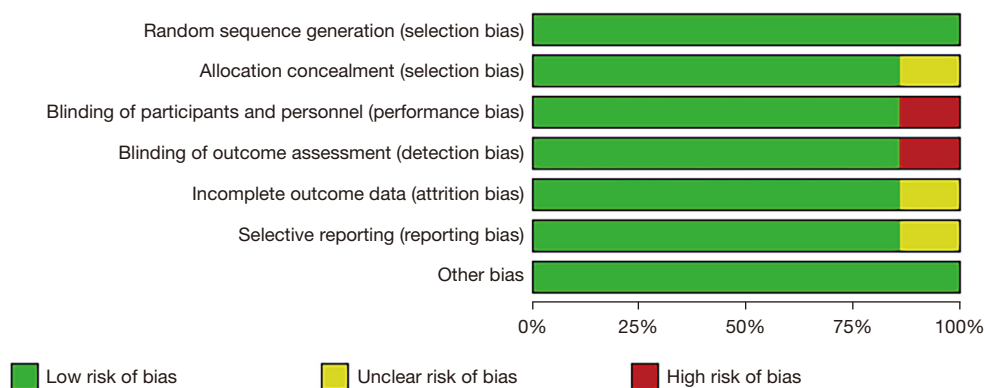
Meta-analysis of PO_2 after combined treatment TCM and WM of COPD + RF

Among the included literature, 5 articles carried out a detailed evaluation of the oxygen partial pressure (PO_2) after combined treatment TCM and WM of COPD with RF, and compared the post-treatment PO_2 between the combined treatment of TCM and WM group and the

Table 1 Included literatures and their general information

First author	Year	Outcome index	Combined medicine treatment	Control
Huang J (19)	2015	Treatment efficiency PO ₂ , PCO ₂	50	50
Zhang Y (20)	2004	Treatment efficiency	30	30
He B (21)	2014	Treatment efficiency PO ₂ , PCO ₂ , FEV1%	50	50
Li W (22)	2008	Treatment efficiency	28	26
Xie YH (23)	2005	Treatment efficiency, PO ₂ , PCO ₂	52	30
Jiu HF (24)	2008	Treatment efficiency, PO ₂ , PCO ₂ , FEV1%	30	30
Chen H (25)	2016	PO ₂ , PCO ₂ , FEV1%	64	64

PO₂, partial pressure of oxygen; PCO₂, partial pressure of carbon dioxide; FEV, forced expiratory volume.

**Figure 2** Bar chart of bias risk of literatures.

control group using traditional WM of patients with COPD. The results are shown in *Figure 5*. PO₂ after treatment showed observable heterogeneity between different groups ($I^2=89\%$, $P<0.00001$), so the analysis was realized using. The analysis structure of PO₂ after treatment of 2 groups was MD (95% CI): 5.92 (2.27 to 9.56), and the statistical analysis suggested $Z=3.18$, $P=0.001$. Great difference could be found in PO₂ between the 2 groups after treatment for COPD complicated with RF.

Meta-analysis on post-treatment PCO₂ in combined TCM and WM for COPD + RF

Among the included literature, there were 5 documents that performed detailed evaluation of combination therapy of TCM and WM for COPD + RF after partial pressure of carbon dioxide (PCO₂), and compared the PCO₂ after treatment of the TCM and WM combination therapy

and conventional WM alone in patients with COPD, and the results are shown in *Figure 5*. There was significant heterogeneity in PCO₂ after therapy in 2 groups of patients ($I^2=84\%$, $P<0.0001$). The REM analysis revealed that analysis structure of PCO₂ in the 2 groups was MD (95% CI): -4.53 (-7.14 to -1.92), and the statistical analysis suggested $Z=3.40$, $P=0.0007$. A substantial difference was found in PCO₂ between the 2 groups after treatment for COPD complicated with RF (*Figure 6*).

Meta-analysis of lung function after combined treatment of TCM and WM in COPD patients with RF

In included the literature, there were 3 studies which evaluated lung function after TCM and WM combination treatment for COPD with RF in detail, the other studies had a simple description, but did not describe the patient's lung function index and specific data after treatment in detail.

We compared the lung function index after combination treatment of TCM and WM and conventional WM alone for COPD with RF patients, and the results are shown in Figure 7. The lung function index data of patients was

heterogeneous ($I^2=75\%$, $P=0.02$), which was analyzed by using REM. The MD (95% CI): 8.16 (2.57 to 13.75) was the analysis structure of lung function index data of patients in 2 groups, and the statistical test structure was $Z=2.86$ ($P=0.004$). The results showed that the lung function index data of patients in 2 groups differed greatly.

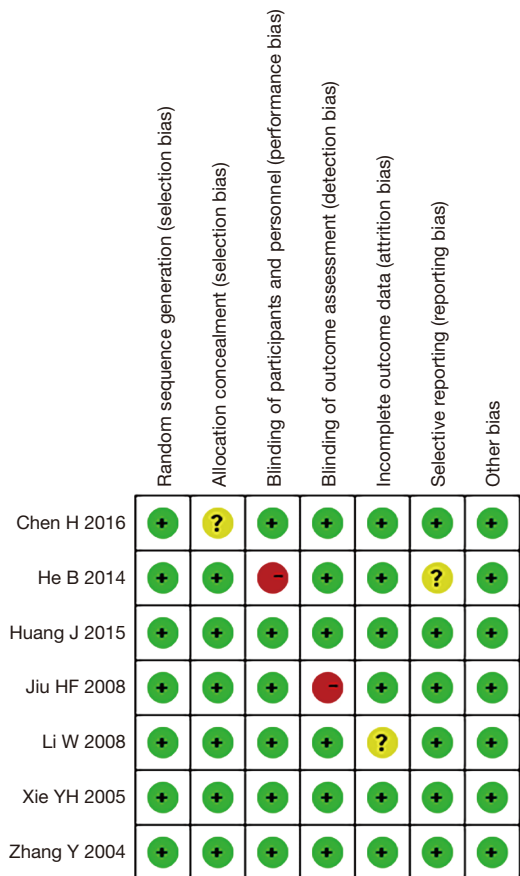


Figure 3 Summary of literature bias risk. +, low risk; -, high risk; ?, unknown risk.

Publication bias analysis

The publication bias of treatment efficiency, PO_2 , PCO_2 , and pulmonary function [forced expiratory volume in 1 second (FEV1)%] was analyzed, and the results are shown in Figure 8. The funnel plots of treatment efficiency, recurrence rate, adverse reaction rate, and pneumonia severity index (PSI) score were basically symmetrical, so the data were relatively concentrated. This indicates that the 4 functional indicators included in this study did not have large publication bias.

Discussion

Pathologic features of COPD include inflammation, protease-antiprotease imbalance, and oxidative stress (26,27). No reliable evidence is found to prove that current drug therapies can reverse the slow decline in lung function during development of COPD. Relevant studies have shown that TCM has obvious advantages in treating COPD (28,29).

Phlegm heat injection is a Chinese medicine preparation, widely used in the treatment of fever, acute bronchitis, and acute pneumonia. The main ingredients include baikal skullcap root, honeysuckle, forsythia, bear fruit kernel, and antelope horn, and a pharmacological study showed that phlegm heat injection has antibacterial and

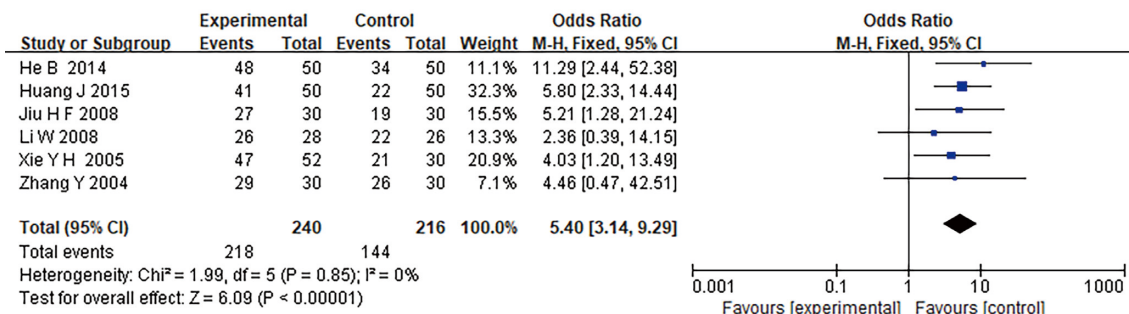


Figure 4 Effective rate of integrated TCM and WM in treating COPD complicated with RF. TCM, traditional Chinese medicine; WM, western medicine; COPD, chronic obstructive pulmonary disease; RF, respiratory failure; CI, confidence interval.

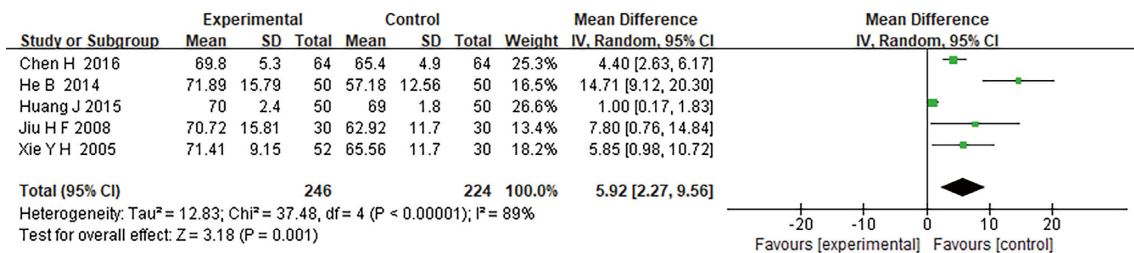


Figure 5 PO₂ of COPD combined with RF treated by integrated TCM and WM. PO₂, partial pressure of oxygen; TCM, traditional Chinese medicine; WM, western medicine; COPD, chronic obstructive pulmonary disease; RF, respiratory failure; SD, standard deviation; CI, confidence interval.

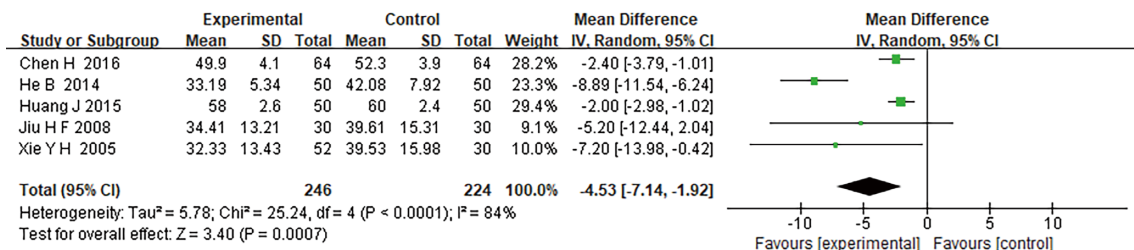


Figure 6 PCO₂ in COPD combined with RF treated by integrated TCM and WM. PCO₂, partial pressure of carbon dioxide; TCM, traditional Chinese medicine; WM, western medicine; COPD, chronic obstructive pulmonary disease; RF, respiratory failure; SD, standard deviation; CI, confidence interval.

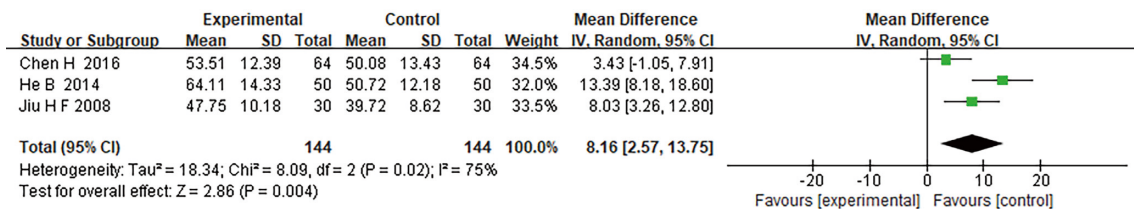


Figure 7 Pulmonary function of COPD combined with RF treated by integrated TCM and WM. TCM, traditional Chinese medicine; WM, western medicine; COPD, chronic obstructive pulmonary disease; RF, respiratory failure; SD, standard deviation; CI, confidence interval.

antiviral effects. Phenolic acids, flavonoids, and lignans are active components of honeysuckle, baikal skullcap root, and forsythia. Massive amounts of inflammatory cells, cytokines, adhesion molecules, and chemokines are involved in the development and progression of COPD. Serum soluble Intercellular Adhesion Molecule-1 (sICAM-1) and interleukin-18 (IL-18) levels are higher in AECOPD and stable COPD groups than in controls (30), and they are positively correlated in AECOPD patients. They in AECOPD patients with RF were increased to non-RF patients, suggesting that the above two indicators reflect the

severity of COPD. Interleukin 10 (IL-10) reduces serum sICAM-1 and IL-18 levels and inhibits COPD associated inflammation (31,32). Systematic analysis in this study found that phlegm heat injection improved lung function, PO₂, and PCO₂, indicating that phlegm heat injection has anti-inflammatory effects. Phlegm heat injection can effectively relieve the signs and symptoms of COPD and RF patients.

However, baicalin in phlegm-heat injections may cause adverse reactions. As research reports by scholars have confirmed that Tanre Injection treatment can cause nausea,

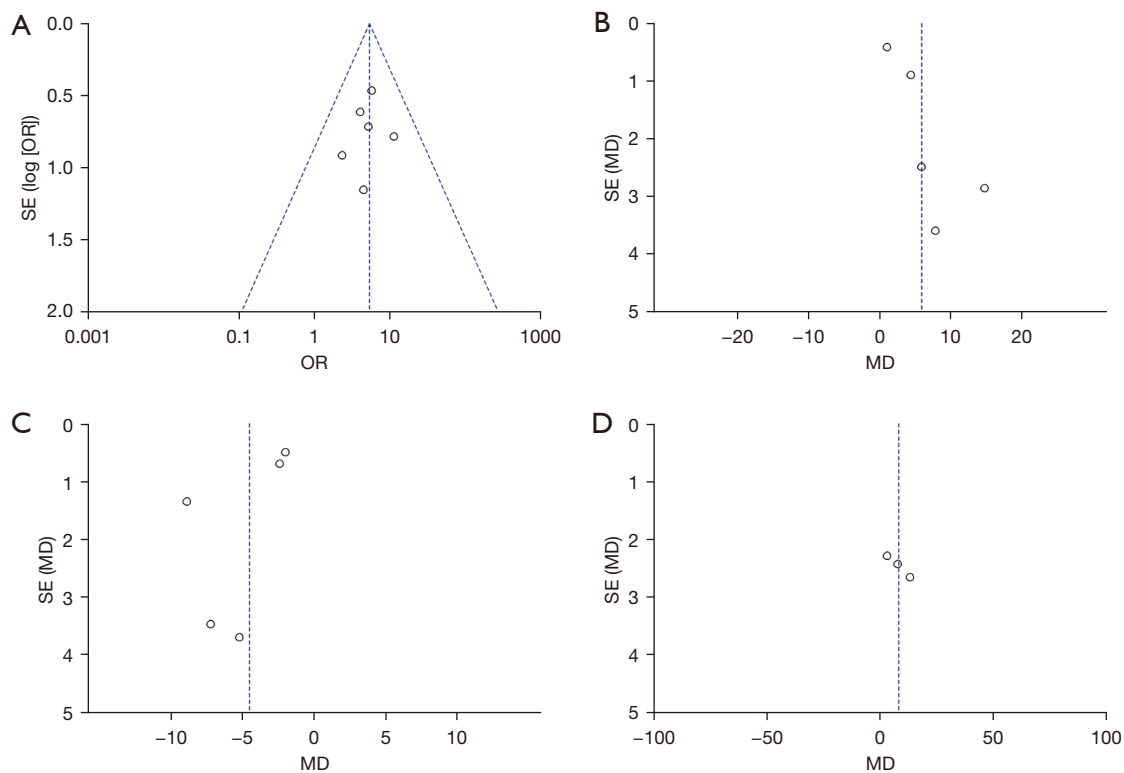


Figure 8 Related indicators shown in funnel plots: (A) treatment efficiency; (B) PO_2 ; (C) PCO_2 ; (D) pulmonary function. PO_2 , partial pressure of oxygen; PCO_2 , partial pressure of carbon dioxide. SE, standard error; MD, mean difference; OR, odds ratio.

mild headache, and chest tightness in patients, but all symptoms disappear after treatment (33). This study had some limitations. Patients were treated for 7–14 days, no long-term effects were observed, and the results of some of these indicators were highly heterogeneous. Although a REM was used, clinical heterogeneity may still have existed. The sample sizes of the studies included in this study were small, ranging from 30 to 64, which may have led to exaggerated or weakened results. It is necessary to expand the sample size in the future.

Conclusions

Seven suitable articles were selected, involving 490 patients. The RevMan 5.3 was used for data analysis. According to the meta-analysis results, the analysis structure of effective rate was MD (95% CI): 5.40 (3.14 to 9.29) and statistical analysis was $Z=6.09$ ($P<0.00001$). The analysis structure of PO_2 after treatment was MD (95% CI): 5.92 (2.27 to 9.56), and the statistical analysis was $Z=3.18$, $P=0.001$. The analysis structure of PCO_2 after treatment was MD (95%

CI): -4.53 (-7.14 to -1.92), and the statistical analysis suggested $Z=3.40$, $P=0.0007$. The analysis structure of lung function index data was MD (95% CI): 8.16 (2.57 to 13.75), and the statistical analysis indicated $Z=2.86$ ($P=0.004$).

In conclusion, the results of this work indicated that TCM combined with WM in treating COPD + RF is more effective than WM alone, and there are no obvious serious adverse reactions. However, due to the effective conditions, there were still few evaluation indexes analyzed, and more indexes should be further analyzed on this basis. This report provides a further theoretical basis for the follow-up study on the curative effect of combined TCM and WM in treating COPD + RF.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the

PRISMA reporting checklist. Available at <https://apm.amegroups.com/article/view/10.21037/apm-22-272/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://apm.amegroups.com/article/view/10.21037/apm-22-272/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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Cite this article as: Huang P, Lin X, Liu Y, Hou Z. The efficacy and safety of combined traditional Chinese and western medicine in the treatment of chronic obstructive pulmonary disease complicated with respiratory failure: a systematic review and meta-analysis study. *Ann Palliat Med* 2022;11(3):1102-1111. doi: 10.21037/apm-22-272