Thymosin Alpha 1 Plus Routine Treatment for the Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

This systematic review was conducted to assess the curative effect of Thymosin alpha 1 in the acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients. Six electronic databases including EMBASE, PubMed, Cochrane Library, China National Knowledge Infrastructure Database, Chinese Biomedical Database, and Wanfang Database were searched for eligible papers focusing on the thymosin alpha 1 treatment in AECOPD patients. The effectiveness outcomes included T cell subset, pulmonary function, arterial blood gases, and the length of hospital stay. Stata and Review Manager Software were used for data analysis. Thirty-nine randomised controlled trials with a total of 3,329 patients were included. Compared with the control treatment, Thymosin alpha 1 therapy significantly improved forced expiratory volume in 1 second [MD = 0.29, 95% (0.26, 0.32), p <0.001] and the ratio of forced expiratory volume in the first second to forced vital capacity [MD = 6.24, 95% (3.83, 8.65), p <0.001], increased the arterial partial pressure of oxygen [MD = 7.24, 95% (3.42, 11.07), p = 0.0002], lowered the arterial partial pressure of carbon dioxide [MD = -5.85, 95% (-9.38, -2.33), p = 0.001], shortened the length of hospital stay [MD = -5.39, 95% (-7.82, -2.97), p <0.001], raised the level of $CD4^+$ T lymphocytes count [MD = 7.54, 95%(6.66, 8.41), p <0.001] and the ratio of $CD4^+/CD8^+$ [MD = 0.40, 95% (0.34, 0.46), p <0.001], and decreased level of $CD8^+$ T lymphocytes count [MD = -2.74, 95% (-3.86, -1.63), p <0.001]. Thymosin alpha 1 could significantly boost the immune function, and improve pulmonary function and arterial blood gas of AECOPD patients than routine treatment only. More high-quality randomised controlled trials are needed to further confirm Thymosin alpha 1 efficacy.

Key Words: *Thymosin alpha 1, Efficacy, Acute exacerbation of chronic obstructive pulmonary disease, Meta-analysis.*

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is now one of the top three causes of death worldwide. Worldwide COPD affects 9-10% of the adult population and in Asian countries, such as China, the prevalence in people aged over 40 years is 13.7%.[1] COPD represents an important public health challenge that is both preventable and treatable. A principal factor affecting COPD-related mortality is the acute exacerbation of COPD (AECOPD). Exacerbation contributes to the overall severity, including quality of life, rates of hospitalisation and readmission, and disease progression.

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At the moment, the conventional treatment protocol for AECOPD includes anti-infection, anti-inflammatory, bronchial expansion, mechanical ventilation, and respiratory therapy. The application of glucocorticoids is beneficial to patients. However, the effects of these measures are limited. High-dose glucocorticoids provide little benefit in terms of improving lung function and may have long-term detrimental effects.[2] Approximately, one-third of patients with COPD experience one or more exacerbations every year.[3] Hence, the clinical efficacy of AECOPD needs to be further improved.

In COPD there is a characteristic pattern of inflammation with increased numbers of neutrophils, macrophages, T-lymhocytes, and B-lymphocytes in the airway lumen. T-lymphocytes comprise a subpopulation of T $CD4^+$ lymphocytes that regulate immune response through secretion of cytokines. A disruption in the regulatory mechanisms of the T-lymphocytes could result in the development and perpetuation of inflammation in COPD.[4]

Thymosin alpha 1 is a 28 amino acid peptide originally isolated from the thymus that has been recognised for modifying, enhancing, and restoring the immune function. It is a peptide hormone that is endogenously produced by the thymus gland and potentiates T cell-mediated immune responses *via* differen-

tiation and maturation of T-cell progenitor cells, activation of dendritic and natural killer cells, and stimulation of cytokine-mediated inflammation.[5] The synthetic form of thymosin alpha 1, thymalfasin, is approved in more than 35 countries for the treatment of immunocompromised states and malignancies, as an enhancer of vaccine response, and as a means of curbing morbidity and mortality in sepsis and numerous infections. Clinical trials had confirmed that Thymosin alpha 1, could enhance the immune function of AECOPD patients, suppress the inflammatory reaction, and ameliorate the patients' quality of life and pulmonary function.[6,7] Nevertheless, no relevant evidence-based evaluations have been published until now. Therefore, a systematic review and meta-analysis was conducted to integrate information presented in studies on the effectiveness of Thymosin α1 in the treatment of AECOPD patients.

METHODOLOGY

This systematic review was conducted following the reporting items for systematic reviews and meta-analyses guidelines. Published researches were retrieved from six databases, including EMBASE, PubMed, Cochrane Library, China National Knowledge Infrastructure Database, Wanfang Database, and Chinese Biomedical Database (from established to August 2023). The first two authors independently searched studies in electronic databases. The search strategy was as follows:

1 "Pulmonary Disease, Chronic Obstructive"[Mesh Terms]

2 "Lung Diseases, Obstructive"[MeSH Terms]

3 COPD [Title/Abstract] OR COAD [Title/Abstract] OR chronic obstructive airway disease [Title/Abstract] OR chronic obstructive lung disease [Title/Abstract] OR chronic obstructive pulmonary disease [Title/Abstract] OR chronic obstructive airflow disease [Title/Abstract] OR chronic obstructive respiratory disease [Title/Abstract] OR emphysema [Title/Abstract] OR chronic bronchitis [Title/Abstract] OR chronic airflow obstruction [Title/Abstract]

4, 1 or 2 or 3

5 thymosin [Title/Abstract]) OR thymosin alpha 1 [Title/Abstract]) thymalfasin [Title/Abstract])

6, 4, and 5

The criteria for the studies to be included in the meta-analysis were as follows: All patients in study were diagnosed as AECOPD according to Global Initiative for Chronic Obstructive Lung Disease criteria; type of study was randomised controlled trial (RCT); the experimental group was given Thymosin alpha 1 plus routine complex treatment, whereas the intervention in the control group was routine complex treatment; at least one of the following outcomes was required in the present study: T cell subset, pulmonary function, arterial blood gases, and / or the length of hospital stay. Relevant studies were manually removed if any of the following criteria were identified: Duplicated articles; Incomplete literature information; studies whose baseline data were significantly inconsistent.

The primary indicator of the present study was the T cell subset, including percentages of $CD4^+$ T lymphocytes, $CD8^+$ T lymphocytes, and the ratio of $CD4^+/CD8^+$. The secondary indicators were arterial blood gases (arterial partial pressure of oxygen and arterial partial pressure of carbon dioxide), the length of hospital stay, and pulmonary function (forced expiratory volume in the first second and the ratio of forced expiratory volume in the first second to forced vital capacity).

The first two authors independently extracted data from the studies included. Data extracted from eligible studies included the first author's name, publication date, study characteristics, and participants' characteristics (age, sample size, details of interventions, and outcomes). If different results were generated, the third author assessed the differences in the forms and had discussion between the first and second authors to come to an agreement.

The methodological quality of the eligible studies was assessed independently by first two authors based on the criteria in the Cochrane evaluation handbook of RCTs 5.1.0,[8] which included five parameters: Sequence generation; allocation concealment; blinding of participants and study personnel and blinding of outcome assessments; incomplete outcome data; and selective outcome reporting. The studies were graded as having low, high, or unclear risk of bias. This course had to be cross-checked in order to ensure accuracy and reliability. The disagreements between the two investigators were resolved by consultation with the third author.

The RevMan 5.3 (Cochrane Collaboration) and Stata 14.0 software were used to calculate the statistical analysis. As continuous variables, pulmonary function, arterial blood gases, length of hospital stay, and T cell subset were assessed using mean difference (MD) and corresponding 95% CIs. I^2 statistics were used to assess the statistical heterogeneity among studies. The random model was conducted in the presence of heterogeneity ($I^2 \geq 50\%$). Otherwise, the fixed model was used ($I^2 < 50\%$). The statistical significance was assessed for $p < 0.05$. Funnel plot and Egger's regression asymmetry test were performed to detect potential publication bias. Evidence of asymmetry from Egger's test was considered to be significant at $p < 0.1$, A value of $p < 0.05$ was considered statistically significant. Sensitivity analysis was performed by sequential omission of individual studies and re-conducting meta-analysis of the remaining studies.

RESULTS

Based on the search criteria, the initial database search identified 443 potentially relevant possible studies. A total of 54 Records were identified after removing duplicates and screening the titles and abstracts. Fifteen trials were excluded for the following reasons: Retrospective study (n = 6), no relative outcomes (n = 8), and duplicate data (n = 1). Finally, 39 clinical trials were involved in this meta-analysis. The flowchart of the detailed searching steps for this meta-analysis is described in Figure 1.

Table I: Baseline characteristics of included studies.

Study, year	Age, years (Mean ± SD/range)	Sample size (N)	Interventions	Course of treatment	Outcome
Jia *et al*. 2015[9]	T:70.10 ± 5.65; C:69.86 ± 5.19	T:42 C:42	T: Tα1+the routine complex treatment; C: placebo+the routine complex treatment	4 weeks	①②③
Wu 2019[10]	79.6 ± 3.7; 80.2 ± 4.4	31/29	T: Tα1+the routine complex treatment; C: the routine complex treatment C: Antibiotics, conventional treatment	10 - 14d	②
Sun *et al*. 2019[11]	73.02 ± 4.22; 72.54 ± 3.65	48/48	T: Tα1+the routine complex treatment; C: the routine complex treatment	14d	②
Fan YJ 2017[12]	51.7 ± 2.19; 45.2 ± 3.16	46/46	T: Tα1+the routine complex treatment; C: the routine complex treatment	12 weeks	②
Xie 2016[13]	67. 71 ± 12. 39; 67. 64 ± 12. 33	30/30	T: Tα1+the routine complex treatment; C: the routine complex treatment	14d	①
Tong *et al*. 2013[14]	67.1 ± 7.2; 69.4 ± 4.5	43/40	T: Tα1+the routine complex treatment; C: the routine complex treatment	7d	①②③
Fan 2017[15]	70.35 ± 3.47; 69.40 ± 3.12	45/45	T: Tα1+the routine complex treatment; C: the routine complex treatment	14d	①②
Yang *et al*. 2018[16]	58.44 ± 7.26; 58.12 ± 7.25	40/40	T: Tα1+the routine complex treatment; C: the routine complex treatment	10d	①
Zhou 2018[17]	64.54 ± 4.58; 64.64 ± 4.60	39/39	T: Tα1+the routine complex treatment; C: the routine complex treatment	10d	①
Yu 2018[18]	57.9 ± 6.5; 58.4 ± 7.8	35/35	T: Tα1+the routine complex treatment; C: the routine complex treatment	10d	①②③
Ye 2019[19]	67.3 ± 4.8; 67.0 ± 4.5	53/52	T: Tα1+the routine complex treatment; C: the routine complex treatment	10d	①②
Hu 2018[20]	76.37 ± 8.04; 74.13 ± 7.51	30/30	T: Tα1+the routine complex treatment; C: the routine complex treatment	4 weeks	①
Wang *et al*. 2017[21]	59.67 ± 3.25; 58.62 ± 4.31	50/50	T: Tα1+the routine complex treatment; C: the routine complex treatment	14d	①
Shao 2019[22]	66.34 ± 6.13; 66.7 5± 6.74	33/32	T: Tα1+the routine complex treatment; C: the routine complex treatment	10d	②
Zhang 2016[23]	70.5 ± 2.7; 70.8 ± 2.5	45/45	T: Tα1+the routine complex treatment; C: the routine complex treatment	8-10d	②
Zhao *et al*. 2016[24]	53.4±6.1; 54.1±6.3	30/30	T: Tα1+the routine complex treatment; C: the routine complex treatment	10d	①②
Cai 2019[25]	62.8 ± 8.3; 62.7 ± 8.2	33/32	T: Tα1+the routine complex treatment; C: the routine complex treatment	7d	①
Jin 2018[26]	74.5 ± 2.8; 73.8 ± 2.6	43/43	T: Tα1+the routine complex treatment; C: the routine complex treatment	7d	①②
Guo 2016[27]	71.47 ± 4.12; 71.35 ± 4.26	25/25	T: Tα1+the routine complex treatment; C: the routine complex treatment	10d	②
Quan 2019[28]	73.30 ± 0.28; 73.24 ± 0.26	44/43	T: Tα1+the routine complex treatment; C: the routine complex treatment	10d	①②
Wang 2019[29]	71.98 ± 5.66; 71.54 ± 4.34	35/35	T: Tα1+the routine complex treatment; C: the routine complex treatment	8-10d	②
Zhang 2020[30]	70.4 ± 2.5; 70.5 ± 2.4	35/35	T: Tα1+the routine complex treatment; C: the routine complex treatment	7-14d	②
Zhao *et al*. 2018[31]	69.5 ± 2.6; 69.9 ± 2.7	65/65	T: Tα1+the routine complex treatment; C: the routine complex treatment	8-10d	②
Peng 2015[32]	70.5 ± 9.8; 69.0 ± 9.5	67/67	T: Tα1+the routine complex treatment; C: the routine complex treatment	10d	②
Cui *et al*. 2012[33]	65-85; 67-84	15/15	T: Tα1+the routine complex treatment; C: the routine complex treatment	7d	①
Jiao *et al*. 2017[34]	70.82 ± 2.20; 70.23 ± 2.23	41/41	T: Tα1+the routine complex treatment; C: the routine complex treatment	8d	①
Liu 2014[35]	68.7 ± 4.9; 67.9 ± 5.2	40/40	T: Tα1+the routine complex treatment; C: the routine complex treatment	10d	①②③
Li J 2018[36]	40-87; 43-85	42/42	T: Tα1+the routine complex treatment; C: the routine complex treatment	10d	②③
Lin *et al*. 2016[37]	65.27 ± 4.21; 62.86 ± 5.87	40/40	T: Tα1+the routine complex treatment; C: the routine complex treatment	14d	①②
Le 2013[38]	69.2 ± 2.3; 69.7 ± 2.6	40/40	T: Tα1+the routine complex treatment; C: the routine complex treatment	8-10d	②
Wu *et al*. 2017[39]	63.4 ± 4.2; 64.5 ± 4.8	38/37	T: Tα1+the routine complex treatment; C: the routine complex treatment	14d	①②③
Jiang 2018[40]	68.53 ± 8.29; 69.47 ± 8.19	133/124	T: Tα1+the routine complex treatment; C: the routine complex treatment	7d	①②
Yu *et al*. 2017[41]	65.5 ± 6.8; 65.3 ± 6.4	44/44	T: Tα1+the routine complex treatment; C: the routine complex treatment	14d	①②③
Ju 2016[42]	65.2 ± 2.4; 65.4 ± 2.6	46/42	T: Tα1+the routine complex treatment; C: the routine complex treatment	10d	①②
Su 2018[43]	53.4 ± 3.2; 53.4 ± 3.2	30/30	T: Tα1+the routine complex treatment; C: the routine complex treatment	14d	②
Li *et al*. 2007[44]	70.7 ± 11.7; 69.9 ± 12.3	56/52	T: Tα1+the routine complex treatment; C: the routine complex treatment	14d	①
Liu *et al*. 2014[45]	71.8 ± 9.76; 69.6 ± 8.81	60/60	T: Tα1+the routine complex treatment; C: the routine complex treatment	14d	①④
Shao 2013[46]	NR	40/40	T: Tα1+the routine complex treatment; C: the routine complex treatment	14d	①④
Jin *et al*. 2012[47]	71.2 ± 19.8; 74 ± 23.4	37/40	T: Tα1+the routine complex treatment; C: the routine complex treatment	10d	①④

T: Treatment group; C: Control group; ① T Cell subset ② Lung function; ③ Arterial blood gases; ④ Hospital stay; NR: Not reported.

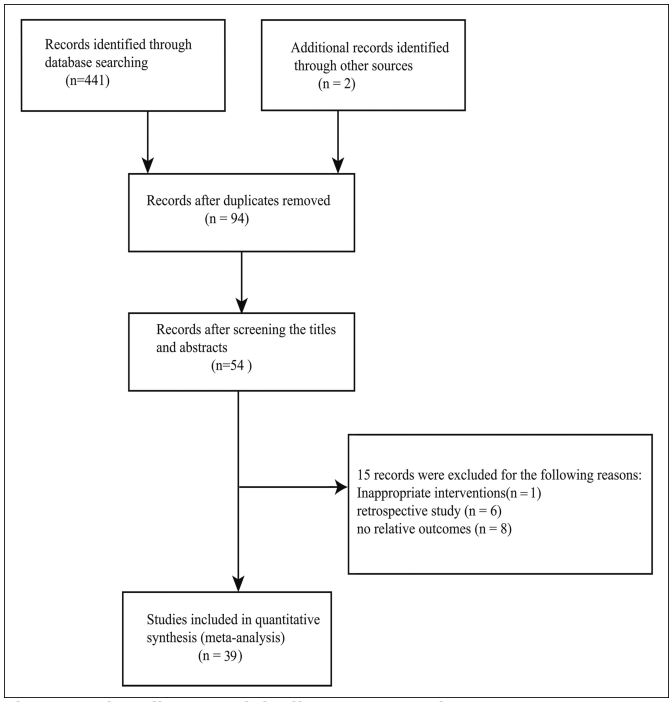

Figure 1: Flow diagram of the literature search process.

A total of thirty-nine randomised controlled trials were included in this meta-analysis (Table I). All the studies used thymosin alpha 1 with routine complex treatment as the experimental group and routine complex treatment as the control group. Routine complex treatment can consist of antibiotics, anti-inflammatory, bronchial expansion, and resolving the phlegm. The duration of therapy was 1 to 12 weeks by intravenous or subcutaneous injection.

According to the criteria in the Cochrane Evaluation Handbook of RCTs, the methodological quality evaluation forms were formulated. The randomisation method used was described in 25 (64.1%) articles. The remaining trials only mentioned randomisation but failed to describe the method of randomisation. Two trials described the process of allocation concealment in sufficient detail.[9,34] Only one trial claimed to have used the blinded method.[9] The risk of outcome assessment was unclear. All the included trials had an unclear risk of bias of incomplete outcome data because insufficient information was provided. Other bias was evaluated as an unclear risk. The risk of bias assessment of all included studies was shown in Figure 2.

Twenty-five studies including $CD4^+$ T lymphocytes count[9,13-21,24,26,33-35,37,39-42,44-47] and the ratio of $CD4^+/CD8^+$[9,13-21,24-26,33-35,37,39-41,44-47] were evaluated after treatment. As the test of heterogeneity was 74% and 93%, respectively, a random effects model was used for the test. The meta-analysis revealed that the $CD4^+$ T lymphocytes count [MD = 7.54, 95% (6.66, 8.41), p <0.001] and the ratio of $CD4^+/CD8^+$[MD = 0.40, 95% (0.34, 0.46), p <0.001] significantly raised after treatment. The $CD8^+$ T lymphocyte count was reported in 22 trials of 1927 patients.[9,13,14,16-18,20,21,24,33-35,37,39-42,44-47] There was statistical heterogeneity between the 2 groups (I^2 = 92%). The meta-analysis results revealed that the $CD8^+$ T lymphocytes count significantly decreased after the treatment [MD = -2.74, 95% (-3.86, -1.63), p <0.001] (Figure 3). Considering the lack of literature and relevant data, the authors did not conduct subgroup analyses.

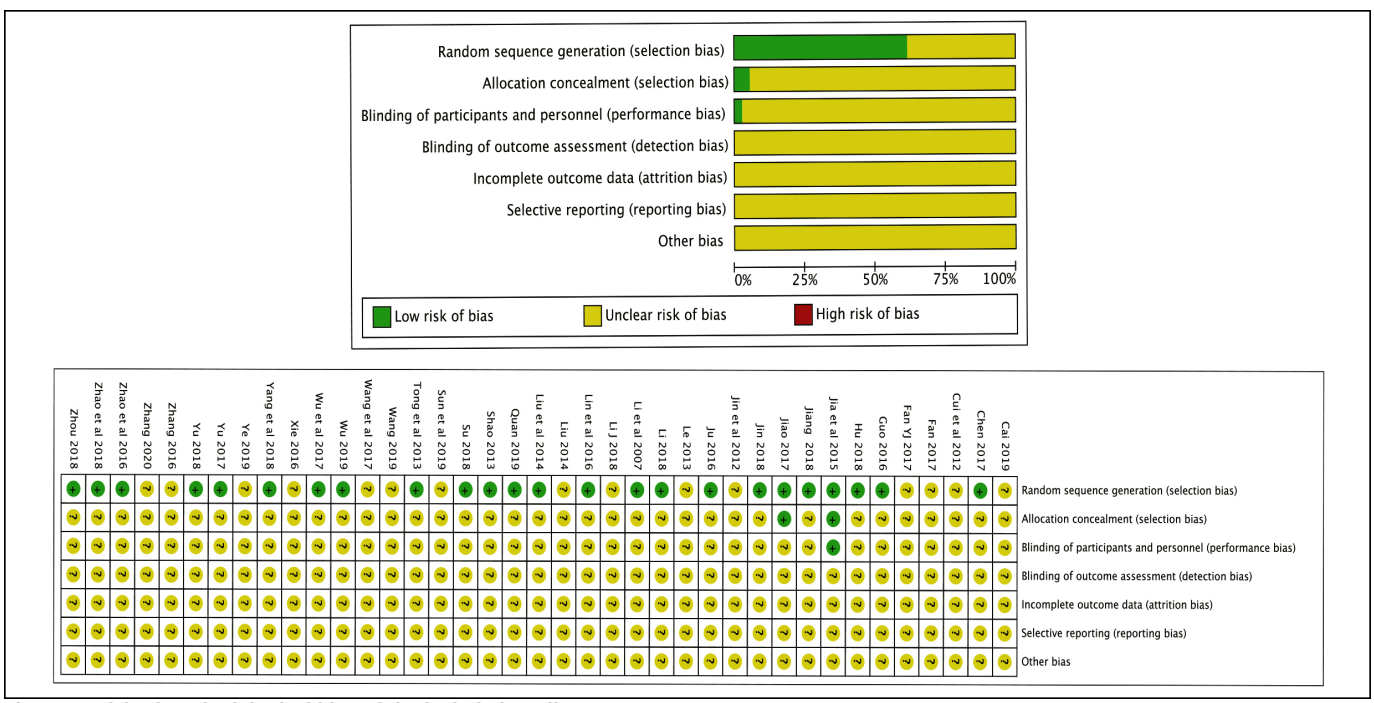

Figure 2: Risk of methodological bias of the included studies.

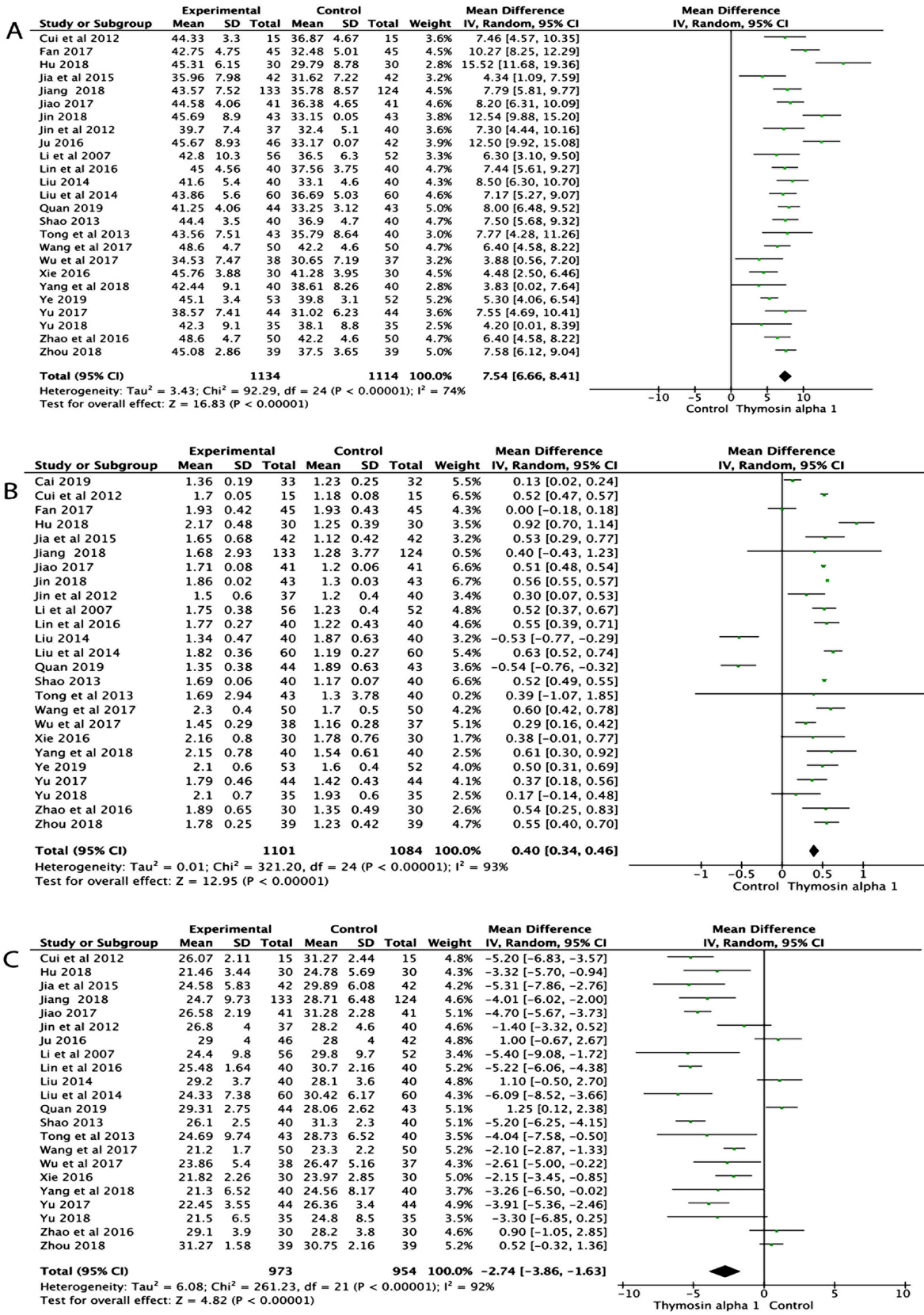

Figure 3: Forest plot. (A) CD4⁺ (B) CD4⁺/CD8⁺ C) CD8⁺.

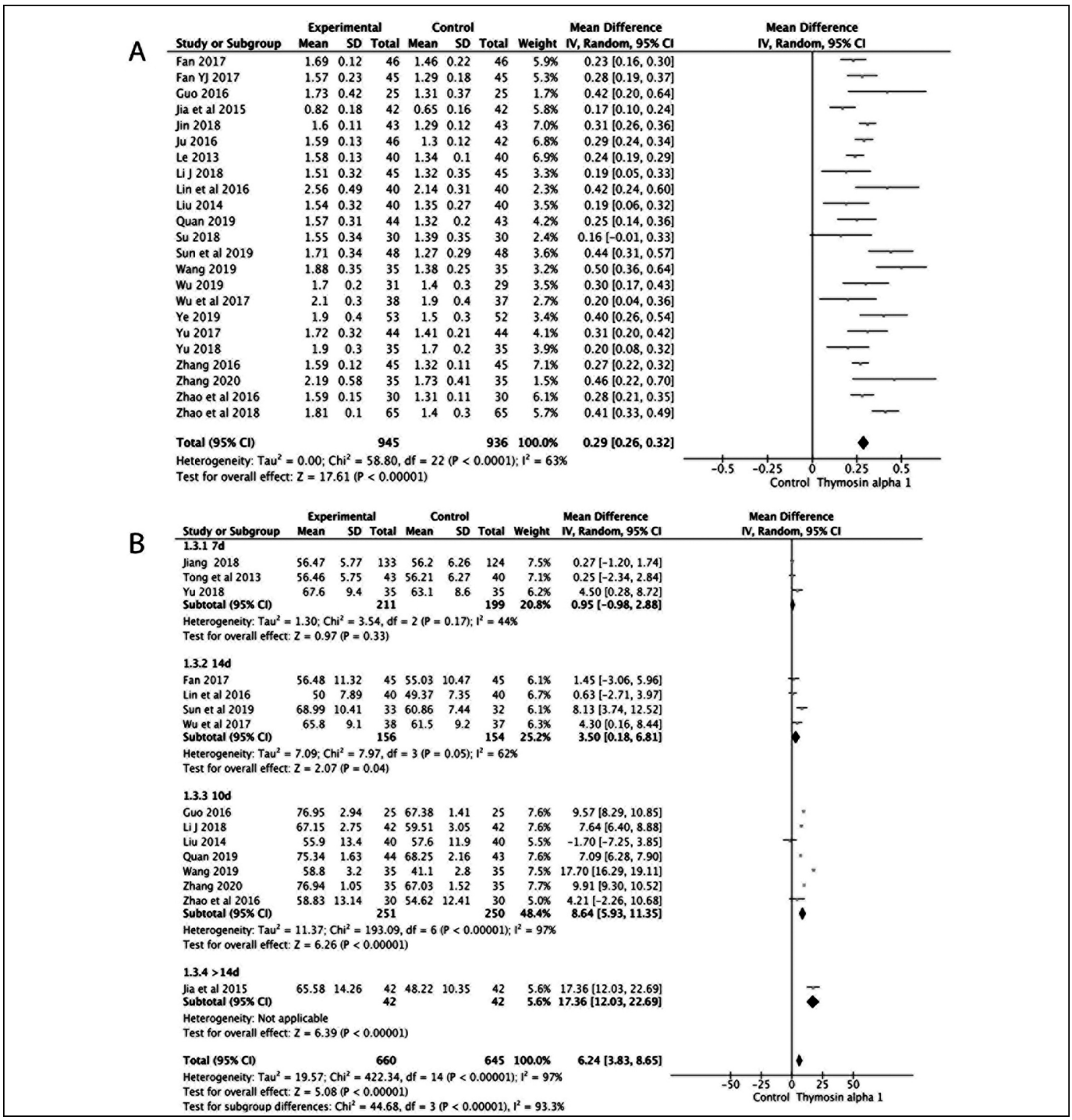

Figure 4: Forest plot. (A) FEV1 (B) FEV1/FVC.

Twenty-three studies including 1,881 patients of AECOPD patients were evaluated for the forced expiratory volume in the first second (FEV1).[9-12,15,18,19,23,24,26-31,35-39,41-43] The ratio of forced expiratory volume in the first second to forced vital capacity (FEV1/FVC) was evaluated and analysed in 15 studies.[9,11,14,15,18, 24,27-29,35-37,39,40] The test of heterogeneity was 63% and 97% (p <0.01), respectively, suggesting that a random-effects model was preferred. Due to the significant heterogeneity, a subgroup analysis was conducted according to the duration of treatment to explore the sources of heterogeneity. This meta-analysis indicated that there were statistically significant differences between the two groups for FEV1 [MD = 0.29, 95% (0.26, 0.32), p <0.001] and FEV1/FVC [MD = 6.24, 95% (3.83, 8.65), p <0.001], which revealed that thymosin α1 was beneficial to the improvement of pulmonary function (Figure 4).

Seven studies involving 564 participants were included in the meta-analysis to explore the impact of thymosin alpha 1 on arterial blood gases by random-effects model.[9,14,18,35,36,39,41]

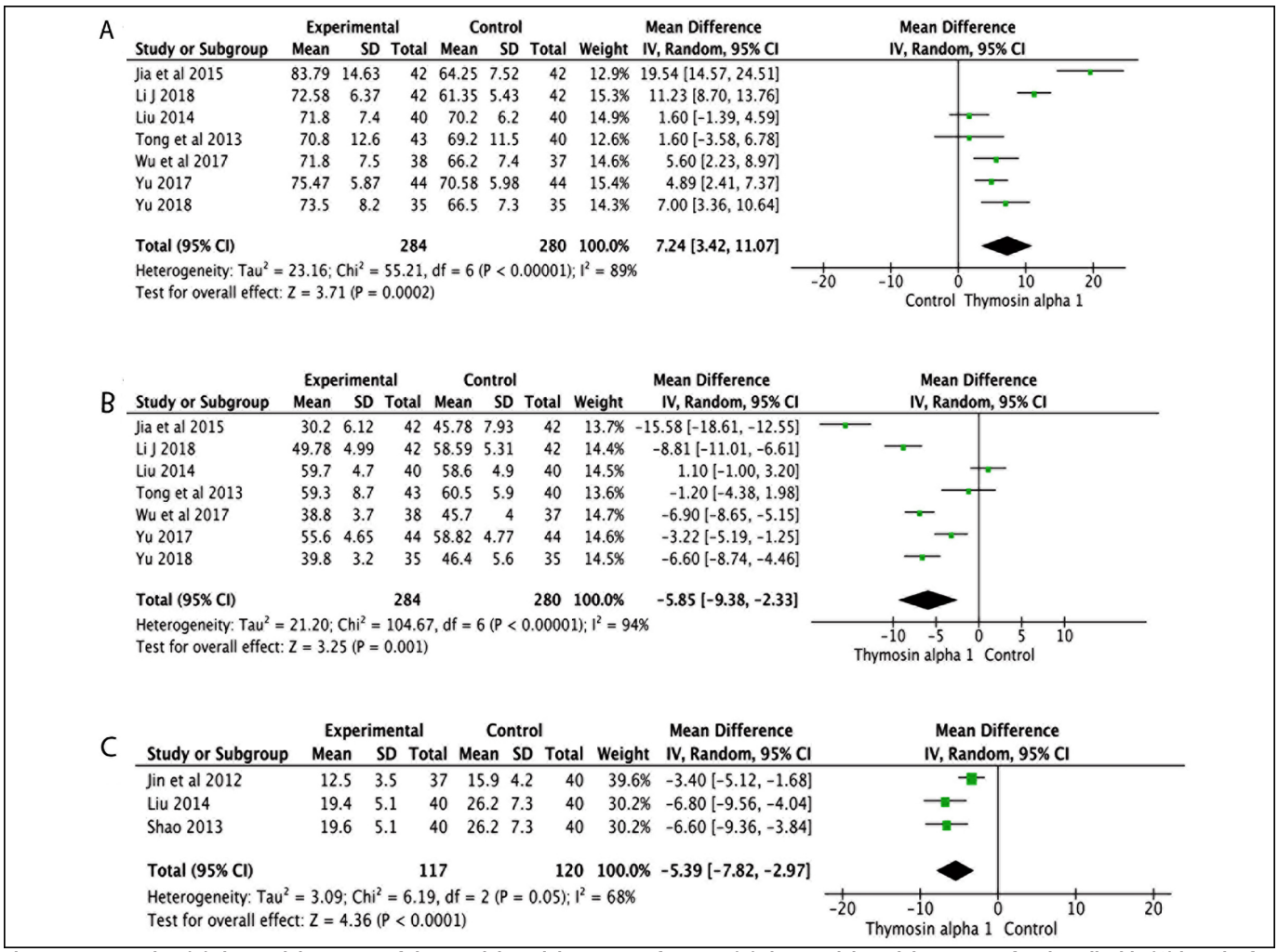

Figure 5: Forest plot. (A) the partial pressure of the arterial partial pressure of oxygen (B) the arterial partial pressure of carbon dioxide (C) length of hospital stay.

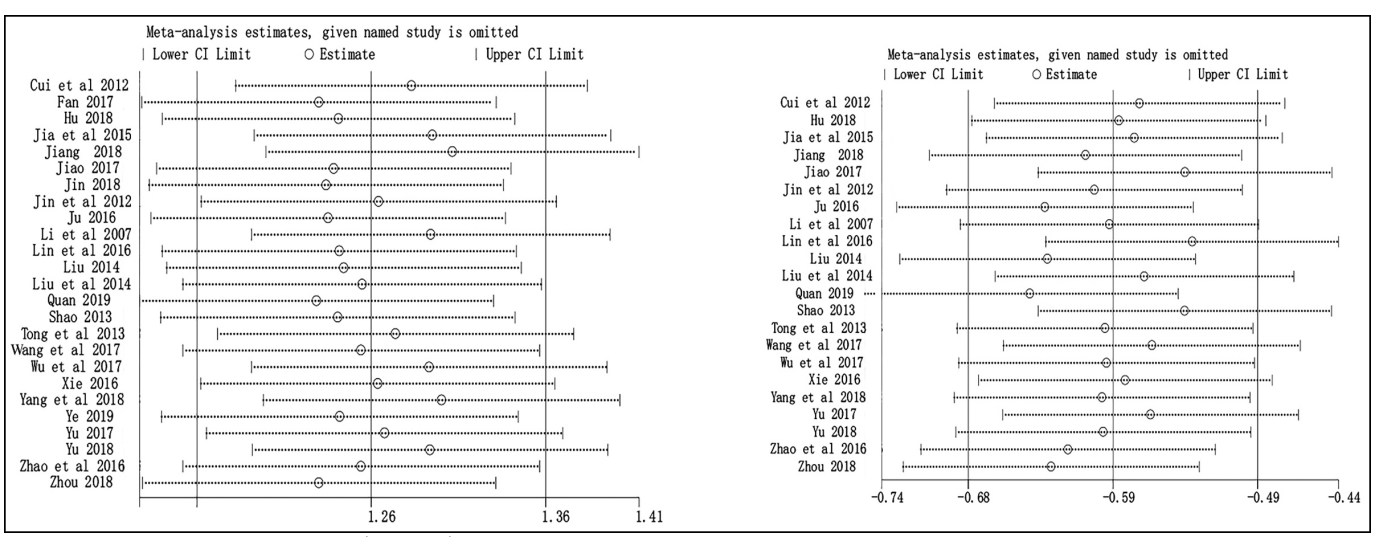

Figure 6: Sensitivity analysis. (A) $CD4^+$ (B) $CD8^+$.

The results of the pooled analysis indicated that thymosin alpha 1 significantly increased the arterial partial pressure of oxygen [MD = 7.24, 95% (3.42, 11.07), p = 0.0002, I^2 = 89%] and lowered the arterial partial pressure of carbon dioxide [MD = -5.85, 95% (-9.38, -2.33), p = 0.001, I^2 = 94%] (Figure 5). A total of three studies involving 237 patients

presented length of hospital stay.[35,46,47] The test of heterogeneity was 68% (p = 0.05), suggesting that a random-effects model was preferred. As shown in Figure 5, the pooled results suggested a significant difference for the length of hospital stay [MD = -5.39, 95% (-7.82, -2.97), p <0.001].

A single study involved in the meta-analysis was deleted each time, and the rest was reanalysed, resulting in similar results compared with the previous ones, indicating that the present study's results were statistically robust. For further verification, the authors implemented a sensitivity analysis of the $CD4^+$ and $CD8^+$ T lymphocyte count by Stata 14.0. Figure 6 indicated that the outcomes were very similar, and had relatively good stability. The funnel plot was applied to assess the publication bias of studies that included the results of the CD4+ T lymphocyte count in this meta-analysis, which showed a significant asymmetry. Egger's test was further performed to assess publication bias. The results for CD4+ T lymphocyte count (p = 0.064) revealed that publication bias might exist in the present study.

DISCUSSION

Recently, accumulated evidence has suggested that autoimmune response plays an important role in the pathogenesis of COPD, and T lymphocytes are believed to be the key cells in regulating airway inflammation in COPD.[48] T lymphocytes subpopulation can be subdivided into T helper lymphocytes and T inhibiter lymphocytes. $CD4^+$ T lymphocytes are a marker for T helper lymphocytes. $CD4^+$ T lymphocytes can activate T lymphocytes and participate in inducing cellular immune responses. $CD8^+$ T lymphocytes are a marker of T inhibiter lymphocytes. $CD8^+$ T lymphocytes have cytotoxic effects and exert inhibitory effects on T lymphocytes' activity.[49] Many animal experiments have verified that thymosin alpha 1 stimulated precursor stem cells into the $CD4^+/CD8^+$ T cells, promoted T-cell maturation, meanwhile modulated lymphocyte phenotypic marker expression and immune response.[50] This meta-analysis revealed that the $CD4^+$ T lymphocytes count and the ratio of $CD4^+/CD8^+$ significantly raised after treatment, while the $CD8^+$ T lymphocyte count significantly decreased after treatment. These results suggested that thymosin alpha 1 could enhance the activity of helper T cells, consequently improving cellular immune function and anti-infection ability.

The results of the meta-analysis showed that the arterial partial pressure of oxygen and carbon dioxide, and the indices of pulmonary function (FEV1 and FEV1/FVC) in the experimental group were significantly improved after treatment. AECOPD is characterised by a sudden worsening of COPD symptoms, which typically leads to decreased lung function, an increased incidence of respiratory failure, and even death. Some studies have shown that increased numbers of $CD8^+$ T cells and reduced ratio of $CD4^+/CD8^+$ T cells in COPD patients have been correlated with a decline in lung function.[51] An inability to upregulate Tregs could lead to a more rapid development of emphysema, and thus to a more rapid decline in lung function.[52] On the other hand, thymosin alpha 1 specifically potentiates immune tolerance in the lung, often breaking the vicious circle that perpetuates chronic lung inflammation in response to a variety of infectious noxae.[53] Hence, thymosin alpha 1 might be adopted in improving pulmonary function and arterial blood gas with AECOPD patients.

This study has certain limitations. First, the bias risk of many studies was unknown. Risk of bias assessments for the randomisation and concealment allocation were frequently inadequate. Second, the thymosin alpha 1 intervention protocol, including frequency and sessions, varied greatly across studies. This could influence the reliability of the pooled effect sizes and make it difficult for the review authors to draw a definitive conclusion about the optimal recommendation. Third, the meta-analysis showed considerable evidence of heterogeneity between trials. The average illness severity, and age differed from trial-to-trial and the diversity of treatment options might be the source of heterogeneity. Considering the lack of literature and relevant data, the authors did not conduct subgroup analyses. Therefore, more well-designed trials in the near future are a feasible solution to remedy this flaw.

CONCLUSION

This is the first systematic review and meta-analysis to evaluate the effectiveness of thymosin alpha 1 in the acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients. Thirty-nine randomised controlled trials including 3,329 patients were included in the analysis, which ensured adequacy specimen to precisely evaluate the efficacy. By the results of this meta-analysis, the authors concluded that thymosin alpha 1 plus routine treatment could more efficiently enhance the immune function, and improve pulmonary function, and arterial blood gas of AECOPD patients than routine treatment only. However, some big international multi-centred and high-quality RCTs are urgently needed to further prove the efficacy.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

XZ, AC: Conceived and designed the project.
AC, FF: Performed the review and analysed the data.
AC: Wrote the paper.
XZ: Was responsible for quality control of the study.
All authors approved the final version of the manuscript to be published.

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