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Shengmai injection as an adjunctive therapy for the treatment of chronic obstructive pulmonary disease: A systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the clinical efficacy of Shengmai injection for the treatment of chronic obstructive pulmonary disease (COPD) through an evidence-based approach.

Methods: Randomized controlled trials (RCTs) investigating the effect of Shengmai injection on COPD were included in this study. Seven electronic databases were searched to obtain eligible studies. The quality of the included RCTs was evaluated according to the Cochrane Risk of Bias Assessment Tool. When appropriate, meta-analysis of the data was conducted by RevMan 5.3 software and Stata 13.0 software. The relative risk (RR) or mean difference (MD) and 95% confidence interval (CIs) were reported for dichotomous or continuous outcomes, respectively. Sensitivity analysis was performed to verify the independence of the results. Funnel plots and the Begg and Egger tests were implemented to determine the potential publication bias.

Results: Ultimately, 23 RCTs were included, involving 1804 participants. Meta-analysis showed that the combination of Shengmai injection and western medicine (WM) could achieve a better effect than WM alone in terms of improving the clinical total effective rate (RR = 1.20, 95% CIs: 1.15–1.24), pulmonary function (FEV_1(L): MD = 0.41, 95% CIs 0.32 to 0.49; FEV_1(%): MD = 6.21, 95% CIs: 2.72–9.71), blood gas index (PaO_2: MD = 6.13, 95% CIs: 2.93–9.32; $PaCO_2$: MD = -6.2, 95% CIs: -11.63 to -0.77), immunoglobulin levels (IgG: MD = 3.55, 95% CIs: 3.10–3.99; IgA: MD = 0.34, 95% CIs: 0.31to 0.38; IgM: MD = 0.35, 95% CIs: 0.27 to 0.42), C-reactive protein levels (MD = −8.05, 95% CIs: −10.11 to −6.00) and the lung rale disappearance time (MD = −2.57, 95% CIs: -3.19 to -1.95). Additionally, the CAT score, mMRC and average hospitalization time were also reduced significantly by Shengmai injection plus WM. Among 11 RCTs that mentioned safety issues, 6 RCTs found no adverse events, and the other 5 RCTs reported the details of adverse events.

Conclusion: Shengmai injection may positively influence COPD in combination with WM. However, firm conclusions could not be draw due to the low quality of the evidence. Further high-quality studies are still required to test the efficacy of Shengmai injection for this condition.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common and frequently occurring sickness with a long disease course and irreversible development. COPD ends with chronic respiratory failure, resulting from an abnormal inflammatory response to harmful particles and gases[1] With the exacerbation of air pollution, acceleration of ageing populations and increase in smokers, COPD has become a disease characterized by high morbidity, disability and mortality. Additionally, COPD treatment may consume enormous social and medical resources[2–3] Western medicine (WM) alone does not achieve satisfactory effects and has other untoward effects.[4] At present, regular WM mainly includes antibiotics, glucocorticoid, bronchiectasis drugs and so on. However, these also have certain side effects. Moreover, the efficacy is temporary in most cases.[5–6] In the meantime, research has shown that traditional Chinese medicine (TCM) theory combined with WM can achieve certain curative effects for the treatment of COPD.[7–8]

In the view of TCM theory, COPD belongs to “lung distension” or

Abbreviations: 95% CIs, 95% confidence intervals; ADEs, adverse drug events; ADRs, adverse drug reactions; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FEV_1, forced expiratory volume in one second; MD, mean difference; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; RCTs, randomized controlled trials; RR, relative risk; WM, western medicine

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"cough asthma" due to deficiencies in both *Qi* and *Yin*. Therefore, tonifying *Qi* and *Yin* is set as the principal treatment goal[6] Among TCM therapies, Shengmai injection is widely utilized for COPD. In the clinic, Shengmai injection is used alongside WM. The main function of Shengmai injection is to replenish *Qi-Yin* deficiency. In addition, pharmacology experiments have shown that Shengmai injection contains ginsenoside, organic acid, schizandrin and various microelements, which play important roles in decreasing pulmonary artery pressure, improving gas exchange function, resisting inflammation, restraining bacteria and boosting immunity[9] Clinically, the chief adverse reaction is the anaphylactic reaction, usually resulting from improper clinical application.[10] Retrieval indicated that many randomized controlled trials (RCTs) have reported the efficacy of Shengmai injection combined with WM for the treatment of COPD. However, the evidence from single trials is weak, and the curative effects of this treatment have not been approved for clinical guidelines. As a result, it is necessary to evaluate the clinical efficacy and safety of Shengmai injection for the treatment of COPD. Based on clinical data, this study was designed to provide more insight for the selection of COPD treatment.

2. Methods

2.1. Inclusion criteria

2.1.1. Types of studies

RCTs that assessed the combination of Shengmai injection and WM relative to drugs alone for COPD were included.

2.1.2. Types of participants

COPD, which is diagnosed by explicit criteria,[11]was the target disease. The participants had no limitations in terms of age, gender, race and disease severity.

2.1.3. Types of comparisons

The control treatments were any kind of WM for the treatment of COPD, including oxygen intake, anti-inflammatories, relief of cough and asthma, reduction of phlegm and so on. The experimental interventions were the combination of Shengmai injection and the controls.

2.1.4. Outcomes

The outcomes included the clinical total effective rate, CAT score, mMRC score, average hospitalization time, pulmonary function index (FEV_1 (L), FEV_1 (%)), blood gas index (PaO_2 (mmHg), $PaCO_2$ (mmHg)), immunoglobulin index (IgG (g/L), IgA (g/L), IgM (g/L) and T cell subsets), C-reactive protein (CRP (mg/L)), the lung rale disappearance time (d) and adverse drug reactions/adverse drug events (ADRs/ADEs). The clinical total effective rate was calculated by the following formula: (number of remarkable recovery participants + number of basic recovery participants)/total number of participants × 100%. For the remarkable recovery participants, clinical symptoms disappeared, and laboratory examinations and X-rays were normal. Basic recovery participants showed improvement of the above symptoms. When the clinical symptoms, laboratory examinations and X-rays showed no amelioration or even started to deteriorate, the treatment was regarded as invalid.

2.2. Exclusion criteria

A study was excluded if no available data were obtained after contact with the original authors. Plagiarism was also excluded.

2.3. Search strategy

Seven databases were searched from initiation to August 25, 2018, including the China National Knowledge Infrastructure Database, China Science and Technology Journal Database, Wanfang database, SinoMed, PubMed, the Cochrane Library and Embase. The search strategy for PubMed is shown below. Furthermore, correlative reference documents were manually retrieved.

#1 "Chronic Obstructive Pulmonary Disease" [Mesh]

#2 "COPD" [Title/Abstract] OR "chronic obstructive airway disease" [Title/Abstract] OR "COAD" [Title/Abstract] OR "chronic obstructive lung disease" [Title/Abstract] OR "chronic air-flow obstruction" [Title/Abstract]

#3 #1 OR #2

#4 "shengmai zhusheye" [Title/Abstract] OR "shengmai zhusheji" [Title/Abstract]) OR "shengmai injection" [Title/Abstract]) OR "shengmai" [Title/Abstract]

#5 #3 AND #4

2.4. Data extraction

Two researchers read the titles and abstracts of the identified literature independently and then filtered out repetitive citations, reviews, pharmacological experiments and irrelevant literature. The rest of the RCTs were screened based on their full text to determine whether they met the included criteria or not. Any disagreement was resolved by discussion or a third researcher. The following information was extracted from RCTs: ① the basic study information: first author and publication date; ② the features of the participants: the experimental group and control group samples, gender proportion, average age and specific intervention; ③ the outcome data; and ④ the type of RCT and the key elements of risk assessment.

2.5. Quality assessment

Two reviewers independently evaluated the methodological quality by using the Cochrane Risk of Bias Assessment Tool, Version 5.1.0[12] The items included random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Each item was categorized into 3 levels: high risk, unclear risk and low risk. The divergence was judged by a third researcher.

2.6. Data analysis

Review Manager 5.3[13–14] was adapted to analyse the data. Relative risk (RR) and its 95% confidence intervals (CIs) were used to estimate dichotomous outcomes, while mean difference (MD) and its 95% CIs were presented to assess continuous variables. The statistical heterogeneity among various studies was analysed by I^2. When $I^2 < 50\%$,[15] a meta-analysis was performed using the fixed-effect model; Otherwise, the random-effect model was applied. Stata 13.0 software was used for the sensitivity analysis to verify the independence of the results. In the sensitivity analysis, we reanalysed the meta-analysis by excluding one of the eligible RCTs at a time and displaying the results with graphical representation. In addition, funnel plots and the Begg and Egger test were conducted to assess potential publication bias if appropriate.

This study gathered only RCT data, and the procedure did not involve any patients' personal data or harm to any patient. Therefore, it was unnecessary to obtain ethics approval and consent to participate.

3. Results

3.1. Literature selection

Through electronic searching, 227 literature citations were identified. After removing repetitive citations, reviews, pharmacological experiments and irrelevant literature, there were 42 RCTs in total. By reading the full text, 23 RCTs were ultimately included. The exclusion

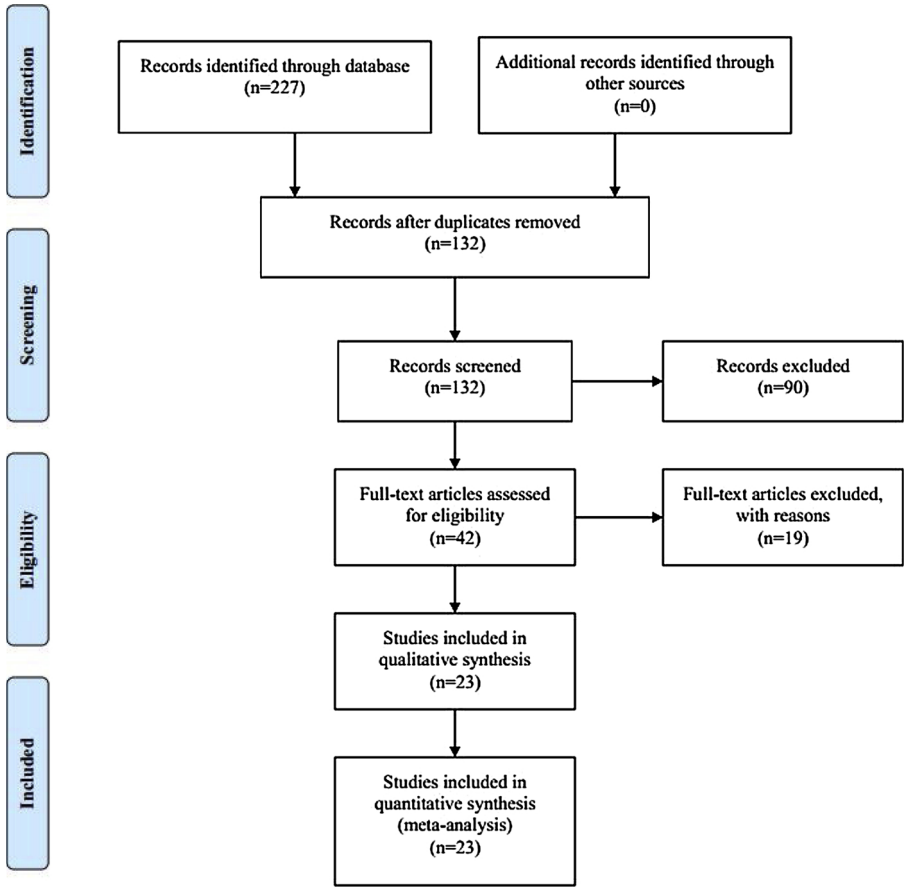

Fig. 1. Flow chart of literature search.

reasons were as follows: ① unmatched interventions (12 RCTs); ② did not complied with the diagnostic criteria (6 RCTs); ③ lack of full text (1 RCT). All included RCTs were published in Chinese from 2002 to 2016. The flow diagram showing filtration is presented in Fig. 1.

3.2. Study characteristics

A total of 1804 participants in 23 RCTs were included, involving 914 cases in the experimental group and 890 cases in the control group. All participants were diagnosed as having COPD by the diagnostic standard, among which male participants accounted for 62.7% of the total population, with centralization of the middle-aged and elderly. The control group intervention was WM, which mainly consisted of: oxygen therapy; anti-inflammatory therapies: piperacillin sodium/tazobactam sodium, levofloxacin injection, glucocorticoids and so on; relief of cough and asthma: for example, theophylline sodium glycinate tablets; reduction in phlegm: ambroxol hydrochloride, acetylcysteine, etc. The experimental group consisted of Shengmai injection plus the same WM therapies. The period of treatment ranged from 7 to 28 days. Characteristics of included RCTs were summarized in Table 1.

3.3. Quality assessment

The meta-analysis used the Cochrane Risk of Bias Assessment Tool to perform quality assessment. ① Selection bias (random sequence generation and allocation concealment): 3 RCTs adapted a random number table to generate randomization, 1 RCT utilized a draw. Therefore, the selection bias of these RCTs was evaluated as "low risk". The remaining RCTs referred to only random grouping, and the selection bias was evaluated as "unclear risk". The selection bias with allocation concealment was "unclear risk" because of insufficient information. ② Performance bias: only 1 RCT was conducted with single blinding, and its performance bias was evaluated as "high risk" because the colour and usage of Shengmai injection had the potential to break the blinding. The rest of the RCTs did not provide information on blinding, and their performance bias was "unclear risk". ③ Detection bias: The detection bias was "unclear" because none of the included RCTs conducted blinding towards outcomes assessors. ④ Attrition bias: none of the included RCTs assessed had incomplete data, so the attrition bias was estimated as "low risk". ⑤ Reporting bias: considering that the complete implementation scheme could not be acquired, the reporting bias was "unclear risk". ⑥ Other bias: this item was assessed as "unclear risk" because of the lack of information. The overall level of the included RCTs was general. Quality assessment of the included RCTs is demonstrated in Fig. 2.

3.4. Outcomes

3.4.1. Clinical total effective rate

In total, 20,[6,16,18–27,29–35,37] RCTs tested the clinical total effective rate. A heterogeneity test showed that I^2 was equal to 30%, and the fixed-effect model was selected. Pooled results showed amelioration in favour of the experimental group in terms of the clinical total effective rate (RR = 1.20, 95% CIs: 1.15–1.24, $P < 0.00001$, Fig. 3). The difference between the two groups was statistically significant.

3.4.2. Sensitivity analysis

A sensitivity analysis for the clinical total effective rate was carried out to verify the independence of the results, which was done by excluding RCTs one at a time to re-synthesize the data. The effect size did not result in a qualitative transformation, and the results signified that the included RCTs had good stability. The full results are shown in

Table 1
Study characteristics.

ID	Sample size (EG/CG)	Sex (M/F)	Age (y)	Intervention of EG	Intervention of CG	Course (d)	Outcomes
Zheng 2016[6]	47/47	62/32	E:61.41 ± 10.67; C:59.59 ± 10.68	Shengmai injection 80 ml + WM	WM	14	①③④⑤⑧⑩
Chen 2016[16]	47/47	57/37	E:62.80 ± 6.20; C:63.32 ± 6.52	Shengmai injection 50 ml + WM	WM	14	①⑨⑪
Nie 2016[17]	58/56	69/45	E:72.40 ± 1.21; C:71.50 ± 1.23	Shengmai injection 50 ml + WM	WM	28	②⑪
Li 2016[18]	39/39	47/31	E:44.30 ± 5.70; C:44.70 ± 4.90	Shengmai injection 50 ml + WM	WM	14	①④⑥
Zhou 2015[19]	31/31	37/25	E:64.63 ± 7.32; C:63.57 ± 6.73	Shengmai injection 50 ml + WM	WM	14	①⑨
Lv 2015[20]	36/36	45/27	70.57 ± 5.76	Shengmai injection 50 ml + WM	WM	14	①⑨⑥⑦⑪
Pu 2014[21]	52/52	61/43	65.3 ± 2.6	Shengmai injection 20 ml + WM	WM	7	①⑪
Zhai 2014[22]	75/75	87/63	E:35.07 ± 5.12; C:33.89 ± 5.19	Shengmai injection 40 ml + WM	WM	14	①④⑪
Zhong 2014[23]	40/38	47/31	E;62.20 ± 9.50; C:57.80 ± 8.30	Shengmai injection 50 ml + WM	WM	14	①⑥⑦
Chen 2013[24]	31/31	37/25	61.4 ± 5.6	Shengmai injection 40 ml + WM	WM	14-28	①⑨⑪
Qian 2013[25]	32/32	49/15	E:74.35; C:75.69	Shengmai injection 60 ml + WM	WM	7-12	①⑪
Cheng 2013[26]	75/75	72/78	E:68.3 ± 8.60; C:68.8 ± 9.10	Shengmai injection 80 ml + WM	WM	14	①④⑤⑧
Ren 2013[27]	30/30	39/21	E:61.70 ± 5.60; C:62.40 ± 5.10	Shengmai injection 50 ml + WM	WM	14	①
He 2013[28]	30/30	37/23	69.20	Shengmai injection 50 ml + WM	WM	14	⑥⑦⑧
Qian 2011[29]	35/35	43/27	E:60.70 ± 5.60; C:61.10 ± 5.50	Shengmai injection 50 ml + WM	WM	14	①⑪
Tan 2008[30]	30/30	43/17	E:63.20; C:64.10	Shengmai injection 40 ml + WM	WM	14	①
Zheng 2008[31]	30/30	51/9	E:66.30; C:67.20	Shengmai injection 80 ml + WM	WM	14	①⑩
Chen 2008[32]	45/40	46/39	E:64.00-92.00; C:63.00-90.00	Shengmai injection 30 ml + WM	WM	14	①
Wang 2007[33]	32/28	18872	E;69.50 ± 7.80; C:69.30 ± 8.00	Shengmai injection 60 ml + WM	WM	14	①⑥⑦⑪
Gao 2006[34]	25/20	33/12	E:60.46 ± 9.58; C:60.52 ± 8.65	Shengmai injection 100 ml + WM	WM	7	①
Wang 2006[35]	32/28	51/9	E:66.30; C:67.20	Shengmai injection 60 ml + WM	WM	14	①⑪
Yin 2006[36]	30/30	39/21	E:49.38; C;47.62	Shengmai injection 50 ml + WM	WM	14	④⑤⑥⑦
Zhong 2002[37]	32/30	35/27	E:41.00-80.00; C:42.00-81.00	Shengmai injection 50 ml + WM	WM	14	⑧

EG = experimental group, CG = control group, M = male, F = female, WM: oxygen therapy; anti-inflammatory therapies: piperacillin sodium/tazobactam sodium, levofloxacin injection, glucocorticoids and so on; relief of cough and asthma: for example, theophylline sodium glycinate tablets; reduction of phlegm: ambroxol hydrochloride, acetylcysteine and et al. y = years, d = days, outcomes: ① = clinical total effective rate, ② = CAT score and mMRC score, ③ = average hospitalization time, ④ = FEV_1(L), ⑤ = FEV_1(%), ⑥ = PaO_2, ⑦ = $PaCO_2$, ⑧ = immunoglobulin, ⑨ = CRP, ⑩ = the lung rale disappearance time, ⑪ = ADRs/ADEs.

Fig. 4.

3.4.3. Publication Bias

A funnel plot illustrating publication bias for the clinical total effective rate is shown in Fig. 5. The distribution of the points was asymmetric, and 3 points were located outside of the line. The overall publication bias was probably subsistent. The dissymmetry of the funnel plot may indicate an association with publication bias. However, the results of the Begg test ($P = 0.08 > 0.05$) and the Egger test ($P = 0.985 > 0.05$) indicated no evidence of significant publication bias. In summary, there may be a small publication bias.

3.4.4. CAT score and mMRC score

One RCT[17] reported the CAT score and the mMRC score. With treatment, the CAT score and the mMRC score of the experimental group showed significant improvement relative to the control group. The difference between the groups was statistically significant. The specific data are shown in Table 2.

3.4.5. Average hospitalization time

One RCT[6] made compared average hospitalization time between the two groups. The outcome revealed that Shengmai injection combined with WM better reduced the average hospitalization time. The reduction was statistically significant. The specific data are shown in Table 2.

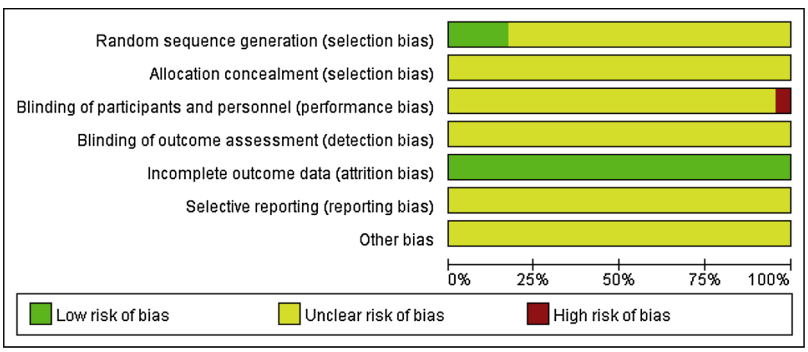

Fig. 2. Risk of bias summary.

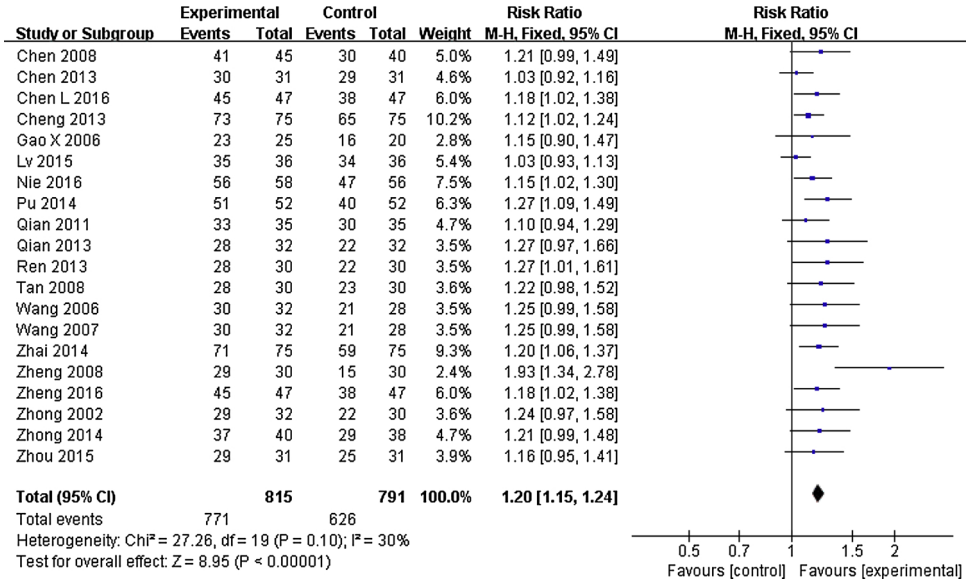

Fig. 3. Forest plot of the clinical total effective rate.

3.4.6. Pulmonary function index

In total, 5[6,18,22,26,36] RCTs referred to FEV_1(L) and 3 RCTs[6,26,36] reported FEV_1(%). The results of a meta-analysis indicated that a combination of Shengmai injection and WM produced better FEV_1(L) and FEV_1(%) values than the control group. This outcome showed statistical significance. The details are given in Table 3.

3.4.7. Blood gas index

The blood gas index of this study included PaO_2 and $PaCO_2$. Six[18,20,23,28,33,36]RCTs reported PaO_2,[20,23,28,33,36] RCTs examined $PaCO_2$. The results indicated that the experimental group showed good effects on PaO_2 and $PaCO_2$. The difference between the two groups was statistically significant. More details are presented in Table 3.

3.4.8. Immunoglobulin index

IgG, IgA, IgM and T cell subsets were investigated in this study. Three[6,26,37]RCTs made comparisons for IgG, IgA and IgM, and 1 RCT[28] reported T cell subsets. The results showed that Shengmai injection plus WM promoted IgG, IgA and IgM relative to WM alone. The difference

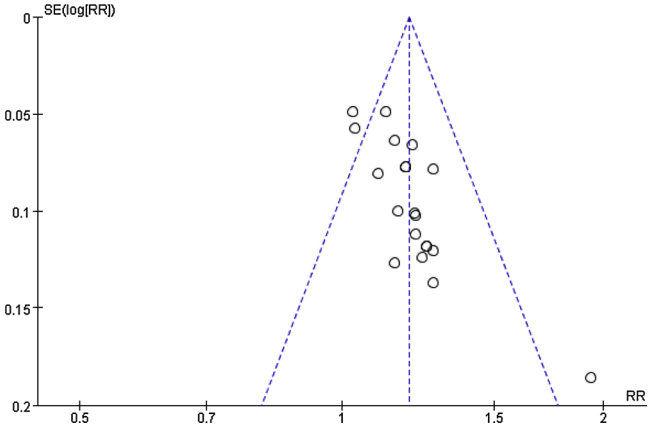

Fig. 5. Funnel plot of the clinical total effective rate.

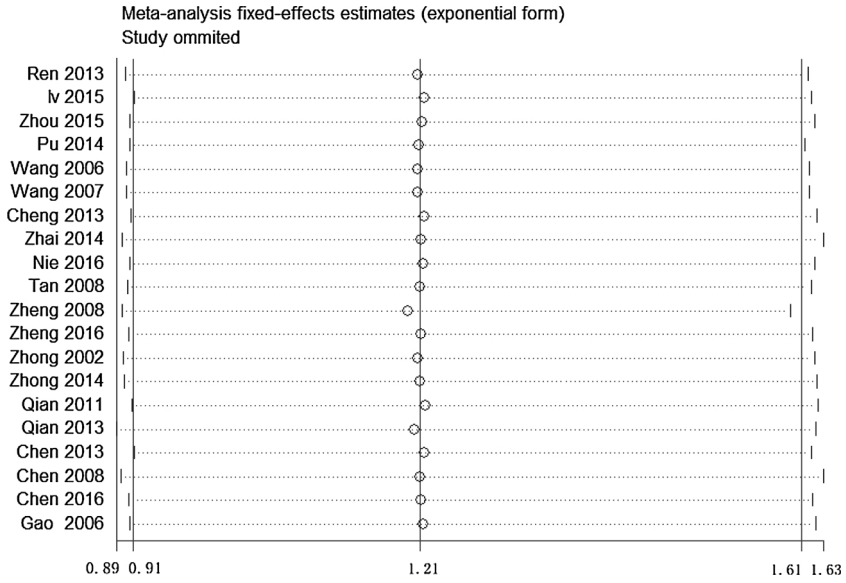

Fig. 4. Sensitivity analysis of the clinical total effective rate.

Table 2
Meta-analysis of CAT score, mMRC score, average hospitalization time and T cell subsets.

outcomes		EG		CG		P (compared between EG and CG
		Mean value	Standard deviation	Mean value	Standard deviation	
CAT score		12.3	–	14.9	–	< 0.05
mMRC score		1.45	–	1.98	–	< 0.05
Average hospitalization time (d)		16.87	3.08	37.64	3.46	< 0.05
T cell subsets (%)	$CD3^+$	68.75	10.28	65.28	11.00	> 0.05
	$CD4^+$	40.74	8.47	47.52	10.04	> 0.05
	$CD8^+$	22.78	6.37	22.44	9.00	> 0.05

was statistically significant between the two groups. More details are presented in Table 3. The levels of the T cell subsets were remarkably ameliorated, although there was no evident difference between the two groups. Specific data on T cell subset levels is shown in Table 2.

3.4.9. CRP

A total of 4 RCTs[16,19,20,24] examined CRP. The meta-analysis results showed that there was a statistically significant difference between the two groups, and a combination of Shengmai injection and WM could better reduce CRP levels. More details are presented in Table 3.

3.4.10. Lung rale disappearance time

Two RCTs[6,31] referred to the lung rale disappearance time. The results demonstrated that the combination of Shengmai injection and WM could significantly shorten the lung rale disappearance time. More details are presented in Table 3.

3.5. Safety

Among the 23 RCTs, 6 [17,21,31–33,35] RCTs indicated that there were no obvious ADRs/ADEs during RCT implementation, while 5 [16,20,22,24,29] RCTs provided details of ADRs/ADEs, as follows: 1 case of local skin rash, 1 case of fever, 1 case of insomnia and 6 cases of gastrointestinal reaction in the control group, and 5 cases of gastrointestinal reaction in the experimental group. Moreover, 5 cases of dry mouth occurred but were not specified by group. In addition, Chen AZ's RCT reported one ADR/ADE in the experimental group and 2 ADRs in the control group, which had no specific symptoms. However, no severe ADRs/ADEs occurred. The rest of the 12,[6,18–19,23,25–28,30,34,36–37] RCTs did not refer to the safety of Shengmai injection.

4. Discussion

COPD is a sickness featuring continuous air-flow limitation, which can be prevented and cured. Additionally, COPD has many complications and is associated with inflammatory reactions[38] WM therapies can relieve symptoms, but tolerance is difficult to avoid and even reduces the efficacy of treatment[6] Shengmai injection consists of *red ginseng, radix ophiopogonis* and *Schisandra chinensis*. Specifically, *radix ophiopogonis* can nourish lung and *Yin*, *Schisandra chinensis* can be used to constrain the lung and nourish the spirit and *red ginseng* reinforces vital energy and enhances immunity[16] In this study, Shengmai injection combined with WM is effective for the treatment of COPD. Shengmai injection not only improves the total clinical efficiency but also has the advantage of ameliorating the pulmonary function index, blood gas index, immunoglobulin index, CRP and the lung rale disappearance time. Attentionally, Shengmai injection plus WM was better than WM alone for lowering $PaCO_2$ according to the results ($P = 0.03 < 0.05$), although the data from Zhong[23] showed the opposite effect. This difference may be caused by faults in the original data or other reasons; more evidence is needed to further verify these results.

Regarding safety, according to relevant RCTs,[39–40] the ADRs/ADEs of Shengmai injection primarily involved tetter, nausea, emesis, diarrhoea, palpitation, dry mouth and so on. ADRs/ADEs mainly occurred in people more than 35 years old and within one hour after medication. Factors mainly included solvent, pH, temperature and primary disease. This study found that ADRs centred around gastrointestinal reaction, including 6 cases in the experimental group and 5 cases in the control group. Obvious differences between the two groups were not reflected. Additionally, approximately half of the included RCTs did not report ADRs/ADEs. Given these findings, the safety of Shengmai injection should be explored in depth.

At present, only 1 meta-analysis published in 2016 concerning Shengmai injection for the treatment of COPD[41] was retrieved. Seven RCTs were included, including RCTs and quasi-RCTs. The outcomes were the clinical total effective rate and pulmonary function index. By contrast, our study's advantages are as follows: ① the method of retrieval was more comprehensive, and the retrieval strategies were detailed. ② The inclusion criteria were more stringent, the control group intervention used only WM, while the experimental group used Shengmai injection plus the control group intervention. ③ The outcomes were more complete, referring to the clinical total effective rate, average hospitalization time, pulmonary function index, blood gas index, immunoglobulin index, CRP and the lung rale disappearance time. Furthermore, the safety of Shengmai injection for the treatment of COPD was analysed as well. ④ As widely used quality of life scales, the

Table 3
Meta-analysis of other outcomes.

Outcomes		heterogeneity		Model	*MD* [95% CI]	*P* (compared between EG and CG)
		P	I^2 (%)			
pulmonary function index	FEV_1 (L)	0.87	0	fixed-effect	0.41 [0.32, 0.49]	< 0.00001
	FEV_1 (%)	0.02	73	random-effect	6.21 [2.72, 9.71]	0.0005
blood gas index	PaO_2 (mmHg)	< 0.00001	94	random-effect	6.13 [2.93, 9.32]	0.0002
	$PaCO_2$ (mmHg)	< 0.00001	96	random-effect	−6.2 [-11.63, -0.77]	0.03
immunoglobulin index	IgG (g/L)	0.10	56	random-effect	3.55 [3.10, 3.99]	< 0.00001
	IgA (g/L)	0.52	0	fixed-effect	0.34 [0.31, 0.38]	< 0.00001
	IgM (g/L)	< 0.0001	90	random-effect	0.35 [0.27, 0.42]	< 0.00001
CRP (mg/L)		0.02	69	random-effect	−8.05 [-10.11, -6.00]	< 0.00001
lung rale disappearance time		0.07	69	random-effect	−2.57 [-3.19, -1.95]	< 0.00001

CAT score and mMRC score were summarized in this study to assess the health conditions of these patients and to determine high-risk patients more comprehensively[42] ⑤ This study performed a sensitivity analysis and publication bias test for the clinical total effective rate to verify the independence and stability of the results.

5. Limitations

There were still insufficiencies in this study. To start, all the participants were Chinese, which meant that the effects on other races are uncertain. Second, missing contents from ongoing experiments and grey literature may result in publication bias. Additionally, the quality of the included RCTs was general because only 5 RCTs mentioned blinding methods, of which most used single blinding, and few evaluated items had low risk. Although the Begg test and Egger test showed that there was no potential publication bias, a few included RCTs were outside the distribution of the funnel plot, indicating that this study may lack RCTs whose sample size was small and quality was high. Despite these limitations, this study provided a comprehensive evaluation of the efficacy and safety of Shengmai injection for the treatment of COPD.

6. Conclusions

In summary, this study verified that Shengmai injection combined with WM had a better effect on the clinical total effective rate, CAT score, mMRC, average hospitalization time, pulmonary function, blood gas index and other factors. Nonetheless, there are some suggestions based on the indicated limitations: on one hand, high-quality, multicentre RCTs with larger sample sizes should be conducted to obtain more scientific and exact conclusions. On the other hand, medical staff ought to use Shengmai injection with instructional guidelines and monitor the occurrence of ADRs/ADEs.

Authors' contributions

Conception and design of the meta-analysis: Jiarui Wu, Xingyue Huang. Performance of the meta-analysis: Xingyue Huang, Xiaojiao Duan. Quality assessment of the meta-analysis: Xingyue Huang, Kaihuan Wang, Jiarui Wu. Analysis of the study data: Xiaojiao Duan, Xiaomeng Zhang. Writing of the paper: Xingyue Huang, Xiaojiao Duan, Kaihuan Wang. All authors read and approved the final version of the manuscript.

Competing interests

The authors declare no competing interests in any respect.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2019.01.020.

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