



Efficacy of Acupuncture in Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis

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Purpose: The effect of acupuncture as adjunctive therapy for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) was controversial. Thus, we aimed to evaluate the effects of acupuncture for treating AECOPD.

Methods: Eight databases were searched from database inception to July 30, 2023. All RCTs compared acupuncture plus conventional western medicine with conventional western medicine alone were included. Outcomes were quality of life, lung function, blood oxygen condition, exercise capacity, daily symptoms, duration of hospitalization, and adverse events. The statistical analyses were conducted using Stata 17.0, and methodological quality was measured by the Cochrane bias risk assessment tool. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the quality of evidence.

Results: Twelve studies including 915 patients were included. Compared with conventional western medicine alone, acupuncture combined with conventional western therapy significantly improved quality of life (CAT: MD: -3.25; 95% CI: -3.73 to -2.78, $P < 0.001$) and arterial blood gas (PaCO₂: MD: -1.85; 95% CI: -2.74 to -0.95, $P < 0.001$; PaO₂: MD: 5.15; 95% CI: 1.22 to 9.07, $P = 0.01$). And for lung function, statistical benefits were found in FEV₁/FVC (MD: 4.66; 95% CI: 2.21 to 7.12, $P < 0.001$), but no difference was seen for FEV₁% (MD: 1.83; 95% CI: -0.17 to 3.83, $P = 0.073$). There was no significant improvement in exercise capacity (6MWD: MD: 96.69; 95% CI: -0.60 to 193.98, $P = 0.051$), hospitalization duration (MD: -5.70; 95% CI: -11.97 to 0.58, $P = 0.075$), and dyspnea (mMRC: MD: -0.19; 95% CI: -0.61 to 0.63, $P = 0.376$) between two groups. Overall bias for CAT and mMRC was in “high” risk, FEV₁%, FEV₁/FVC, PaCO₂, and PaO₂ was in “some concern” and 1 RCT assessing hospitalization duration was in “low” risk. And the overall assessments were either moderate, low or very low certainty. Seven trials performed safety assessment of acupuncture, and no serious adverse events were reported.

Conclusion: Acupuncture might have auxiliary effects on AECOPD. However, the quality of the evidence is limited, and more high-quality RCTs are needed to be performed in the future.

Keywords: acute exacerbation of chronic obstructive pulmonary disease, acupuncture, systematic review, meta-analysis

Introduction

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is defined as an acute worsening of respiratory symptoms, such as cough, dyspnea, and increased sputum purulence and volume, which results in additional therapy or even hospitalization.^{1,2} AECOPD severely affects lung function and health-related quality of life and has a poor long-term prognosis and increased risk of death after hospitalization, with a 5-year mortality rate of approximately 50%.^{3,4} In addition, exacerbations burden patients, caregivers, and their families.⁵ It is reported that acute exacerbations can be found 0.5–3.5 times for patients with stable COPD annually,^{6,7} and the average hospitalization cost for a person per year may be as high as 11,598 RMB.⁸ AECOPD is responsible for up to 70% of COPD-related healthcare costs, and hospital readmissions alone account for over \$15 billion per year in the US.^{1,9} In the past

20 years, no substantial progress has been made in the treatment of AECOPD¹⁰ and still focuses on bronchodilators, anti-inflammatory drugs, and glucocorticoids.^{1,11} These drugs are effective, but they cannot completely cure some symptoms in AECOPD patients.¹ Therefore, reasonable and effective complementary treatments are still needed to better manage AECOPD symptoms.

Acupuncture, as a kind of complementary and alternative therapy, has been proven to be effective in anti-inflammatory, immune regulation and enhancing the strength of diaphragm.^{12,13} The findings of past systematic reviews and meta-analyses have proved that acupuncture can effectively enhance lung function, quality of life, exercise performance, and dyspnea of COPD patients in stable phase.^{14–16} Acupuncture was recommended as a palliative treatment in patients with advanced COPD by Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines,¹ which may improve dyspnea and quality of life.¹² In recent years, research on acupuncture for AECOPD has been growing, but the findings have been inconsistent. For example, some clinical studies showed that acupuncture was beneficial in improving quality of life, lung function, and exercise performance and reducing the length of hospital stay,^{17–19} while some studies suggested negative results.^{20,21} The reason for the difference in curative effect may be caused by variability in included patients, methodological design, differences in comparison interventions, etc. Besides, variation in acupuncture protocols, such as style of acupuncture, acupoint prescription, location and number of needles, number of treatment sessions, frequency and duration of treatment sessions, needle retention time, may lead to differences in efficacy of acupuncture.^{22,23} Thus, the efficacy of acupuncture for AECOPD was still controversial. Yet, no meta-analysis has been conducted to integrate the results of acupuncture for AECOPD. Therefore, it is necessary to have data regarding its role as adjunctive therapy for patients with acute exacerbations of COPD.

Thus, the purpose of this meta-analysis was to identify the efficacy and safety of acupuncture as adjunctive therapy for patients with AECOPD by incorporating current evidence from existing clinical studies. To the best of our knowledge, this is the first meta-analysis to explore the therapeutic effect of acupuncture on AECOPD patients.

Materials and Methods

This systematic review was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement^{24,25} (Supplementary Table S1). This article was registered at PROSPERO (CRD42022372670) and is available on: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=372670.

Inclusion Criteria

1. Only randomized controlled trials (RCTs) were included.
2. Participants: males or females with AECOPD according to the GOLD guidelines,¹ Chinese expert consensus on the diagnosis and treatment of AECOPD,²⁶ and Guidelines for the diagnosis and treatment of COPD of Chinese Society of Respiratory Medicine.²⁷
3. Interventions: RCTs used acupuncture as an adjuvant to conventional western medicine were included. The type of acupuncture must be the invasive treatment with needles, such as filiform acupuncture, warm acupuncture and electroacupuncture.
4. Controls: the control group used conventional western medicine, which included health care, medication (antibiotics, glucocorticoids, bronchodilators, etc.), or mechanical ventilation, etc.
5. Regarding the data in the multi-arm trials, the groups that fit our experimental design would be compared separately with the control group, and if only one treatment group and one control group met the purpose of our study, then these two groups were extracted directly.
6. Outcomes: Primary outcome: the COPD assessment test (CAT). The secondary outcomes: the ratio of forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC), the percentage of predicted values of FEV₁ (FEV₁%), arterial partial pressure of oxygen (PaO₂), arterial partial pressure of carbon dioxide (PaCO₂), six-minute walking distance (6MWD), duration of hospitalization, and modified British Medical Research Council (mMRC) questionnaire. At least one of the above-mentioned outcomes were measured.

Exclusion Criteria

1. Studies that focus on complications related to AECOPD, such as pulmonary encephalopathy, and complications due to mechanical ventilation;
2. Qualitative studies, animal experiments, case reports and conference abstract reviews were excluded;
3. Studies that investigated acupuncture at specific “micro-systems” (such as scalp, ear or abdominal acupuncture), or investigated non-invasive acupuncture treatments (such as acupressure or transcutaneous electrical stimulation), or used injected fluids at acupuncture or trigger points;
4. Studies with incomplete and incorrect data.

Search Strategy

Relevant articles were searched and retrieved from the following databases, from database inception to July 30, 2023, without any language restrictions: China National Knowledge Infrastructure (CNKI), Wanfang Data, Chongqing VIP, Chinese Biomedical Literature Database (CBM), PubMed, Embase, Web of Science, and the Cochrane Library. The keywords used were chronic obstructive pulmonary disease (COPD), exacerbation, hospitalization, and acupuncture. Existing systematic reviews were examined to identify additional trials. The full search strategy for each of the electronic databases was shown in [Supplementary Table S2](#).

Data Extraction

Two reviewers (YCY and XGX) independently extracted the data and preliminarily screened the titles and abstracts and cross-checked them. And then, they read the full text of preliminarily included literature and make the final decision strictly following the inclusion and exclusion criteria. A third reviewer (LFR) was consulted in case of inconsistency. We examined all the retrieved articles and extracted data using a preordained form. The following information was recorded: the first author, the year of publication, diagnostic criteria, duration of COPD, sample number, intervention arms, comparative arms, acupuncture details, acupoints, outcome measurements, and adverse events.

Assessment of Risk of Bias

Two independent reviewers (LQ and TH) assessed the methodological quality of the included studies using the Version 2 of the Cochrane tool for assessing risk of bias in randomized trial (RoB2, 2019 revision).²⁸ Any disagreement was solved through discussions with a third reviewer (LFR). Five aspects are evaluated, including randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Alternative answers to the questions include Yes (Y), Probably yes (PY), Probably no (PN), No (N), and No information (NI). The risk of bias in each area can be divided into three levels: low risk, some concerns, and high risk. Finally, an overall risk of bias judgement will be summarized in terms of all five aspects above.

Certainty of Evidence

The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.²⁹ It includes 5 downgrade factors (risk of bias, indirectness, inconsistency, imprecision and publication bias) and 3 upgrade factors (large effect, dose–response gradient and plausible confounding). The quality of evidence was finally rated as high, moderate, low, and very low. Two reviewers (LQ and YCY) made the assessment independently, and if there was any disagreement, it would be checked again by a third reviewer (SMS).

Statistical Analysis

Statistical analysis was conducted performed with Stata (version 15.0, StataCorp LLC). We used mean difference (MD) with 95% confidence intervals (CI) for continuous outcomes and odds ratio (OR) with 95% CI for dichotomous outcomes. The outcome data were pooled using a random effects model. The I^2 test and χ^2 was used to identify heterogeneity among trials. Two-sided $P < 0.05$ was considered statistically significant. I^2 test would be performed to estimate the degree of heterogeneity. We regarded heterogeneity as substantial when I^2 was greater than 50% or a P value

< 0.10 on the χ^2 test.³⁰ If there was substantial heterogeneity between studies, sensitivity analysis was performed through omitting individual study by turns to evaluate the reliability and robustness of our meta-analysis results. We would try to find out possible sources of heterogeneity, and then, meta-analysis was performed by removing the study that induced heterogeneity. The funnel plots and Egger's test were conducted to assess publication bias.

Results

Search Results

A total of 561 articles were retrieved from 8 databases, and the flow chart of the screening process is displayed in Figure 1. After removing duplicated records, 369 articles remained. After reading titles and abstracts, 344 articles were excluded for not meeting the inclusion criteria. And then, the 25 articles that met the initial screening were re-screened through reading the full text, 13 articles were excluded for not meeting the inclusion criteria, and finally, 12 RCTs were included in meta-analysis.

Characteristics of Included Participants and Treatments

A total of 12 studies involving 915 individuals were included in this meta-analysis, with 460 in the experimental group, 455 in the control group. And 11 studies were published in Chinese, while one in English. All eligible studies were published from 2013 to 2022. The minimum sample size was 22 patients, while the maximum was 37 patients. Of the 12 studies, 1 study²⁰ used electroacupuncture, 11 studies used manual acupuncture. All acupuncture treatments were based

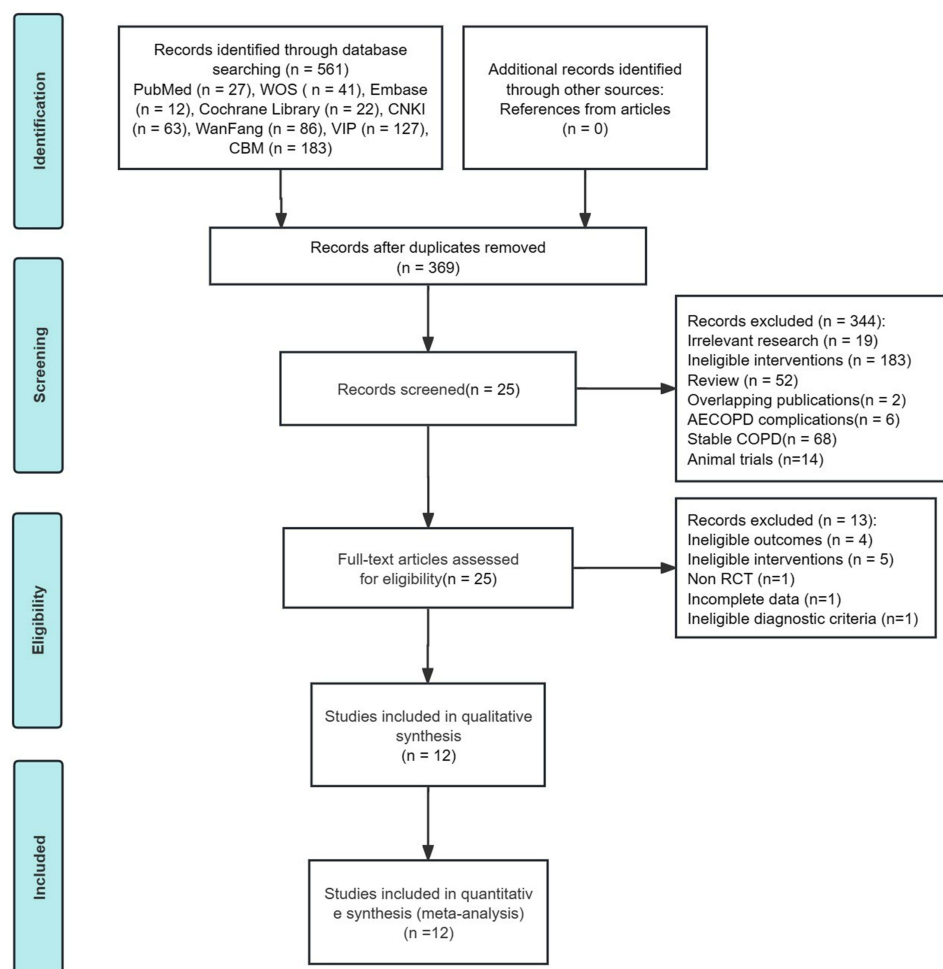


Figure 1 Flow chart of literature screening.

Notes: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Creative Commons.²⁴

on conventional western medicine. Of which, 1 study³¹ compared two kinds of hand needles with conventional western medicine, and 1 study³² compared three different acupoint selection schemes with conventional western medicine.

And 4 studies reported CAT, 6 studies reported FEV₁%, 5 studies reported FEV₁/FVC, 3 studies reported PaO₂ and PaCO₂, 2 studies reported duration of hospitalization, and 2 studies reported 6MWD. The basic characteristics of the included studies are shown in [Table 1](#).

Methodological Quality Assessment

The risk of bias assessment for each outcome was conducted according to ROB 2 ([Supplementary Figure S1](#), and [S2](#)). Eight studies^{21,32,34,36,38–41} reported adequate methods for sequence generation, while 3 studies^{20,35,37} were unclear, 1 study³³ reported inadequate methods. Only 2 studies^{21,41} reported adequate methods for allocation concealment, while 10 studies^{20,32–40} were unclear. Thus, 10 studies^{20,32–40} reported “some concern” on randomization process, 2 studies reported “low risk”.^{21,41} This study evaluated acupuncture as an adjuvant to conventional western medicine, and blinding of participants was not possible; however, FEV₁%, FEV₁/FVC, PaCO₂, PaO₂, and hospitalization duration were objective outcomes, which showed a low risk of bias in deviations from intended interventions. However, for CAT and mMRC, both of them were self-reported outcomes, and participants are not blinded; thus, high risk of bias was reported in deviations from intended interventions. All the studies and outcomes were at low risk of bias on missing outcome data and measurement of the outcome. One study²¹ assessing hospitalization duration reported “low risk” on selection of the reported result, the rest studies^{20,32–41} and outcomes reported “some concern” as no study protocol was registered or published. To sum up, the results showed that overall bias for CAT and mMRC was in “high” risk, FEV₁%, FEV₁/FVC, PaCO₂, and PaO₂ were in “some concern” and 1 RCT assessing hospitalization duration was in “low” risk.

Quality of Evidence

Quality of evidence was evaluated based on the GRADE classification. The quality of the evidence for the outcomes was not high, most of which were downgraded because of high risk of bias, inconsistency, and imprecision ([Supplementary Table S3](#)). The overall assessments were either moderate, low or very low certainty.

Outcomes

Quality of Life

The COPD assessment test (CAT)⁴² is commonly used to assess health status and quality of life in routine practice. In this review, CAT was reported in 4 studies.^{20,34,40,41} The pooled results showed that participants receiving acupuncture and conventional western medicine reported a greater improvement than participants receiving conventional western medicine alone (MD: -3.25; 95% CI: -3.73 to -2.78, $P < 0.001$). And there was no heterogeneity of results between the 4 trials ($I^2 = 0\%$) ([Figure 2](#)). Egger’s test showed that there was no significant publication bias ($P = 0.308$).

Lung Functions

FEV₁%

Pooled results from 6 studies^{20,33–35,38,39} found no statistically significant differences between acupuncture plus conventional western medicine and conventional western medicine on FEV₁% (MD: 1.83; 95% CI: -0.17 to 3.83, $P = 0.073$). The results of the 6 RCTs were homogeneous ($I^2 = 0\%$) ([Figure 3](#)). And Egger’s test showed that there was no significant publication bias ($P = 0.682$).

FEV₁/FVC

Besides, a total of 5 trials^{32,38–40,34} reported FEV₁/FVC and were included in the meta-analysis. One study (Zhang 2013)³² compared three different acupoint selection schemes with conventional western medicine, thus, the results were split into three pairwise comparisons. Pooled results showed that participants receiving adjuvant acupuncture plus conventional western medicine were more likely to have reported improvement than those treated with conventional western medicine alone (MD: 4.66; 95% CI: 2.21 to 7.12, $P < 0.001$). However, there was substantial heterogeneity of results between the 5 studies ($I^2 = 63.3\%$) ([Figure 4](#)). Sensitivity analysis was performed by excluding studies one by one. After removing one

Table 1 The basic characteristics of the included studies

Study ID	N (T/C)	Diagnostic Criteria	Age (T/C)	Course (T/C)	Acupuncture Details	Acupoints	Treatment	Control	Outcomes
Zhang 2013 (a) ³²	33/30	①	68.53±7.58/69.76±7.21	11.50±1.09/12.46±2.01	twice/day, 30min, 14d	BL13	Acupuncture+CWM	CWM	FEV1/FVC (%), Adverse events
Zhang 2013 (b) ³²	32/30	①	72.21±7.53/69.76±7.21	10.32±1.17/12.46±2.01	twice/day, 30min, 14d	SJ6	Acupuncture+CWM	CWM	FEV1/FVC (%), Adverse events
Zhang 2013 (c) ³²	30/30	①	71.47±7.48/69.76±7.21	09.43±2.15/12.46±2.01	twice/day, 30min, 14d	BL13, SJ6	Acupuncture+CWM	CWM	FEV1/FVC (%), Adverse events
Zhan 2013 (a) ³³	30/30	①	67.13±7.88/6.03 ±8.45	15.7±4.25/15.4±6.25	once/day, 3h, 10d	RN17, RN19	Acupuncture+CWM	CWM	FEV1 (%)
Zhan 2013 (b) ³³	30/30	①	66.77±7.37/6.03 ±8.45	16±5/15.4±6.25	once/day, 3h, 10d	RN17, RN19	Acupuncture+CWM	CWM	FEV1 (%)
Chen 2013 ³⁴	29/28	①③	71.72±6.73/73.14±6.33	–	Once every other day, 40min, 2 weeks.	DU20, EX-HN1, ST9, LI18, SJ17, GB21, LU9, PC6, ST36, GB34, SP9	Acupuncture+CWM	CWM	FEV1 (%), FEV1/FVC (%), CAT, Adverse events
Gao 2014 ²⁰	31/31	③	67.5±7.5/68.2±7.5	–	once/day, 30min, 20d	EX-BI	Electroacupuncture+CWM	CWM	FEV1 (%), FEV1/FVC (%), CAT, mMRC
Wang 2015 ³⁵	32/31	①	64±4.8	20.56±3.47	once/day, 30min, 40d	ST36, ST40, SP6, SP15, RN12, RN13, RN6, RN4, LU9, LU5, LU6, EX-BI	Acupuncture+CWM	CWM	PaO ₂ , PaCO ₂ , FEV1 (%)
He 2015 ³⁶	30/30	①	64.5 ±8.6	–	Once every other day, 30min, 10d	RN17, ST36, PC6, SP4, RN12, ST25, RN6	Acupuncture+CWM	CWM	Duration of hospitalization, Adverse events
Zhang 2016 ³⁷	30/30	①	64.5±8.6	–	Once every other day, 30min, 14d	RN17, ST36, PC6, SP4, RN12, ST25, RN6	Acupuncture+CWM	CWM	PaO ₂ , PaCO ₂ , FEV1/FVC (%)
Ji 2017 ³⁸	31/30	③	56.94±6.56/55.63±6.97	10.81±1.78/10.57±1.36	once/day, 30min, 14d	RN17, RN12, PC7, BL13, SJ6, GB20, BL12	Acupuncture+CWM	CWM	FEV1 (%), FEV1/FVC (%), mMRC, Adverse events
Dai 2018 ³⁹	33/35	①	66.46±5.41/66.79±5.59	6.48±3.55/7.51±2.81	once/day, 30min, 14d	BL13, BL15, BL18, BL20, BL23, SP6, ST40, HT7, RN17	Acupuncture+CWM	CWM	FEV1 (%), FEV1/FVC (%)
Xie 2019 ⁴⁰	30/29	③	64±9/65±8	8.5±3.2/9.3±1.8	once/day, 30min, 14d	BL13, ST40, LU9, ST36, LU1, SP9	Warm acupuncture+CWM	CWM	FEV1/FVC (%), CAT, Adverse events
Yuan 2021 ⁴¹	37/37	②	78±7.41/83±5.19	9.5±1.56/9.5±1.11	once/day, 30min, 10d	EX-BI, BL13, RN17, RN15, RN12, LU9, ST36, ST40	Acupuncture+CWM	CWM	Duration of hospitalization, PaO ₂ , PaCO ₂ , CAT, mMRC, Adverse events
Levy I 2022 ²¹	22/24	③	69.2 ±10.1/70.7 ±8.1	–	once/day, 15-20 min, 4d	According to different TCM syndromes	Acupuncture+CWM	CWM	Duration of hospitalization, Adverse events

Notes: (a), (b), (c): Different groups in the same article. ①: Guidelines for the diagnosis and treatment of COPD of Chinese Society of Respiratory Medicine. ②: Chinese expert consensus on the diagnosis and treatment of AECOPD. ③: GOLD guidelines.

Abbreviations: T/C, treatment group/control group; min, minute; d, day; min, minute; 6MWD, 6-minute walking distance; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; PaO₂, partial pressure of oxygen; PaCO₂, partial pressure of carbon dioxide; CWM, conventional western medicine; CAT, COPD assessment test; mMRC, modified British Medical Research Council; TCM, traditional Chinese medicine.

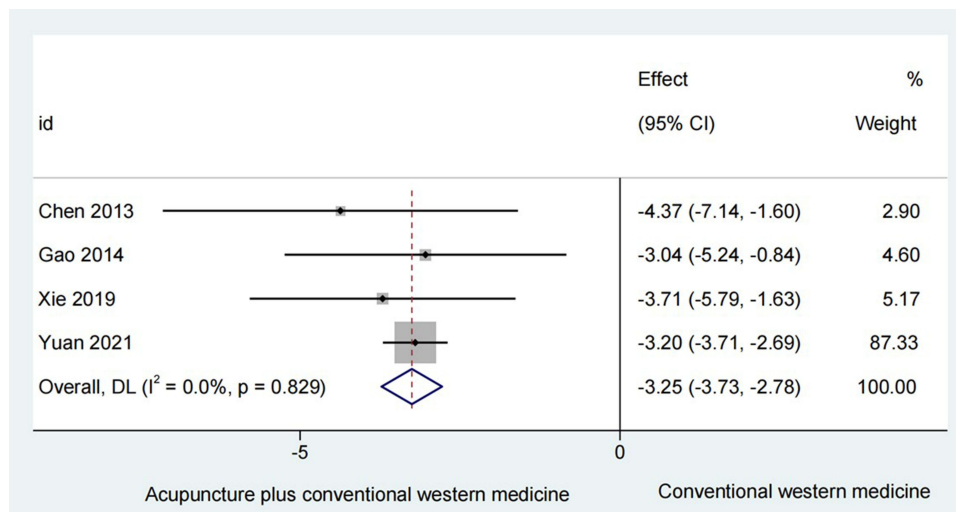


Figure 2 Acupuncture and conventional western medicine versus conventional western medicine with CAT.

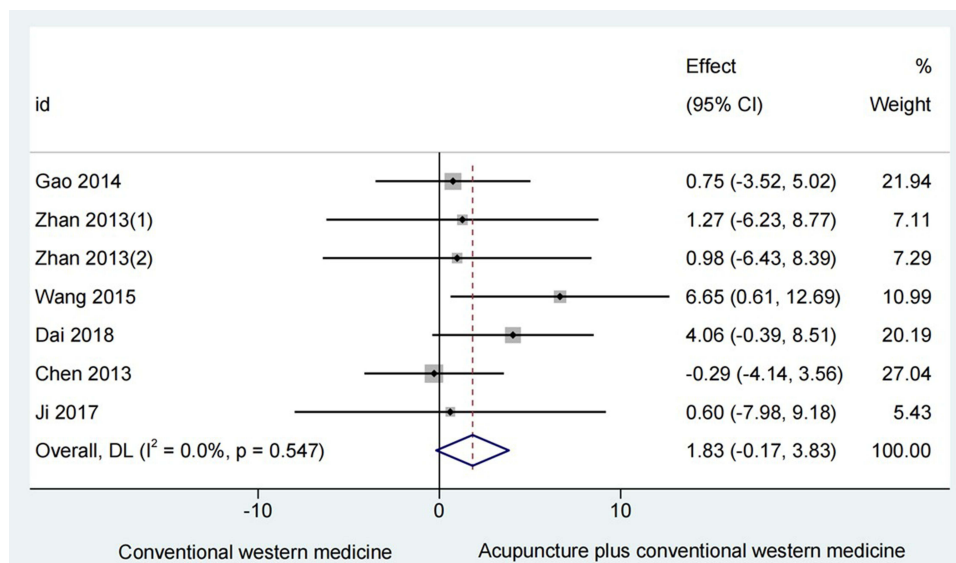


Figure 3 Acupuncture and conventional western medicine versus conventional western medicine with FEV₁%.

group of a study (Zhang 2013),³² there was no heterogeneity among studies ($I^2 = 0\%$), and a statistically significant difference was maintained between studies (MD: 3.74; 95% CI: 2.22 to 5.26, $P < 0.001$), and the results were reliable (Supplementary Figure S3, and S4). And Egger's test showed that there was no significant publication bias ($P = 0.839$).

Arterial Blood Gas

PaCO₂

A total of 3 studies^{35,37,41} reported PaCO₂ and were included in the meta-analysis. Analysis of the data indicated that there was no heterogeneity of results among the 3 trials ($I^2 = 0\%$). It showed a statistically significant benefit of acupuncture for improving PaCO₂ of AECOPD patients (MD: -1.85; 95% CI: -2.74 to -0.95, $P < 0.001$) (Figure 5). And Egger's test showed that there was no significant publication bias ($P = 0.695$).

PaO₂

Three studies^{35,37,41} evaluated the effects of adjuvant acupuncture plus conventional western medicine on PaO₂. The

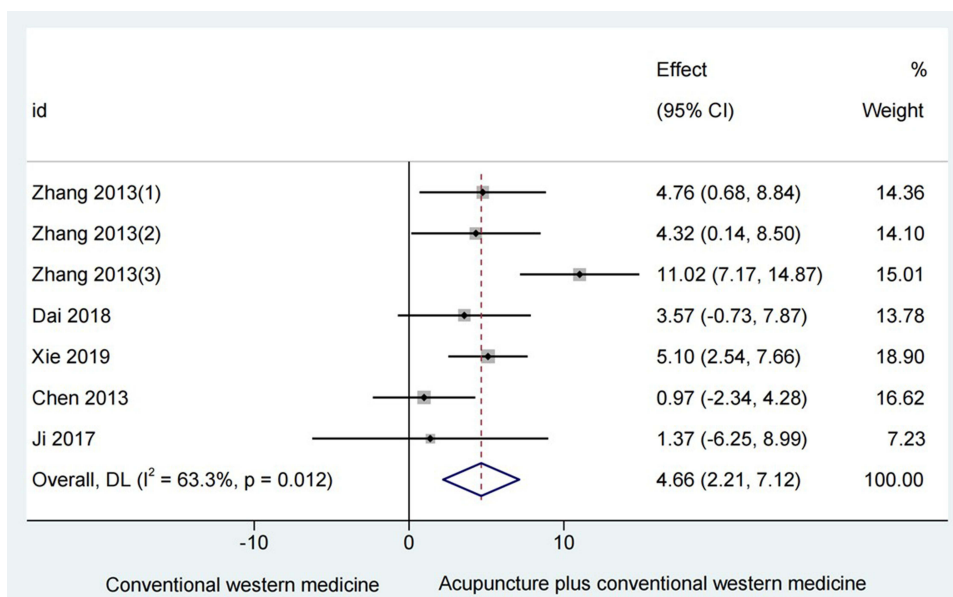


Figure 4 Acupuncture and conventional western medicine versus conventional western medicine with FEV₁/FVC.

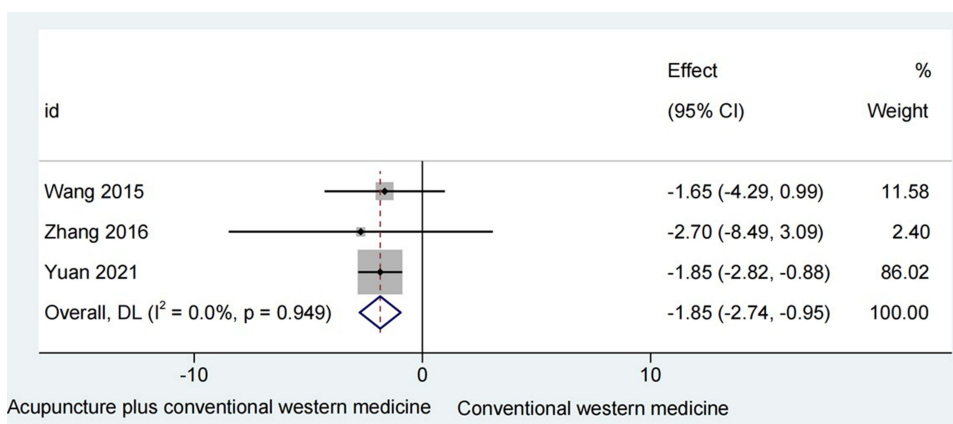


Figure 5 Acupuncture and conventional western medicine versus conventional western medicine with PaCO₂.

pooled results showed that acupuncture can significantly improve PaO₂ (MD: 5.15; 95% CI: 1.22 to 9.07, $P = 0.01$), although substantial heterogeneity was seen ($I^2 = 79.8\%$) (Figure 6). Sensitivity analysis was performed by excluding studies one by one. And after removing one study (Zhang 2016),³⁷ reduced heterogeneity was seen for PaO₂ ($I^2 = 18.3\%$), and adjuvant acupuncture could still improve PaO₂ (MD: 2.90; 95% CI: 1.22 to 4.57, $P = 0.001$) and the results were reliable (Supplementary Figure S5 and S6). And Egger’s test showed that there was no significant publication bias ($P = 0.281$).

Exercise Capacity

Two trials^{20,33} assessed exercise capacity through six-minute walking distance (6MWD) were included in the meta-analysis, of which, one study (Zhan 2013)³³ compared two kinds of hand needles with conventional western medicine. The data showed that acupuncture did not have a benefit in improving exercise capacity (MD: 96.69; 95% CI: -0.60 to 193.98, $P = 0.051$), but there was substantial heterogeneity of results ($I^2 = 90.8\%$) (Figure 7). However, sensitivity analysis performed by removing one study at a time showed opposite results after one study (Gao 2014)²⁰ was removed (Supplementary Figure S7). And Egger’s test showed that there was no significant publication bias ($P = 0.331$).

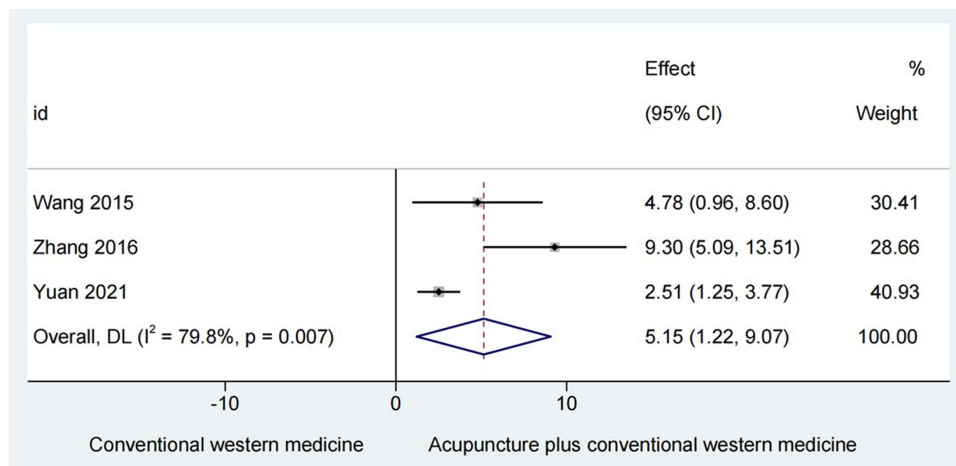


Figure 6 Acupuncture and conventional western medicine versus conventional western medicine with PaO₂.

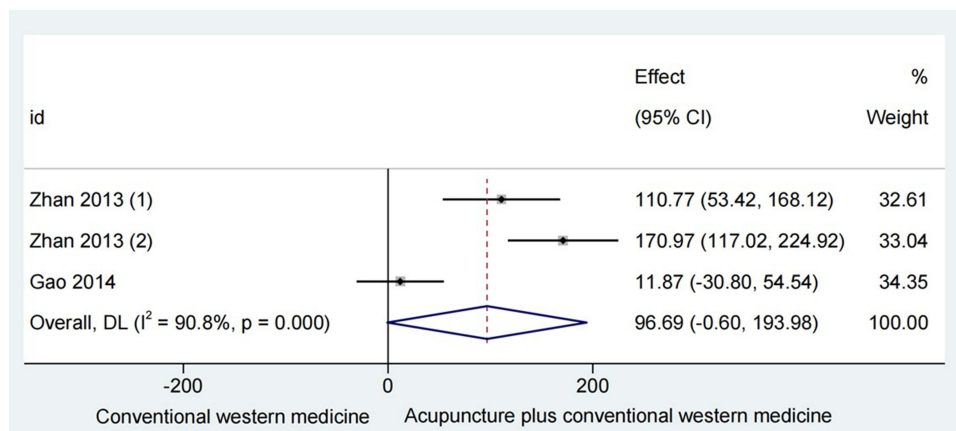


Figure 7 Acupuncture and conventional western medicine versus conventional western medicine with 6MWD.

Duration of Hospitalization

Three trials^{21,36,41} evaluated duration of hospitalization were included into meta-analysis. The between-group comparison of adjuvant acupuncture plus conventional western medicine versus conventional western medicine showed a non-significant decrease after treatment (MD: -5.70 ; 95% CI: -11.97 to 0.58 , $P = 0.075$), and there was a significant heterogeneity between trials ($I^2 = 97.7\%$) (Figure 8). Sensitivity analysis conducted by removing one study at a time. After one study (Levy I 2022)²¹ was removed, opposite result was showed (Supplementary Figure S8). Egger's test showed that there was no significant publication bias ($P = 0.909$).

Dyspnea

The modified British Medical Research Council (mMRC) questionnaire was used to evaluate breathlessness severity of AECOPD patients, and 3 trials^{20,38,41} were included in meta-analysis. The pooled results showed that there was a non-significant reduction between groups after treatment (MD: -0.19 ; 95% CI: -0.61 to 0.23 , $P = 0.376$), and significant heterogeneity was seen between trials ($I^2 = 86.4\%$) (Figure 9). However, sensitivity analysis performed by removing one study at a time showed opposite results after one study (Gao 2014)²⁰ was removed (Supplementary Figure S9). And Egger's test showed that there was no significant publication bias ($P = 0.819$).

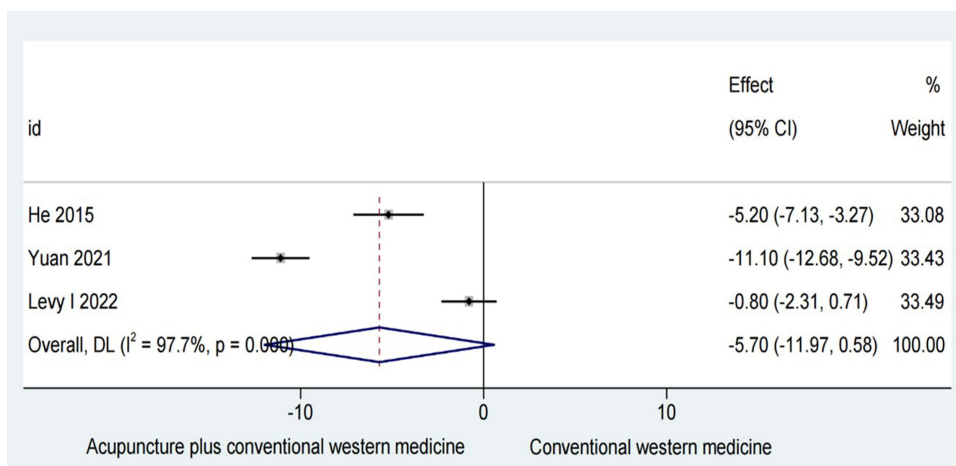


Figure 8 Acupuncture and conventional western medicine versus conventional western medicine with duration of hospitalization.

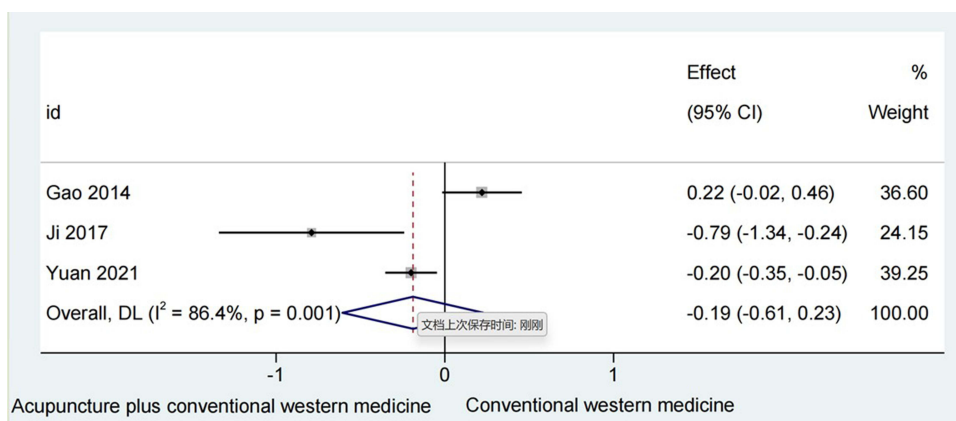


Figure 9 Acupuncture and conventional western medicine versus conventional western medicine with mMRC.

Safety of Acupuncture

Seven trials^{21,32,34,36,38,40,41} mentioned safety assessment of acupuncture, six of which reported no adverse events associated with acupuncture. Only one study³² reported mild adverse events in 45 patients, and the reported adverse events were minor and did not need any additional intervention, and no serious adverse events were reported. However, it did not describe the type of adverse events in detail. No dropouts were attributed to acupuncture-related adverse events.

Discussion

The specific drug therapy for AECOPD has not made substantial progress¹⁰ in the past 20 years, and it is still dominated by antibiotics, bronchodilators and glucocorticoids. These drugs are the cornerstones of AECOPD treatment, but alternative and more effective treatments are still in need. The purpose of this meta-analysis was to identify the efficacy and safety of acupuncture as an adjunctive treatment in patients with AECOPD. This is the first meta-analysis to investigate the effect of acupuncture on COPD patients in acute stage.

Evidence from 12 clinical trials with 915 AECOPD patients showed that compared to conventional western medicine alone, adjuvant acupuncture plus conventional western medicine could significantly improve health status and quality of life (CAT), and arterial blood gas (PaCO₂, PaO₂), but no statistically significant improvement was found in hospitalization duration, exercise performance (6MWD), and dyspnea (mMRC). For lung function, acupuncture can improve FEV₁/FVC, but no difference was found in FEV₁%. The results of existing RCTs demonstrate that acupuncture was a safe

complementary approach for AECOPD, as no serious adverse events were reported associated with acupuncture in our review. The result of methodological quality assessment showed that the quality of the included studies was not high, as the overall bias for the 12 studies was 11 RCTs in “some concern” and 1 RCT in “low” risk. There was no heterogeneity for CAT, FEV₁%, and PaCO₂. However, substantial heterogeneity was found in FEV₁/FVC, PaO₂, hospitalization duration, 6MWD, and mMRC. For FEV₁/FVC, one parallel group of Zhang et al³² may contribute to heterogeneity due to the variations in acupuncture protocols, as it selected more acupoints (more needles) than the other two groups. At the same time, the frequency of acupuncture in Zhang et al study was twice a day, while in other studies it was once a day or once every other day, which was more than in other studies. For PaO₂, the substantial heterogeneity may be due to the severity of disease, as patients in the study of Yuan et al⁴¹ and Wang et al³⁵ suffered from respiratory muscle fatigue, thus, the condition was severer than patients in the study of Zhang et al.³⁷ Sensitivity analyses were attempted through removing single studies at a time, which showed reduced heterogeneity for FEV₁/FVC and PaO₂. The substantial heterogeneity of 6MWD, mMRC, and hospitalization duration may be due to the details of acupuncture operations, such as needle retaining time, acupoints, depth of needle insertion, type of needles, treatment duration and the severity of disease, type and dose of conventional western medicine between studies. Sensitivity analyses were conducted, but the heterogeneity was not reduced.

Few evidence-based studies have focused on acute exacerbation of COPD. One systematic review⁴³ included 4 studies of acupuncture in the treatment of AECOPD, which showed that acupuncture can improve lung function, hypoxia, and carbon dioxide retention. However, due to the heterogeneity of the acupuncture scheme, the results were not pooled, and three of them were abdominal acupuncture, which belongs to micro-system acupuncture and was excluded in our review. The existing RCTs demonstrated the effect of acupuncture as adjunctive therapy in patients with AECOPD, for example, acupuncture can improve CAT,^{20,41} FEV₁/FVC,^{32,40} PaCO₂,^{37,41} and PaO₂,^{37,41} which was consistent with our findings. CAT is used for a comprehensive assessment of symptoms, including cough and sputum, chest tightness, dyspnea, fatigue, activity limitation, sleep and energy.⁴² It is useful in determining the impact of COPD on the patient's health status, and the risk of exacerbation, hospitalization, or death, in order to guide treatment. Thus, trends and changes in CAT are more valuable than a single measurement.¹ In our review, acupuncture is effective in CAT, and no heterogeneity was reported. Thus, acupuncture may improve AECOPD symptoms, such as cough, phlegm, dyspnea, and exercise capacity. However, inconsistency was existed in the effect of acupuncture for 6MWD, mMRC and hospitalization duration. Although, the pooled results of this meta-analysis showed a negative effect on these outcomes, sensitivity analysis showed unstable pooled results of these three outcomes. For 6MWD, Gao et al²⁰ study showed there was no difference between acupuncture plus conventional western medicine and conventional western medicine, while the two groups of Zhan et al³³ study showed that acupuncture plus western medicine significantly improved exercise endurance. The reason may be that in Gao et al study, only one acupoint was selected, while Zhan et al study selected multiple acupoints, leaving the needle for a longer time (3 hours) and a deeper depth. For mMRC, Gao et al²⁰ study also showed a negative result, while the study of Ji et al and Yuan et al^{38,41} showed a significant improvement. For hospitalization duration, Levy et al²¹ study showed no difference between two groups, while the study of He et al and Yuan et al^{36,41} showed that adjunctive acupuncture significantly shortened the length of hospital stay. This may be because in Levy et al study, patients received fewer acupuncture treatment sessions (only 4 sessions). Besides, the small number of included studies, small sample size and low quality may also contribute to the negative effects of acupuncture on these outcomes. And evidence-based studies^{14–16} have showed that acupuncture can improve 6MWD (exercise capacity) and mMRC (breathlessness) in stable COPD patients. Thus, based on the problems in the existing RCTs, the effect of acupuncture AECOPD deserves more attention.

In general, available evidence showed that acupuncture may be a safe and effective complementary therapy for AECOPD patients. It can be used as adjunctive therapy to improve quality of life, lung function (FEV₁/FVC) and arterial blood gas (PaCO₂ and PaO₂), but it showed no effect on lung function (FEV₁%). From a clinical perspective, this review provides an alternative non-pharmacological approach for patients and physicians. Although, exercise capacity, hospitalization duration and dyspnea were controversial, this may be solved through more high-quality and large-sample RCTs in the future.

Limitations

There were some limitations in this study. Firstly, the number of included studies and the sample size in each study are relatively small, with a total of 12 articles involving 915 subjects, which may decrease the power of the evidence for trials supporting the benefits of acupuncture for AECOPD. Secondly, the quality of the included studies is generally not high. For example, randomization and allocation concealment were unclear in some studies, and because of the nature of acupuncture and our design, it is difficult to achieve blinding for participants and acupuncturists, which could affect the estimation of outcome measures. Most of the studies have not been registered or published a study protocol; thus, there is a bias for selection of the reported result. Fortunately, most of the outcome measurements in this meta-analysis were objective outcomes, which decreased the detection bias of outcomes and deviations from intended interventions. For the limitations, we may call for clinical studies to follow the CONSORT statement⁴⁴ strictly. For example, stringent process of randomization and allocation concealment, adequate outcome measurements and effective sample size should be considered in the future clinical studies.

Conclusion

This meta-analysis suggested that acupuncture may be an effective and safe adjunctive therapy in improving quality of life and arterial blood gas for AECOPD patients, but controversy was found in lung function, hospitalization duration, exercise performance, and dyspnea. The quality of evidence is limited; thus, more high-quality RCTs are needed to be designed and performed in the future.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

All data used for this review were extracted from published RCTs; thus, ethics approval and patient consent were not required. The results of this study will be published in peer-reviewed journals and conference presentations.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest in this work.

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