Original Article

The efficacy and safety of herbal formulas for adults with pulmonary hypertension combined with chronic obstructive pulmonary disease: a systematic review and meta-analysis involving 1,865 participants

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Background: There is currently no effective treatment for the majority of patients with chronic obstructive pulmonary disease combined with pulmonary hypertension (COPD-PH). Numerous clinical trials have demonstrated the use of traditional Chinese medicine (TCM) herbal formulas in combination with routine western pharmacotherapy (WP) for the treatment of COPD-PH, with positive results. This meta-analysis was designed to evaluate the efficacy and safety of TCM herbal formulas in the treatment of COPD-PH.

Methods: A systematic literature search was conducted using Web of Science, PubMed, Chinese National Knowledge Infrastructure (CNKI), WanFang, and Chinese Science and Technology Journal (VIP) from database inception until October 2023. The primary outcome was pulmonary artery pressure parameters, including pulmonary artery systolic pressure (PASP) and mean pulmonary artery pressure (mPAP). Secondary outcomes included pulmonary ventilation function parameters, such as forced expiratory volume in one second (FEV1) and the ratio of FEV1 to forced vital capacity (FEV1/FVC%), as well as functional capacity assessments measured by the six-minute walk distance (6MWD). Reviewer Manager software was used for both random-effects and fixed-effects meta-analyses. We registered the protocol for this study with the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY, registry

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Results: Twenty randomized control trials with a total of 1,865 patients were included in the meta-analysis. The results of our meta-analysis revealed that TCM herbal formulas in combination with basic WP significantly reduced pulmonary artery pressure in patients with COPD-PH, including PASP [mean difference (MD) =−4.50 mmHg, 95% confidence interval (CI): −6.04, −2.95] and mPAP (MD =−4.47 mmHg, 95% CI: −5.07, −3.88). Additionally, pulmonary ventilation function and 6MWD (MD =48.13 m, 95% CI: 39.92, 56.34) were also improved in COPD-PH patients. Pulmonary ventilation function was reflected by FEV1 (MD =0.83 L, 95% CI: 0.35, 1.30) and FEV1/FVC% (MD =4.76, 95% CI: 3.75, 5.77). A total of six studies reported adverse events in detail, and all claimed that no adverse events were observed in COPD-PH patients using TCM herbal formulas.

Conclusions: The combination of TCM herbal formulas and basic WP might be more effective in improving the quality of life and exercise capacity of patients with COPD-PH than basic WP alone. However, the firm conclusions of our study were hampered by the low quality of the evidence.

Keywords: Traditional Chinese medicine (TCM); chronic obstructive pulmonary disease (COPD); pulmonary hypertension (PH); meta-analysis

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease characterized by progressive and incompletely reversible airflow restriction, usually associated with exposure to noxious particles or gases (1). Up to 90% of patients with stage IV COPD have mean pulmonary artery pressure (mPAP) >20 mmHg, with the majority between 20 and 35 mmHg. Approximately 1% to 5% of patients with COPD have resting mPAP >35 to 40 mmHg (2). The development of pulmonary hypertension (PH) is associated with clinical deterioration, worsening of gas exchange and increased mortality rates in patients with COPD. Patients with COPD combined with PH (COPD-PH) have worse functional impairment and prognosis than patients with idiopathic pulmonary arterial hypertension (PAH), with gender and six-minute walk distance (6MWD) being predictors of death in patients with COPD-PH (3).

Progress in treating COPD-PH has been much slower than in treating PAH. There is currently no effective treatment for the majority of patients with COPD-PH, and existing treatments for COPD-PH focus on the primary disease and long-term oxygen therapy (4). Although several studies have been conducted using drugs approved for PAH in patients with COPD-PH, most of these are small series with conflicting results (5-7). Therefore, the evidence is insufficient to support the general use of drugs approved for PAH in patients with COPD-PH due to the limited number of large randomized trials (8). Numerous clinical trials have demonstrated the use of traditional Chinese medicine (TCM) herbal formulas in

Highlight box

Key findings

- The combination of traditional Chinese medicine (TCM) herbal formulas and basic western pharmacotherapy (WP) was found to be more effective than standard WP alone in patients with chronic obstructive pulmonary disease combined with pulmonary hypertension (COPD-PH).

What is known and what is new?

- Numerous clinical trials have demonstrated the use of TCM herbal formulas in combination with routine WP for the treatment of COPD-PH, with positive results.
- TCM herbal formulas combined with basic WP could provide additional benefits in terms of reducing pulmonary arterial pressure, improving pulmonary ventilatory function and promoting exercise capacity in patients with COPD-PH.

What is the implication, and what should change now?

- Our research implies that the main pharmacological component of TCM in these formulas may have effective ingredients in the treatment of COPD-PH. More well-designed clinical studies and basic studies are needed to provide more solid evidence.

combination with routine western pharmacotherapy (WP) for the treatment of COPD-PH, with positive results. It is important to evaluate the efficacy and safety of TCM herbal formulas in the treatment of COPD-PH patients, but no large sample size and multicenter clinical trials have been reported. To our knowledge, the potential benefits of TCM herbal formulas for patients with COPD-PH have not been evaluated enough to justify the recommendation or clinical role. To gather reliable evidence to verify the efficacy and safety of TCM herbal formulas, we retrieved relevant clinical randomized controlled trials (RCTs) and performed a meta-analysis. The purpose of this study was to analytically understand the efficacy and potential benefits of TCM herbal formulas in COPD-PH patients. We present this article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-471/rc) (9).

Methods

We registered the protocol for this study with the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY, registry number: INPLASY2022100041).

Data searches and extraction

We performed a systematic literature search of PubMed, Web of Science, Chinese National Knowledge Infrastructure (CNKI), WanFang and Chinese Science and Technology Journal (VIP) from their inception to October 2023. All databases were searched using a combination of medical subject headings and text words, with appropriate adjustments for specific databases. Search terms included "chronic obstructive pulmonary disease", "pulmonary hypertension" and "traditional Chinese medicine". Articles were not restricted to the Chinese language.

Two independent reviewers (R.L. and D.L.) read the titles and abstracts of the literature to preliminarily screen candidate articles, and then the full articles were further scanned to select eligible articles in accordance with the criteria. Any disagreements were resolved to reach a consensus through discussion with the third author (H.L.). The following information was extracted from the included studies: title, year of publication, first author, age and gender of participants, sample capacity, intervention, treatment duration, outcomes, and adverse events.

Eligibility criteria

Studies were considered eligible if they fulfilled the following criteria: (I) type of study: RCTs, participants with or without drop-outs. (II) Participants: (i) ≥18 years old, with no restrictions on gender, race, or economic status; (ii) the patients were diagnosed with COPD (10,11) and PH (12), respectively. COPD was defined as the ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC%) <70% after the use of inhaled bronchodilators. PH was defined as mPAP ≥20 mmHg measured by right heart catheterization at rest, and studies using echocardiography as a diagnostic criterion were also included; (iii) respiratory physicians clinically considered PH to be caused by COPD. (III) Interventions: the treatment group received TCM herbal formulas or Chinese patent drugs based on basic WP, with no time limit. (IV) Comparisons: the control group was treated only with basic WP. (V) Outcomes: the primary outcomes were changes in pulmonary artery systolic pressure (PASP) (mmHg) and mPAP (mmHg), while the secondary outcome measures included FEV1 (L), FEV1/FVC (%), and 6MWD (m). Studies in which patients were treated with TCM injections or TCM herbal formulas combined with other interventions of Chinese medicine therapies, such as moxibustion and acupuncture, were excluded.

Statistical analysis and quality assessment

Statistical analysis were performed using Review Manager software 5.4 (Cochrane Collaboration), which was used to assess outcome measures and to analyze the data quantitatively using meta-analytic techniques (13). The results are presented using forest plots. All outcome measures were evaluated using mean difference (MD) with a 95% confidence interval (CI), except for FEV1, which was evaluated using standard MD (SMD). A P value <0.05 was considered to be statistically significant. A random effects model was used for the combined analysis if I^2>50% and P<0.1, otherwise a fixed effects model was used. Of all outcome measures, only PASP and FEV1 were calculated using a random effect model. The heterogeneity of the studies was examined by using the χ^2 and I^2 statistics, and the test level was set at α=0.1. Due to heterogeneity between studies, subgroup and sensitivity analyses were performed for PASP and FEV1. A funnel plot was used to assess for publication bias.

We assessed the risk of bias in each trial using the Cochrane Handbook for Systematic Review of Interventions (14).

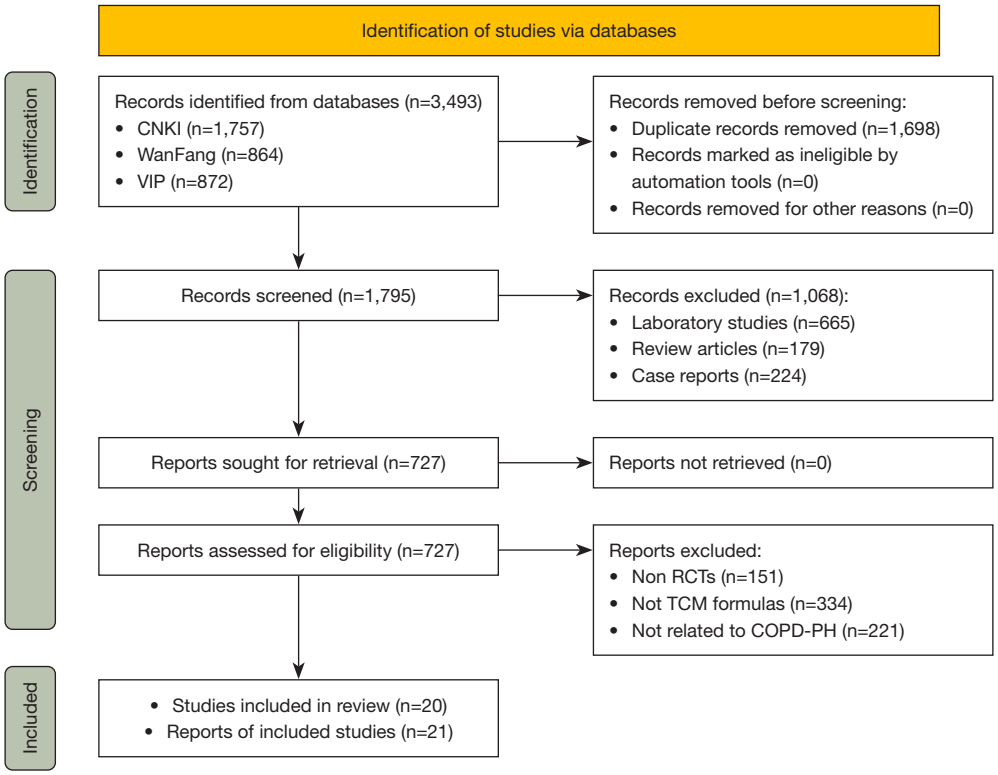

Figure 1 Flow chart of the process for selecting trials. CNKI, Chinese National Knowledge Infrastructure; VIP, Chinese Science and Technology Journal; RCTs, randomized control trials; TCM, traditional Chinese medicine; COPD-PH, chronic obstructive pulmonary disease combined with pulmonary hypertension.

Random sequence generation, allocation concealment, use of blinding, integrity of outcome data, selective outcome reporting and other risks of bias were assessed, and these items were rated as "high risk", "low risk" or "unclear risk".

Results

Study flow

A total of 1,757 studies were found in CNKI, 864 in WanFang Database, and 872 in VIP Database. After removing 1,698 replicated studies, we were left with 1,795 studies. We then excluded 1,068 articles that were laboratory studies, reviews, or case reports. Additionally, we excluded 706 full-text articles based on the inclusion and exclusion criteria of this study. Finally, we included the remaining 20 studies in this meta-analysis (*Figure 1*).

Study characteristics and assessment of evidence credibility

The 20 studies deemed eligible included a total of 1,865 participants. *Table 1* displays the basic characteristics of the included studies. We evaluated the certainty of evidence for each study using the Grading of Recommendation, Assessment, Development and Evaluations (GRADE) framework, which classified evidence as very low, low, moderate, or high.

Risk of bias

The methodological quality of the included studies was assessed independently by two reviewers (R.L. and H.L.), using the Cochrane Collaboration's risk of bias tool. The results are presented in *Figure 2A,2B*. In summary, most of the included studies had an unclear risk of bias or a low risk of bias.

Outcomes of meta-analysis

Forest plots were performed to visually inspect the efficacy of the TCM herbal formulas compared with basic WP.

Table 1 Characteristics of the studies included in the meta-analysis

Study	Participants		Average age (years) (T/C)	Female (T/C)	Average disease duration (years) (T/C)	Intervention		Treatment duration	Outcomes	Assessment of evidence credibility (GRADE)
	Treatment group	Control group				Control group	Treatment group			
Liu HJ 2021 (15)	47	47	66.72/66.86	17/15	10.67/10.72	WP	WP + Chuanxiongpingchuan decoction	2 weeks	①	Moderate
Liang HX 2021 (16)	40	40	60.47/60.22	15/17	6.65/6.13	WP	WP + Ningfeihuoxuelishui decoction	4 weeks	①③④	Low
Feng GP 2020 (17)	50	50	64.12/63.23	17/21	6.82/6.23	WP	WP + Jiaweichuanxiongpingchuan mixture	12 weeks	①③	Low
Wu XY 2020 (18)	38	38	65.2/63.8	21/23	12.2/11.9	WP	WP + Bufeihuoxue decoction	4 weeks	①	Low
He YL 2020 (19)	60	60	68.4/68.2	17/18	6.9/6.7	WP	WP + Wenfeigubenhuoxue decoction	2 weeks	①②③④	Low
Fan CX 2020 + 2018 (20,21)	40	40	69.18/69.78	14/10	24.45/25.93	WP	WP + Jiaweichuanxiongpingchuan mixture	2 weeks	①④	Low
Xu XQ 2019 (22)	40	40	63.2/66.35	5/11	3.94/4.55	WP	WP + Jiaweichuanxiongpingchuan mixture	12 weeks	①③	Moderate
Zhang HJ 2019 (23)	38	38	60.04/59.65	13/11	7.68/7.85	WP	WP + Yiqihuoxuebushen decoction	8 weeks	①③④	Low
Tian H 2019 (24)	42	42	68.8/59.3	16/12	12.1/12.4	WP	WP + Tongluolifei decoction	2 weeks	①③	Low
Zhang DF 2018 (25)	45	45	60.43/60.12	15/16	10.10/9.80	WP	WP + Peitushengjin decoction (self-prescribed formulas)	12 weeks	①②③	Low
Li HH 2017 (26)	63	64	70.56/68.45	24/23	18.77/19.23	WP	WP + Bufeihuoxuehuatan decoction	8 weeks	①④	Low
Yin TT 2018 (27)	18	20	62.66/61.2	8/9	–	WP	WP + Qibaipingfei capsule	30 days	①②③	Very low
Qin H 2016 (28)	32	33	63.5/66.8	9/10	8-38/9-37	WP	WP + Bushenhuoxuequtan decoction (self-prescribed formulas)	3 months	①②	Very low
Zhao DF 2016 (29)	50	50	65.3/65.0	26/23	25.1/24.9 (months)	WP	WP + Runfeihuoxue decoction	4 weeks	①②③④	Low
Li W 2016 (30)	80	80	63.97/64.51	31/32	13.05/12.72	WP	WP + Gubenyangzang decoction (self-prescribed formulas)	15 days	①④	Low
Zhao SW 2015 (31)	45	54	62.4/61.9	17/20	7.2/7.5	WP	WP + Tongfeixiezhuo decoction	2 weeks	①	Low
Liu Z 2015 (32)	49	49	64.8/65.6	17/14	8.7/9.1	WP	WP + Huoxueyifeixiezhuo decoction	2 weeks	①	Very low
Zhong GW 2015 (33)	26	30	62.5/63.2	10/12	–	WP	WP + Yiqiwenyanghuoxuehuatan decoction	12 weeks	①②	Very low
Chen C 2015 (34)	63	63	64.14/64.03	23/16	10.93/11.08	WP	WP + Sansanghuoxue decoction	3 months	①②③	Very low
Qu NN 2015 (35)	60	60	64.3/63.9	25/35	7.8/7.4	WP	WP + Yiqiwenyanghuoxue decoction	2 weeks	①	Moderate

Outcomes: ① pulmonary artery systolic pressure or mean pulmonary artery pressure; ② six-minute walk distance; ③ forced expiratory volume in one second or the ratio of forced expiratory volume in one second to forced vital capacity; ④ adverse events. T/C, treatment group/control group; WP, western pharmacotherapy; GRADE, Grading of Recommendation, Assessment, Development and Evaluations framework.

Figure 2 The assessment of each bias risk. (A) The risk of bias graph, indicating the review authors' evaluation of each risk of bias as a percentage of all included studies. (B) The risk of bias summary, demonstrating the review authors' assessment of each risk of bias for each included study.

All included studies reported changes in pulmonary artery pressure, with 10 studies measuring mPAP and 11 studies measuring PASP. The data showed that mPAP decreased by 4.47 mmHg (MD =−4.47, 95% CI: −5.07, −3.88, P<0.01) and PASP decreased by 4.50 mmHg (MD =−4.50, 95% CI: −6.04, −2.95, P<0.01) in patients treated with TCM herbal formulas based on basic WP compared with controls (*Figure 3A,3B*). Improvements in pulmonary ventilation function were reported in 19 studies, including 770 patients assessed by FEV1 and 714 patients assessed by FEV1/FVC%. Based on the available analyses, patients in the treatment groups had an increase in FEV1 of 0.83 L (SMD =0.83, 95% CI: 0.35, 1.30, P<0.01) and an improvement in FEV1/FVC of 4.76% (MD =4.76, 95% CI: 3.75, 5.77, P<0.01) (*Figure 4A,4B*). In functional assessments in COPD-PH patients, we observed that the length of the 6MWD was longer in the treatment group as a proportion of the control group (MD =48.13, 95% CI: 39.92, 56.34, P<0.01) (*Figure 4C*).

Adverse events

Out of the twenty studies, no adverse events were reported in fourteen studies. Descriptive analysis was used because of limited data in the six trials that reported adverse events (19,22,23,25,29,30). Li (30) and Xu (22) reported that neither group of patients experienced acute COPD exacerbations or right heart failure events. Other studies reported no significant differences in liver and kidney function between groups throughout treatment, and no rash or other allergic symptoms were reported (19,23,25,29). In conclusion, no adverse events requiring medical care were observed during the entire treatment.

Subgroup analysis and publication bias

To further explore the source of heterogeneity in the studies that reported PASP and FEV1, we performed subgroup

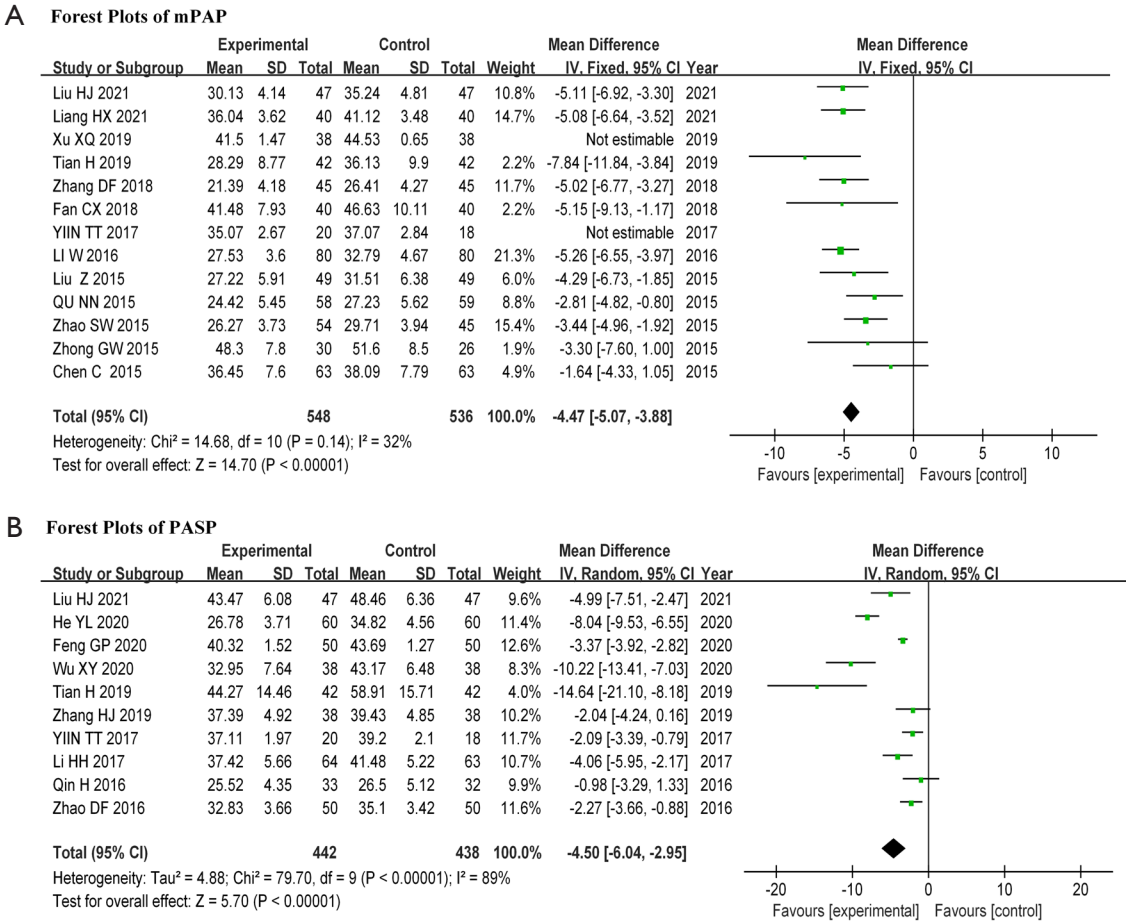

Figure 3 Forest plots of the primary outcome. (A) The changes in mPAP for patients with COPD-PH. (B) The changes in PASP for patients with COPD-PH. PASP, pulmonary artery systolic pressure; mPAP, mean pulmonary artery pressure; COPD-PH, chronic obstructive pulmonary disease combined with pulmonary hypertension; SD, standard deviation; CI, confidence interval.

analysis. The studies were divided into subgroups of TCM syndrome, including sthenic syndrome, asthenia syndrome, and mixture of asthenia and sthenia syndrome. The results suggested that there were statistical differences in the three subgroups, which might be the source of heterogeneity (*Figure 5A*,*5B*).

The funnel plot analysis revealed a possible publication bias due to the significant asymmetry in the funnel plots (*Figure 6*). A possible publication bias was contributed by the small sample size, lack of homogeneity and lack of allocation concealment in the included studies.

Discussion

In this meta-analysis of 20 studies, the combination of TCM herbal formulas and basic WP was found to be more effective than basic WP alone in reducing pulmonary artery pressure, improving pulmonary ventilation, and enhancing activity tolerance in patients with COPD-PH. The results of safety analysis suggested that TCM herbal formulas did not increase the occurrence of adverse events.

As far as we know, there are currently no special drugs approved for use in patients with COPD-PH, but studies have been conducted to evaluate the effectiveness of pulmonary vasoactive therapies. In 2014, Goudie and colleagues conducted a 12-week randomized trial on 120 patients diagnosed with COPD-PH, confirmed by echocardiography. The trial group was administered 10mg of tadalafil per day, while the control group was given a placebo. The trial did not meet the primary endpoint of 6MWD, with a mean increase of only 0.5 m (95% CI: 11.6, 12.5, P=0.937) (7). In a separate study, Valerio and

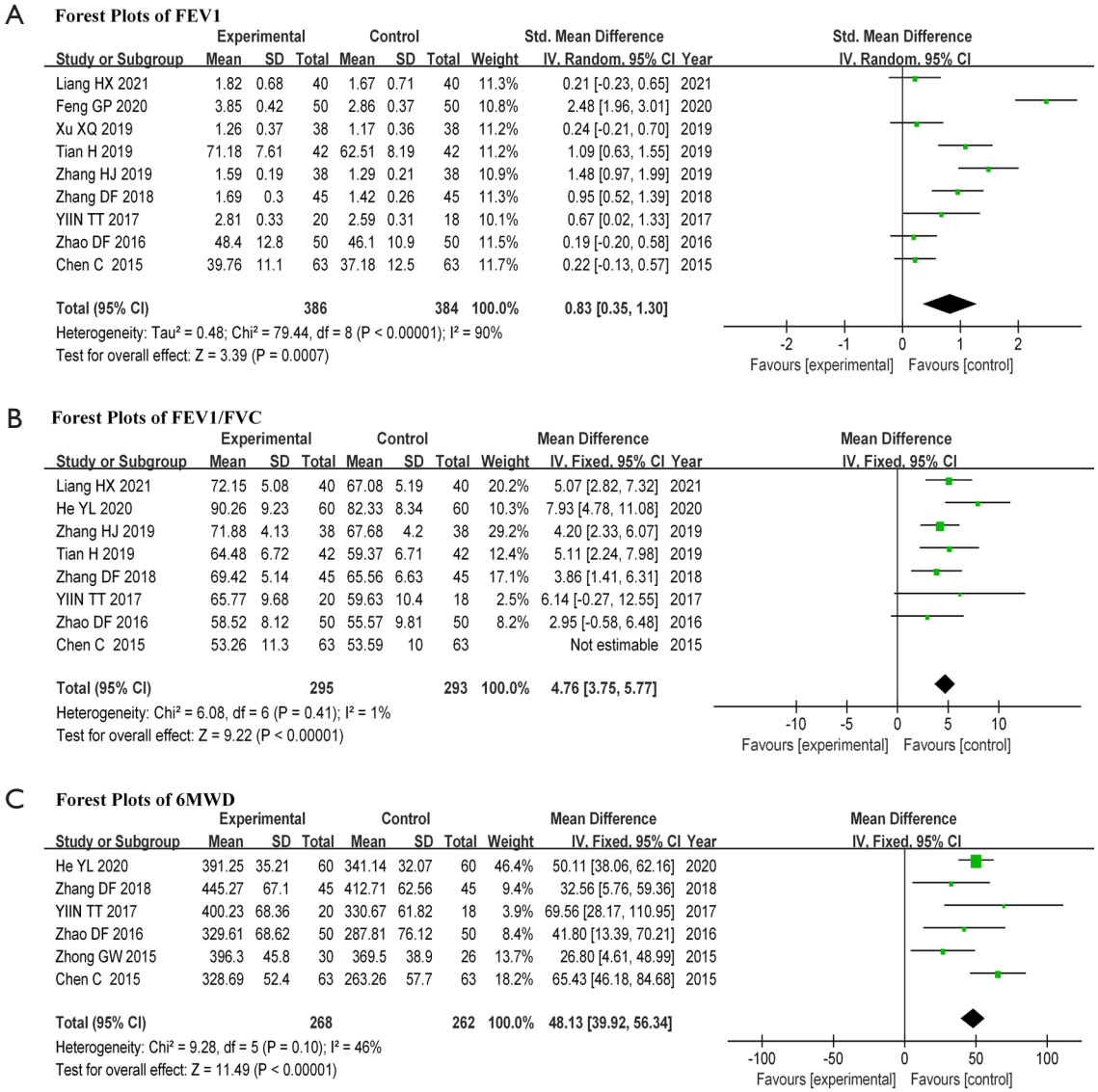

Figure 4 Forest plots of the secondary outcome. (A) The changes in FEV1 for patients with COPD-PH. (B) The changes in FEV1/FVC for patients with COPD-PH. (C) The changes in 6MWD for patients with COPD-PH. FEV1, forced expiratory volume in one second; FEV1/FVC, the ratio of forced expiratory volume in one second to forced vital capacity; 6MWD, six-minute walk distance; COPD-PH, chronic obstructive pulmonary disease combined with pulmonary hypertension; SD, standard deviation; CI, confidence interval.

colleagues evaluated patients with PH who had been diagnosed with COPD through right heart catheterization over an 18-month period. The trial involved 16 patients who were treated with bosentan and 16 patients who were randomized to placebo. The treatment group experienced a reduction in pulmonary artery pressure and pulmonary vascular resistance with an improvement in 6MWD of 64 meters, but a reduction in 6MWD of 20 meters was observed in placebo group (36). A meta-analysis of five trials involving 257 patients with COPD-PH reported an increase in 6MWD (mean increase of 42.7 m, 95% CI: 1.0, 86.3), although this was not statistically significant (37). The efficacy of pulmonary vascular therapies for COPD-PH is uncertain or there are even conflicting results, so we synthesized the results of RCTs of TCM herbal formulas for COPD-PH by meta-analysis to draw valid conclusions about the efficacy and safety of TCM herbal formulas. This is the first meta-analysis to explore the use of TCM herbal

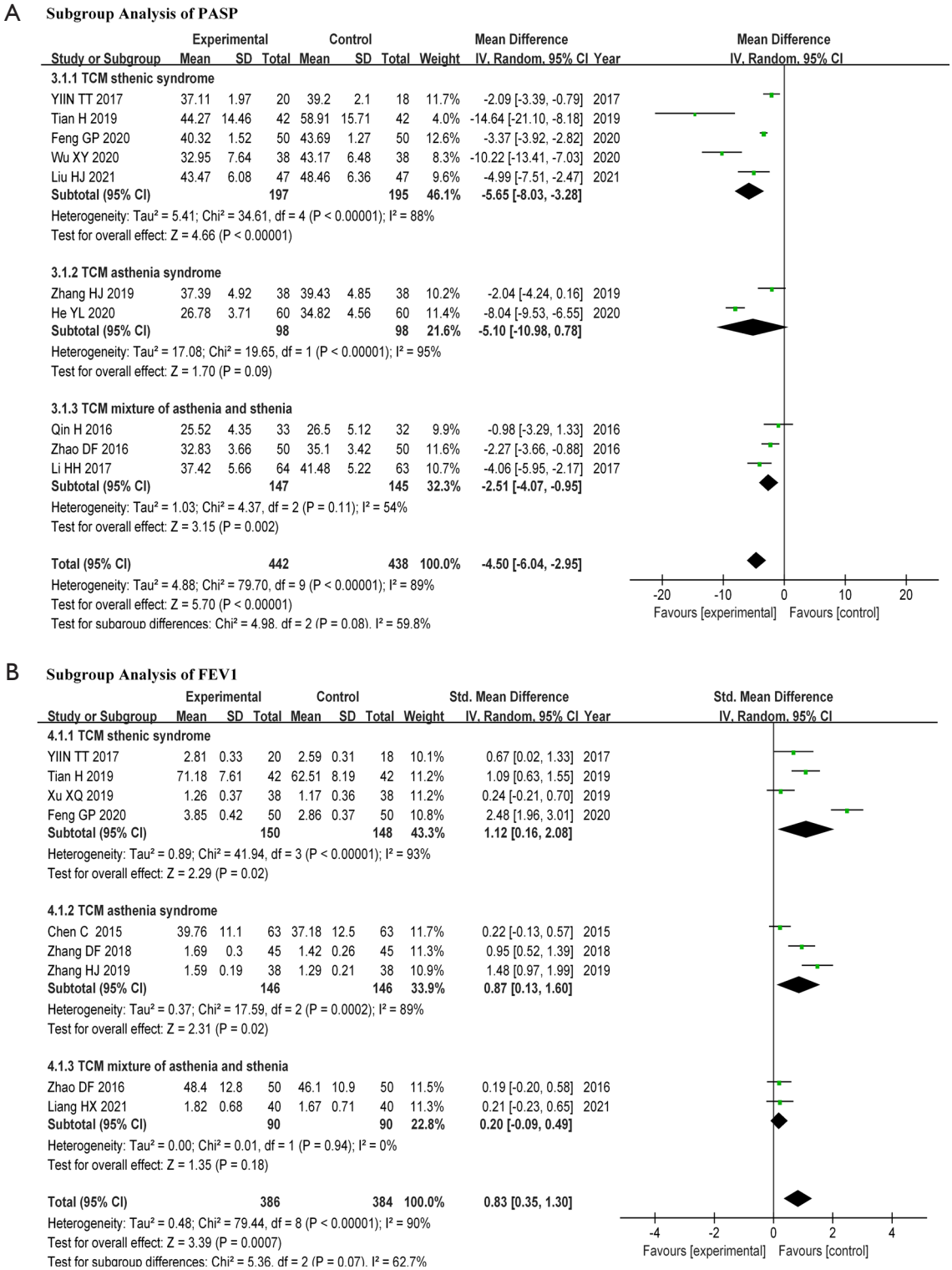

Figure 5 The results of the subgroup analysis by classifying PASP and FEV1 into three subgroups based on the type of TCM evidence. (A) The subgroup analysis of PASP; (B) the subgroup analysis of FEV1. PASP, pulmonary artery systolic pressure; FEV1, forced expiratory volume in one second; TCM, traditional Chinese medicine; SD, standard deviation; CI, confidence interval.

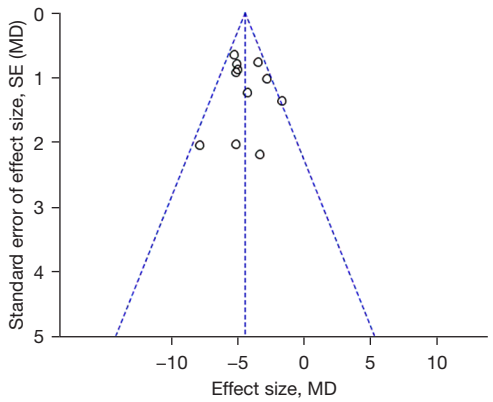

Figure 6 A funnel plot was shown using mPAP as the effector indicator. The two diagonal dashed lines indicated the 95% confidence intervals. The vertical dotted line in the center represented the ideal state mean difference. MD, mean difference, the effect size of mPAP; SE (MD), standard error, and it represented the standard error of the logarithm of the mean difference; mPAP, mean pulmonary artery pressure.

formulas in the treatment of patients with COPD-PH. Given the results of our study, TCM herbal formulas might be an added therapy for COPD-PH. The study implied that the main pharmacological component of TCM contained in these formulas might be an active ingredient in the treatment of COPD-PH.

The meta-analysis included 20 TCM herbal formulas, with the herbs and their functions listed in Table S1. Thirteen of these formulas were self-prescriptions, while the remaining seven were classical prescriptions based on Chinese materia medica. The frequency of each Chinese herb used in the TCM herbal formulas is shown in Figure S1. Chuanxiong (*Ligusticum chuanxiong hort*), Danshen (*Salvia miltiorrhiza Bge*), Danggui (*Angelica sinensis*), and Taoren [*Prunus persica (L.) Batsch*] were the most commonly used herbs in our meta-analysis. Modern pharmacological studies had shown that chuanxiong could reduce pulmonary artery pressure by suppressing pulmonary artery smooth muscle cell proliferation and improve airway remodeling by regulating the phosphoinositide 3-kinase (PI3K)/AKT pathway (38). Tanshinone IIA (TIIA), the main pharmacological component of danshen, could regulate blood pressure and vascular tone by inhibiting endothelin-1 release and stimulating nitric oxide (NO) production by inducing endothelial nitric oxide synthase (eNOS) activation and activating transcription factor-3 expression (39,40). In addition, its water-soluble form (sodium TIIA sulfonate) has been shown to protect against COPD by upregulating miR-486-5p (41). Huangqi and Danggui contribute to lung disease by protecting against lung injury (42-45), by ameliorating allergic airway inflammation (46), and improving lung ventilation (47).

There are some limitations in this study. Firstly, all included studies were conducted in China, which limited the generalizability of the results to different populations and geographical locations. Secondly, PH was not diagnosed by right heart catheterization in any of the patients in the studies we included, thus there was no hemodynamic evidence to infer whether PH was caused by COPD. Finally, heterogeneity between studies could have influenced the results and might be related to different underlying conditions, such as 'basic WP' without specific drug and dose.

Conclusions

In conclusion, TCM herbal formulas in combination with basic WP might provide additional benefits in terms of reducing pulmonary arterial pressure, improving pulmonary ventilatory function. However, the findings that TCM herbal formulas could enhance exercise capacity in patients with COPD-PH without inducing adverse effects are based on only six studies of limited quality. Therefore, it is imperative to conduct further safety surveillance and high-quality research to ascertain the long-term efficacy and safety of these TCM herbal formulas.

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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-24-471/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-24-471/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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