International Journal of Chronic Obstructive Pulmonary Disease

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REVIEW

A Systematic Review and Meta-Analysis on the Safety and Efficacy of Rosuvastatin as an Adjunctive Therapy in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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Purpose: Acute exacerbations of chronic obstructive pulmonary disease (COPD) severely impact patient health, and current treatments often fail to adequately control inflammation and lung function decline. Statins have shown potential in managing AECOPD. This study conducts a systematic review and meta-analysis to evaluate the effects of rosuvastatin, aiming to provide precise treatment recommendations.

Research methods: Using "Pulmonary Disease, Chronic Obstructive" and "Rosuvastatin Calcium" as MeSH terms, randomized controlled trials (RCTs) evaluating the efficacy and safety of rosuvastatin in AECOPD patients were retrieved from databases including PubMed, EMBASE, the Cochrane Library, Sinomed, CNKI, WanFang Data, and QIVIP. The search period extended through September 15, 2024. Two researchers independently screened the literature, extracted data, and assessed the risk of bias in the included studies. Meta-analysis was performed using RevMan 5.3 software, while sensitivity analyses and publication bias tests were conducted with Stata 17.0.

Results: Eleven RCTs involving 911 patients were included, with a certain risk of bias. Rosuvastatin was found to improve forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio, and peak expiratory flow (PEF). Additionally, it significantly reduced levels of hs-CRP, TNF-α, IL-6, IL-8, NE, and Gal-3.

Conclusion: Despite the limited number of studies and potential bias, evidence suggests that rosuvastatin improves lung function and reduces inflammation in AECOPD, underscoring its potential value and emphasizing the need for further high-quality research.

Keywords: rosuvastatin, acute exacerbations of chronic obstructive pulmonary disease, meta-analysis, randomised controlled trials

Introduction

According to the 2023 data from the World Health Organization, Chronic Obstructive Pulmonary Disease (COPD) remains the third leading cause of death globally.[1,2] Among these, the acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is the primary cause of mortality in COPD patients. Common triggers include respiratory infections, climate changes, air pollution, and sputum retention.[3] During an acute exacerbation, patients may experience worsened respiratory symptoms such as dyspnea, cough, and wheezing, along with systemic manifestations like fatigue and drowsiness.[4]

The pathogenesis of AECOPD is closely linked to inflammatory responses.[5] During this period, both airway and systemic inflammation are markedly intensified, typically triggered by viral or bacterial infections, resulting in an increase in inflammatory cells such as neutrophils and associated mediators. Oxidative stress is also exacerbated, further promoting the inflammatory response[6] The intensification of systemic inflammation not only aggravates respiratory symptoms but may also impair the function of other organs.

Received: 16 January 2025
Accepted: 5 June 2025
Published: 12 June 2025

The optimal management of AECOPD necessitates a multifaceted strategy that integrates both pharmacological and non-pharmacological modalities. Pharmacological interventions, including the administration of corticosteroids and antibiotics, play a pivotal role in modulating the inflammatory cascade and attenuating the frequency and severity of exacerbations, thereby contributing to the enhancement of patients' quality of life. In parallel, non-pharmacological measures—such as chest physiotherapy, supplemental oxygen therapy, structured pulmonary rehabilitation, and tailored nutritional support—are equally indispensable, facilitating symptom alleviation and comprehensive disease management.[7,8] Notably, the recurrent nature of AECOPD is associated with the development of serious complications, including pulmonary hypertension and heart failure, which substantially elevate the risk of morbidity and mortality if not effectively addressed. Consequently, the implementation of timely and integrated therapeutic approaches is imperative for optimizing clinical outcomes and long-term prognosis in patients with AECOPD.[9]

Currently, common pharmacological treatments include bronchodilators, corticosteroids, expectorants, and antibiotics. However, the efficacy of existing therapies remains suboptimal for some patients. Studies suggest that statins, typically used for lipid-lowering, may have anti-inflammatory effects, improve lung function, and slow disease progression in COPD treatment.[10–12] Among statins, rosuvastatin is notable for its strong anti-inflammatory and antioxidant effects, high hydrophilicity, and superior efficacy in lowering systemic inflammatory markers such as CRP, IL-6, and TNF-α compared to other statins. Evidence suggests that rosuvastatin is more effective than simvastatin or atorvastatin in reducing inflammation and is associated with fewer adverse effects due to its hydrophilic nature, making it suitable for patients with AECOPD and comorbidities.[13,14] Mechanistically, rosuvastatin inhibits the NF-κB pathway, thereby reducing pro-inflammatory cytokine expression and improving endothelial function. Recent studies indicate that adjunctive rosuvastatin may lower the risk of acute exacerbations, reduce systemic inflammation, and improve lung function in AECOPD patients.[15] These pharmacological advantages support further evaluation of rosuvastatin's safety and efficacy as adjunctive therapy in AECOPD.

Although several studies have suggested potential benefits of statins in patients with AECOPD, the current body of evidence remains inconclusive regarding their definitive efficacy. This inconsistency may be attributed to the limited number of high-quality studies, methodological heterogeneity, and potential biases present in existing research. Therefore, this research aims to conduct a systematic review and meta-analysis of clinical studies on the use of rosuvastatin calcium in AECOPD treatment to evaluate its safety and efficacy, thereby providing practical guidance for the clinical management of AECOPD patients.

Methods

This systematic review and meta-analysis was registered with PROSPERO (registration number: CRD42024621579; http://www.crd.york.ac.uk/prospero). The study was designed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] See Supplementary Table S1 for details.

Inclusion and Exclusion Criteria

Types of Research

Clinical randomized controlled trials (RCTs) are the only method capable of effectively avoiding systematic errors arising from baseline characteristic imbalances between intervention groups due to confounding factors.[17] Furthermore, compared with non-randomized controlled trials, they can more effectively reduce the risk of bias. Therefore, this study included only clinical RCTs that reported the use of rosuvastatin as adjunctive therapy for AECOPD.

Study Population

Patients diagnosed with AECOPD according to the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines or the relevant guidelines of the Chinese Medical Association.[7,8]

Interventions

Experimental group: Oral administration of rosuvastatin as adjunctive therapy, with a treatment duration of more than two weeks.

Control group: Placebo treatment, blank control, or conventional therapy. Other COPD treatment measures were consistent between the two groups.

Conventional therapy: Bronchodilators, glucocorticoids, anti-infective therapy, respiratory support, and other treatments.[7,8]

Outcome Indicators

Primary outcome indicators:

1. Forced vital capacity (FVC);
2. Forced expiratory volume in one second (FEV_1);
3. FEV_1/FVC Ratio;
4. Peak expiratory flow (PEF);
5. Incidence of adverse reactions;

Secondary outcome indicators:

1. High-sensitivity C-reactive protein (hs-CRP);
2. Tumour necrosis factor-alpha (TNF-α);
3. Interleukin-6 (IL-6);
4. Interleukin-8 (IL-8);
5. Neutrophil elastase (NE);
6. Galectin-3 (Gal-3);

All outcome measures were assessed one day prior to the initial treatment and again following the final treatment at the conclusion of the study observation period.

Exclusion Criteria

1. Duplicate publications;
2. Studies with inaccessible full text or severely missing data;
3. Patients with severe hepatic or renal dysfunction or allergies to the investigational drug;
4. Individuals with severe psychiatric disorders or cognitive impairment;
5. Patients with other severe cardiac diseases or malignant tumors;
6. Failure to meet the above inclusion criteria;

Search Strategy

Following the Cochrane Handbook for Systematic Reviews (Version 6.4)[16] and drawing upon recommendations from relevant experts, we performed comprehensive literature searches across databases such as PubMed, EMBASE, the Cochrane Library, Web of Science, CNKI, WanFang Data, Sinomed, and QIVIP. Utilizing "Pulmonary Disease, Chronic Obstructive" and "Rosuvastatin Calcium" as subject terms, combined with relevant keywords and without language limitations, the search period ranged from the establishment of each database up to November 15, 2024.[18] The search strategies are exemplified using the Sinomed and PubMed databases, with details provided in Supplementary Tables S2 and S3, respectively. Furthermore, the main databases and their search addresses are summarized in Supplementary Table S4.

Literature Screening and Extraction

All the retrieved literature was uniformly managed using the NoteExpress 4.1 reference management software. Literature screening and data extraction were independently performed by two researchers; any disagreements were resolved through discussion or, if necessary, consultation with a third researcher. For studies with missing data or unavailable full texts, attempts were made to contact the authors to obtain relevant information. Following literature screening, data

were extracted from all studies meeting the inclusion criteria using a predefined data extraction form. The main items extracted included the title, authors, publication year, study location, sample size of the experimental and control groups, basic patient information, medication details, interventions of the experimental and control groups, treatment duration, and outcome measures.

Subgroup Analysis

To explore the sources of heterogeneity among the studies and the impact of different key influencing factors on the results, this study plans to conduct subgroup analyses from the following aspects:

(1) Subgroup analyses were conducted according to the severity of AECOPD. The criteria for severity classification were as follows:

Mild: patients treated exclusively with short-acting bronchodilators (SABDs) or without respiratory failure;

Moderate: patients managed with SABDs and oral corticosteroids, with or without antibiotics, or those experiencing non-life-threatening acute respiratory failure;

Severe: patients requiring hospitalization or emergency room visits, or those with life-threatening acute respiratory failure.[7]

(2) Conduct a subgroup analysis based on the presence or absence of severe comorbidities to evaluate their impact on the results;[19]

(3) If substantial heterogeneity exists among the studies, we will attempt to perform a subgroup analysis based on the risk of bias of each study. Studies will be categorized into a high-risk of bias group and another risk of bias group to analyze the influence of bias risk on heterogeneity.

Risk of Bias Assessment

This study utilized Version 2 of the Cochrane tool for assessing risk of bias in randomized trials (RoB 2). Based on 23 signaling questions across the following five domains, the risk of bias of the included studies was evaluated: (1) The randomization process; (2) Deviations from intended interventions; (3) Missing outcome data; (4) Measurement of the outcome; and (5) Selection of the reported result.

Two researchers independently addressed the relevant signaling questions for each included study using RoB 2. They meticulously recorded and interpreted the associated bias risks, providing evidential support for the risk of bias assessment. Additionally, risk of bias analyses were performed separately for different outcome measures. Any discrepancies arising during the quality assessment were resolved through discussion or by consulting a third investigator.[20]

Sensitivity Analysis and Publication Bias Assessment

In this paper, RevMan 5.3 software will be employed to construct funnel plots to explore publication bias. If the plot is generally symmetrical, it may be considered that the risk of publication bias is low; however, if the plot is markedly asymmetrical, it indicates the presence of a higher risk of publication bias. Furthermore, linear regression (Egger's test) will be utilized to assess the asymmetry of the funnel plot; if $P \leq 0.05$, it suggests that the study has a significant risk of publication bias.[21]

Statistical methods

This study utilized RevMan 5.3 software to perform the meta-analysis. Sensitivity analyses and publication bias assessments were conducted using Stata 17.0. Categorical data were expressed as relative risk (RR), while continuous data were presented as mean difference (MD); both with 95% confidence intervals (CI). Heterogeneity among studies was assessed using the chi-squared (χ^2) test and the I^2 statistic. If no significant heterogeneity was detected ($P > 0.1$, $I^2 < 50\%$), a fixed-effect model was employed. Conversely, a random-effects model was adopted, and the sources of heterogeneity were explored to eliminate it before data synthesis. We attempted to contact the authors of the original studies to obtain missing data; if complete data remained unavailable, only the accessible data were analyzed, accompanied by a systematic descriptive analysis.

Results

Literature Search Results

According to the predefined search strategy, an initial search identified 308 potentially relevant studies. After a rigorous screening process based on the inclusion and exclusion criteria, 11 RCTs were included in the final analysis.[22–32] The literature screening process and results are presented in Figure 1.

Main Characteristics of the Included Literature

All 11 included studies were RCTs, comprising a total of 911 patients with AECOPD, with 453 in the treatment group and 458 in the control group. The basic characteristics of these studies are detailed in Table 1. Among them, patients in three studies—Liu, Yao, and Zhang—had concomitant pulmonary hypertension.[22,23,25] Two studies, Yu and Sheng[28,29,] utilized adjunctive non-invasive positive pressure ventilation. According to the guidelines,[8] respiratory support was included in the conventional treatment regimen of this study; therefore, these two studies were not excluded. Although the study by Huan[30] involved results related to inflammatory factors, it was not included in the meta-analysis due to its sampling of sputum specimens; instead, its findings were systematically described. Moreover, it should be noted that

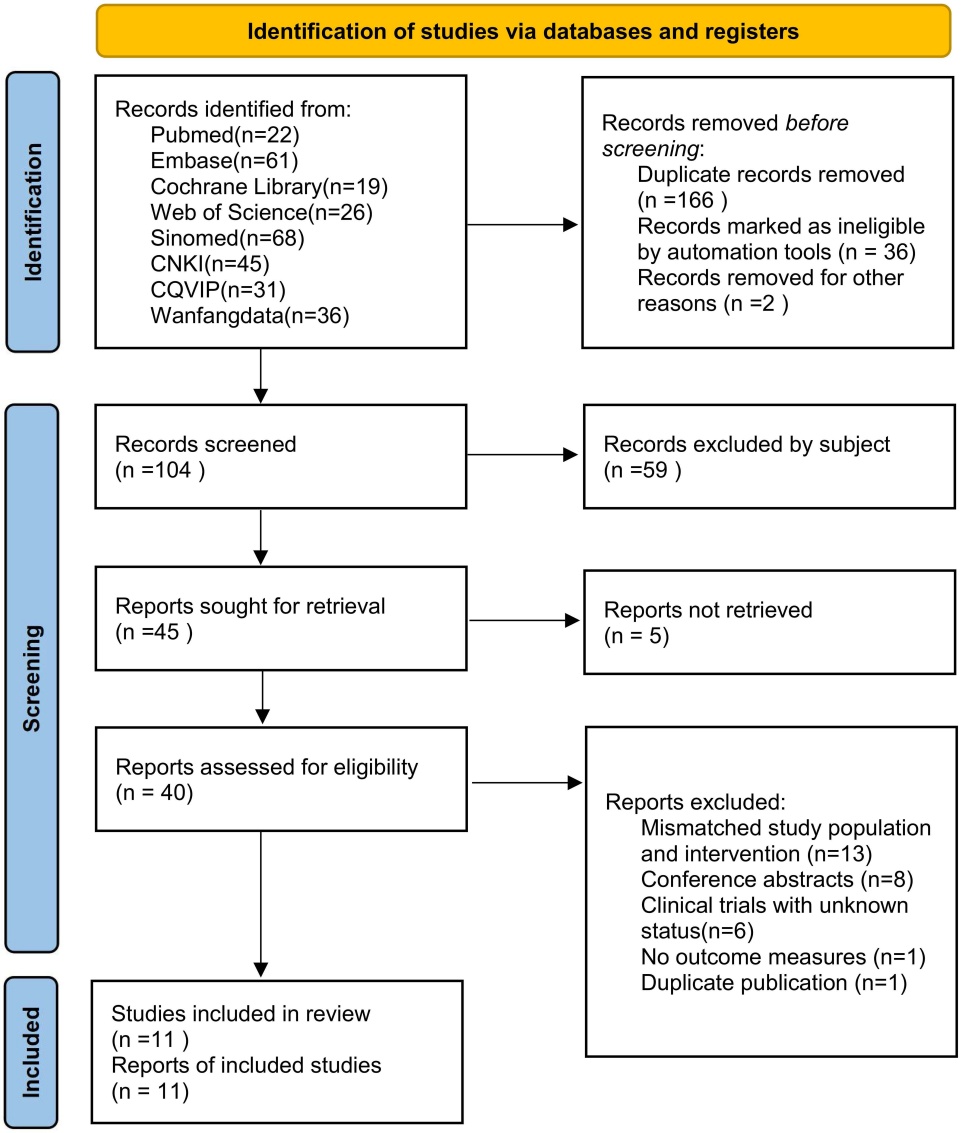

Figure 1 Literature screening flow chart.

https://doi.org/10.2147/COPD.S513918

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Table 1 Characteristics of Studies Included in the Systematic Review

Study	Location	Sample Size (T/C)	Age(y) (T/C)	Male/Female (T/C)	Intervention		Outcome Index	Treatment Course	Funding
					Experimental Group	Control Group			
Liu YQ 2023[22]	Shanxi, China	28/31	61.72±9.64 /59.38±10.49	17:11/19:12	Rosuvastatin Calcium (10mg, qn, po) and control group	Budesonide suspension for inhalation + sterile water for injection (1mg + 2mL, bid, inh) and other standard treatments	(1) (2) (3) (4) (5) (10) (11)	24w	Nonindustry grant
Yao W 2020[23]	Henan, China	50/50	65.3±3.9/64.8±1.5	25:25/24:26	Rosuvastatin Calcium (10mg, qn, po) and control group	Standard treatment	(2) (3) (4) (7) (9) (10) (11)	Unclear	Not stated
Xu WW 2020[24]	Liaoning, China	52/56	65.42±6.14 /65.31±6.23	28:24/30:26	Rosuvastatin Calcium (10mg, qd, po) and control group	Standard treatment	(1) (2) (3) (4)	6m	Not stated
Zhang YN 2019[25]	Zhejiang, China	60/60	68.93±5.31 /68.87±4.98	33:27/32:28	Rosuvastatin Calcium (10mg, qd, po) and control group	Standard treatment	(1) (2) (3) (4) (6) (9)	24d	Nonindustry grant
Tang GJ 2018[26]	Hebei, China	30/30	69.84±7.07 /68.12±7.19	14:16/13:17	Rosuvastatin Calcium (10mg, qn, po) and control group	Standard treatment	(1) (2) (3) (4) (5) (7) (10) (11)	24w	Nonindustry grant
Yu H 2017[28]	Guangxi, China	59/59	65.26±6.95 /64.92±6.81	36:32/38:21	Rosuvastatin Calcium (5mg, qn, po) and control group	Noninvasive positive pressure ventilation(3 to 5 hours per session, bid) and other standard treatments	(1) (2) (3) (6)	Unclear	Nonindustry grant
Sheng H 2017[29]	Zhejiang, China	55/55	65.21±5.70 /65.30±5.74	33:22/31:24	Rosuvastatin Calcium (20mg, qd, po) and control group	Noninvasive positive pressure ventilation and other standard treatments	(2) (3) (6) (8)	8w	Not stated
Liu DM 2017[27]	Jiangsu, China	40/40	64.28±2.39	51:29	Rosuvastatin Calcium (10mg, qd, po) and control group	Standard treatment	(5) (6) (7) (8)	7d	Not stated
Tian CR 2013[31]	Jiangsu, China	27/27	68.3±2.7	33/21	Rosuvastatin Calcium (10mg, qn, po) and control group	Standard treatment	(6) (7) (8)	2d	Not stated
Huan YF 2013[30]	Sichuan, China	20/20	73.5±7.2 /71.2±5.9	9:11/12:8	Rosuvastatin Calcium (5mg, qn, po) and control group	Standard treatment	(6) (8) (9)	2d	Not stated
Chen Y 2013[32]	Shandong, China	32/30	68±9 /69±8	8:24/7:23	Rosuvastatin Calcium (20mg, qd, po) and control group	Standard treatment	(3) (6) (8)	10–14d	Not stated

Notes: (T/C): Experimental group /Control group; qd, bid, qn: once daily, twice daily, once nightly; inh, po: inhalation, oral administration; m, d, w: month, day, week; (1): FVC (Forced vital capacity); (2): FEV1 (Forced expiratory volume in 1 second); (3): FEV1/FVC (FEV1/FVC ratio); (4): PEF (Peak expiratory flow); (5): Incidence of adverse reactions; (6): hs-CRP (high-sensitivity C-reactive protein); (7): TNF-α (Tumor necrosis factor-alpha); (8): IL-6 (Interleukin-6); (9): IL-8 (Interleukin-8); (10): NE (Neutrophil elastase); (11): Gal-3 (Galectin-3); Standard treatment: Bronchodilators, glucocorticoids, anti-infective therapy, respiratory support, and other treatments.

Abbreviations: WHO, World Health Organization; COPD, Chronic Obstructive Pulmonary Disease; AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease; RCTs, Clinical Randomised Controlled Trials; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FVC, Forced Vital Capacity; FEV_1, Forced Expiratory Volume in one second; FEV_1/FVC, FEV_1 to FVC Ratio; PEF, Peak Expiratory Flow; hs-CRP, High-sensitivity C-reactive Protein; TNF-α, Tumour Necrosis Factor-alpha; IL-6, Interleukin-6; IL-8, Interleukin-8; NE, Neutrophil Elastase; Gal-3, Galectin-3.

a study by Peiman et al[33] was published in the form of a conference abstract. We attempted to contact the authors, but to date have received no response; thus, the abstract data from this RCT were not included in our analysis.

Risk of Bias Assessment Results

This study rigorously adhered to the quality assessment standards outlined in the Cochrane Handbook for Systematic Reviews, employing the RoB 2.0 tool to evaluate the included research literature. A total of 11 RCTs were included, with results depicted in Figures 2 and 3.

The Randomization Process

Among these studies, the randomization process in 10 trials was assessed as having a low risk of bias. However, the study by Liu DM 2017[27] did not specify the randomization method, resulting in an uncertain risk of bias, despite no significant baseline differences between the experimental and control groups.

Deviations from Intended Interventions

As the outcomes of the included studies were primarily objective measures, they were minimally influenced by subjective factors, resulting in a low risk of bias in intervention allocation across all studies.

Missing Outcome Data

The studies by Liu and Xu[22,24] presented an unclear risk of bias due to the extended treatment duration and the lack of specific reporting on data attrition. This may be attributed to various patient-related factors during prolonged treatment, with authors only including final data. The studies by Yao and Yu[23,28] did not report treatment duration, leading to an unclear risk of bias regarding missing data.

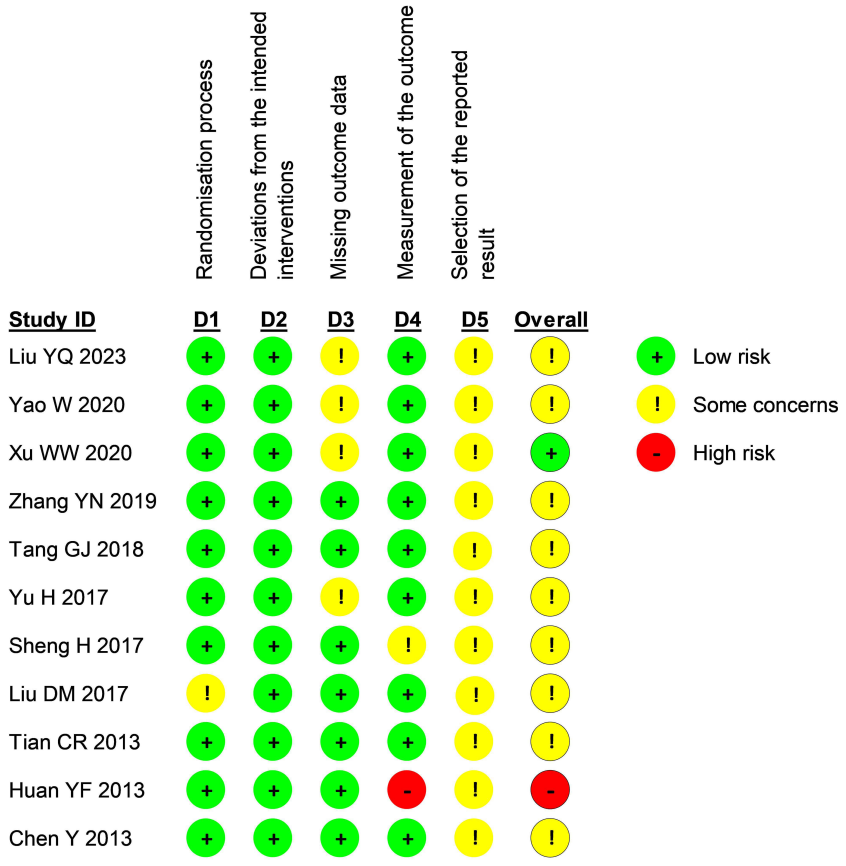

Figure 2 The Risk of Bias Assessment 1.

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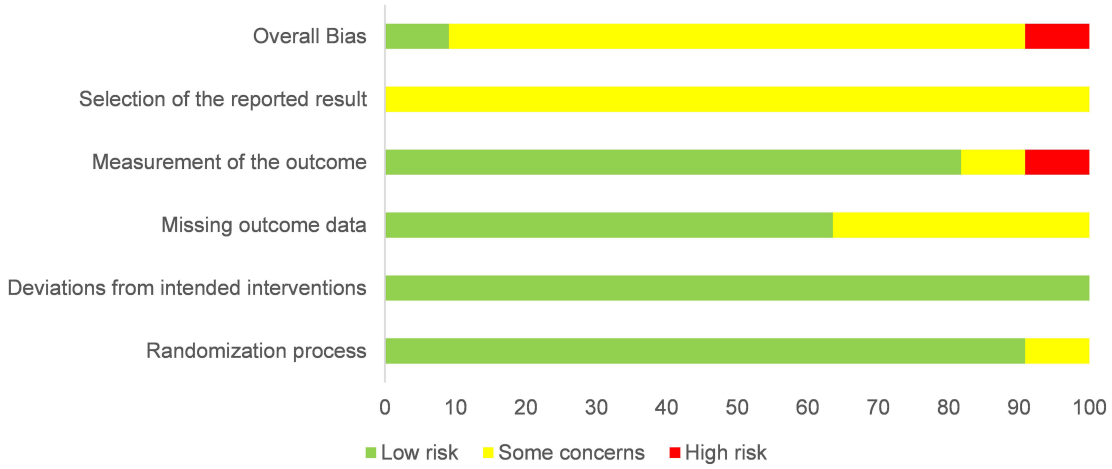

Figure 3 The Risk of Bias Assessment 2.

Measurement of the Outcome

In terms of outcome measurement, the study by Sheng[29] exhibited significant differences in IL-8 measurements that could not be explained by heterogeneity, resulting in an unclear risk of bias. Furthermore, the study by Huan[30] had a high risk of bias due to differing sample measurements, and thus its data were not included in the meta-analysis.

Selection of the Reported Result

Due to the inability to contact the authors and the absence of referenceable study protocols, the risk of bias in selective reporting was unclear for all studies.

Primary Outcome Indicators

Forced Vital Capacity

Five studies reported FVC values. Due to inconsistent measurement units in Liu,[22] which could not be converted, only four studies were included in the meta-analysis,[24–26,28] with a total sample size of 378 participants, comprising 201 in the experimental group and 177 in the control group. The heterogeneity test results (P = 0.12, I^2 = 49%) indicated that the heterogeneity among studies was not statistically significant; thus a fixed-effects model was employed for analysis. Meta-analysis results demonstrated that the combined effect size MD was 0.60, with a 95% confidence interval of [0.48, 0.73], and the difference was statistically significant (Z = 9.18, P < 0.00001). This suggests that adjunctive treatment with rosuvastatin can effectively improve FVC values in patients with acute exacerbations of chronic obstructive pulmonary disease, as illustrated in Figure 4. The findings of Liu[22] indicated that there was no significant difference in FVC values between the experimental and control groups before treatment (t = 0.348, P = 0.729). However, post-treatment, the improvement in the experimental group was significantly superior to that in the control group, with a significant difference observed between the two groups (t = 2.187, P = 0.033).

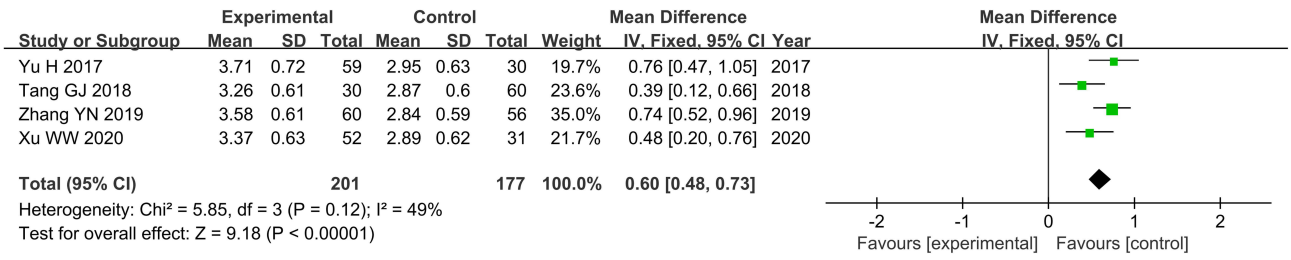

Figure 4 FEV Forest plot.

Forced Expiratory Volume in One second

A total of seven studies reported FEV1 values. Due to inconsistent measurement units in Liu YQ 2023, which could not be converted, only six studies were included in the meta-analysis,[24–26,29] with an aggregate sample size of 616 participants, comprising 306 in the experimental group and 310 in the control group. The heterogeneity test results ($P < 0.00001$, $I^2 = 99\%$) indicated significant heterogeneity; thus a random-effects model was utilized for analysis. The meta-analysis results revealed that the combined effect size MD was 0.63, with a 95% confidence interval of [0.27, 0.99], and the difference was statistically significant ($Z = 3.42$, $P = 0.0006$), as shown in Figure 5. Upon performing sensitivity analysis by sequentially excluding studies, it was found that heterogeneity might have originated from Yao W 2020 and Yu H 2017. Re-analysis of the remaining four trials yielded a heterogeneity test result of ($P = 0.27$, $I^2 = 24\%$), with an MD of 0.35 and a 95% confidence interval of [0.31, 0.40]. The findings of Liu YQ 2023 demonstrated that there was no significant difference in FEV1 values between the experimental and control groups prior to treatment ($t = 0.050$, $P = 0.960$). However, post-treatment, the improvement in the experimental group was significantly superior to that in the control group, with a significant difference observed between the two groups ($t = 3.252$, $P = 0.003$).

FEV_1/FVC Ratio

Eight studies reported FEV_1/FVC values,[22–26,28,29,32] all of which were included in the meta-analysis. The overall sample size was 737 participants, with 366 in the experimental group and 371 in the control group. The heterogeneity test results ($P < 0.00001$, $I^2 = 95\%$) necessitated the use of a random-effects model to combine effect sizes. The meta-analysis results indicated that the combined effect size MD was 6.36, with a 95% confidence interval of [2.86, 9.86], and the difference was statistically significant ($Z = 3.56$, $P = 0.0004$), as illustrated in Figure 6. Sensitivity analysis suggested that the heterogeneity might have originated from Yao W 2020. Re-analysis of the remaining seven trials yielded a heterogeneity test result of ($P = 0.40$, $I^2 = 4\%$), with an MD of 4.99 and a 95% confidence interval of [4.05, 5.92].

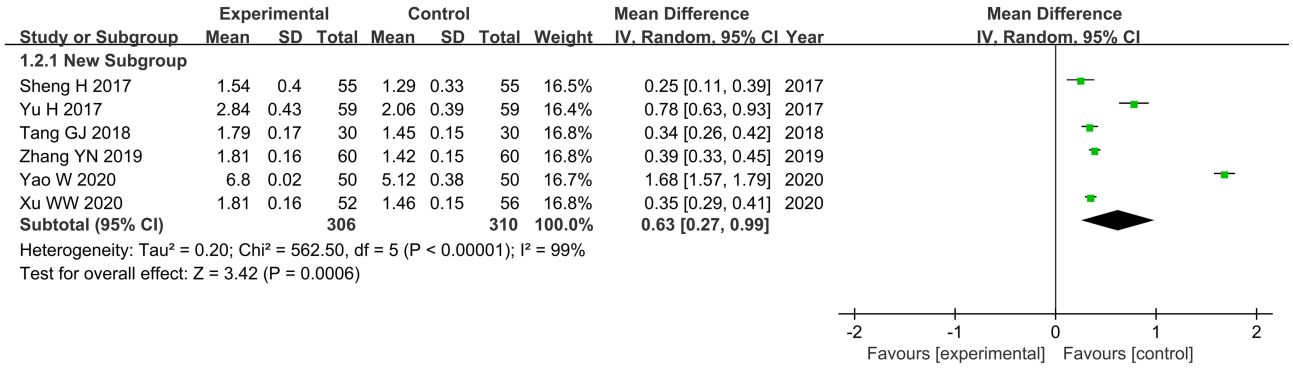

Figure 5 FEV1 Forest plot.

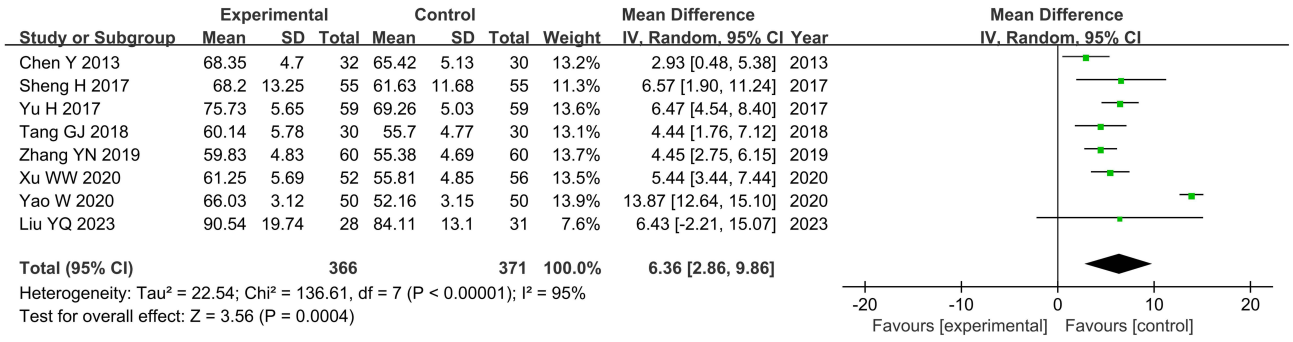

Figure 6 FEV_1/FVC Ratio Forest plot.

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Peak Expiratory Low

Five studies reported PEF values. However, due to inconsistent measurement units in Liu YQ 2023 that could not be converted, only four studies were ultimately included in the meta-analysis.[23–26] The total sample size was 388 participants, with 192 in the experimental group and 196 in the control group. The heterogeneity test results ($P = 0.46$, $I^2 = 0\%$) indicated no significant heterogeneity; thus a fixed-effects model was employed for analysis. The meta-analysis results showed that the combined effect size MD was 0.67, with a 95% confidence interval of [0.61, 0.73], and the difference was statistically significant ($Z = 21.64$, $P < 0.00001$), as depicted in Figure 7. Furthermore, the findings of Liu YQ 2023 indicated that there was no significant difference in FVC values between the experimental and control groups prior to treatment ($t = 0.121$, $P = 0.904$). However, post-treatment, the improvement in the experimental group was significantly superior to that in the control group, with a notable difference between the two groups ($t = 2.240$, $P = 0.029$).

Incidence of Adverse Reactions

Only three studies have documented the incidence of adverse reactions. According to Liu,[22] adverse reactions linked to adjunctive therapy were mainly attributed to budesonide. The study found no significant difference in the incidence of adverse reactions between the two groups. Tang[26] observed that no myalgia occurred in the observation group during treatment. Both adverse reactions and side effects were relatively mild, requiring no special intervention, and no differences were reported between the two groups. Liu[27] demonstrated that the incidence of adverse reactions in the observation group was significantly lower than in the control group ($\chi^2 = 4.0556$, $P < 0.05$). These findings suggest that rosuvastatin as adjunctive therapy is relatively safe for patients experiencing acute exacerbations of chronic obstructive pulmonary disease. However, given the limited number of studies included, the risk of bias in these findings is relatively high, necessitating cautious interpretation.

Secondary Outcome Indicators

High-Sensitivity C-Reactive Protein

Seven studies reported hs-CRP values. The measurement units in Chen[32] were incompatible and could not be converted, while Huan[30] utilized sputum samples. Consequently, only five studies were included in the meta-analysis[25,27–29,31,] with a total sample size of 482 participants, comprising 241 in the experimental group and 241 in the control group. The heterogeneity test results ($P = 0.27$, $I^2 = 22\%$) indicated low heterogeneity, and thus a fixed-effects model was applied for analysis. The meta-analysis revealed that the combined effect size MD was −4.54, with a 95% confidence interval of [−5.02, −4.06], demonstrating statistical significance ($Z = 18.64$, $P < 0.00001$), as illustrated in Figure 8. The findings of Chen Y 2013 demonstrated a statistically significant difference in the change from pre-treatment to post-treatment between the experimental and control groups, with a mean difference of 19.49 ± 7.10 ($P < 0.05$). Similarly, the results from Huan YF 2013 indicated that, following treatment, the experimental group exhibited significantly greater improvement in inflammation in sputum samples compared to both the conventional treatment and blank groups ($P < 0.05$).

Tumor Necrosis Factor-Alpha

A total of three studies reported TNF-α values. The units used in Zhang and Yao[23,25] were inconsistent and could not be converted, and Huan[30] utilized sputum samples; therefore, no effect size combination was performed for the TNF-α analysis. The findings from Yao W 2020 and Huan YF 2013 both demonstrated that the experimental group significantly

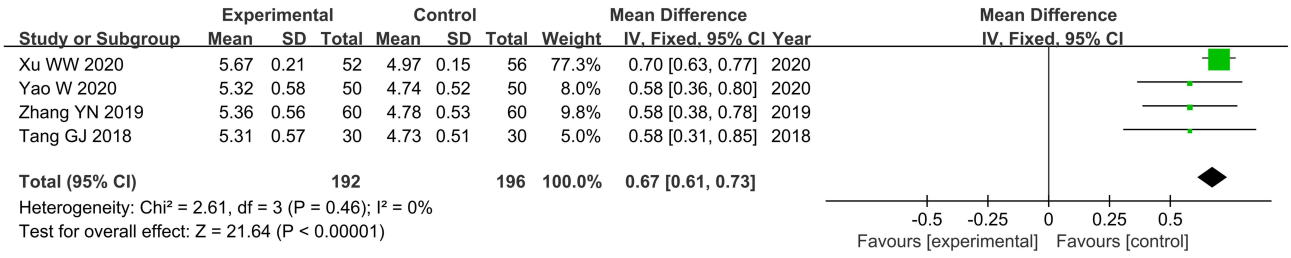

Figure 7 PEF Forest plot.

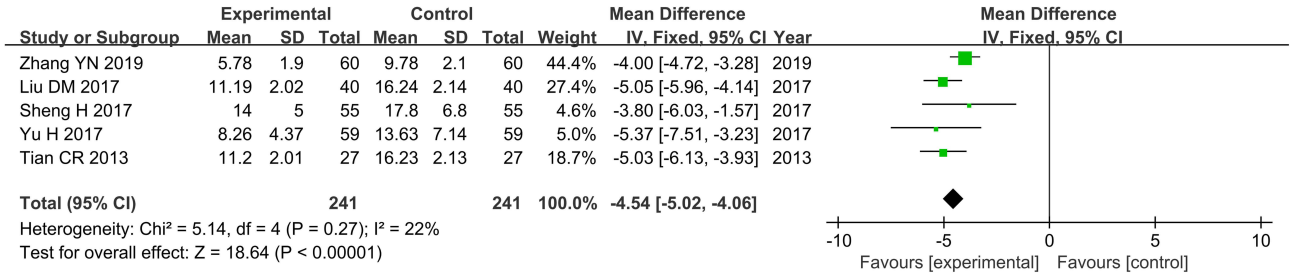

Figure 8 Hs-CRP Forest plot.

reduced TNF-α values compared to the control group ($P < 0.05$), indicating statistical significance. The results of Zhang YN 2019 indicated that there was no significant difference in TNF-α values between the experimental and control groups prior to treatment (t = 11.023, $P = 0.063$). However, post-treatment, the experimental group showed markedly greater improvement than the control group, with a significant difference observed between the two groups (t = 8.564, $P = 0.000$).

Interleukin-6

Four studies reported IL-6 values. The measurement units in Yao and Tian[23,31] were inconsistent and could not be converted, leading to the inclusion of only two studies in the meta-analysis.[26,27] The total sample size was 140 participants, with 70 in the experimental group and 70 in the control group. The heterogeneity test results ($P = 0.24$, $I^2 = 27\%$) indicated low heterogeneity; thus a fixed-effect model was employed for analysis. The meta-analysis indicated that the combined effect size MD was −13.58, with a 95% confidence interval of [−17.52, −9.64], demonstrating statistical significance ($Z = 6.76$, $P < 0.00001$). The findings from Yao W 2020 and Tian CR 2013 demonstrated that, post-treatment, the experimental group significantly reduced IL-6 levels compared to the control group, with the difference being statistically significant ($P < 0.05$).

Interleukin-8

Five studies reported IL-6 values. The measurement units in Chen[32] were inconsistent and could not be converted, Huan[30] utilized sputum samples, and there were some ambiguities in the data from Sheng H 2017. Ultimately, two studies were included in the meta-analysis,[27,31] with a total sample size of 134 participants, comprising 67 in the experimental group and 67 in the control group. The heterogeneity test results ($P = 0.004$, $I^2 = 88\%$) indicated substantial heterogeneity; thus a random-effects model was employed for the analysis. The meta-analysis revealed that the combined effect size MD was −38.87, with a 95% confidence interval of [−68.27, −9.48], indicating statistical significance ($Z = 2.59$, $P = 0.010$). The findings from Chen Y 2013 and Huan YF 2013 demonstrated that, post-treatment, the experimental group significantly reduced IL-8 levels compared to the control group, with the difference being statistically significant ($P < 0.05$).

Neutrophil Elastase and Galectin-3

Three studies reported on NE and Gal-3,[22,23,26] all of which were included in the meta-analysis. The combined sample size was 219 participants, with 108 in the experimental group and 111 in the control group. The heterogeneity test for NE showed results of ($P = 0.98$, $I^2 = 0\%$) and for Gal-3 ($P = 0.87$, $I^2 = 0\%$), indicating no significant statistical heterogeneity among the studies.

Consequently, a fixed-effect model was utilized for the analysis. The meta-analysis results indicated that the combined effect size for NE was MD = −3.26, with a 95% confidence interval of [−3.93, −2.59], showing statistical significance ($Z = 9.53$, $P < 0.00001$). Similarly, for Gal-3, the combined effect size was MD = −6.01, with a 95% confidence interval of [−6.75, −5.28], also demonstrating statistical significance ($Z = 16.01$, $P < 0.00001$). Detailed results are presented in Figures 9 and 10.

Subgroup Analysis

Subgroup and sensitivity analyses were conducted on the FEV1/FVC outcome measure. A subgroup analysis based on the presence of pulmonary hypertension was performed, revealing higher heterogeneity in the non-comorbid group

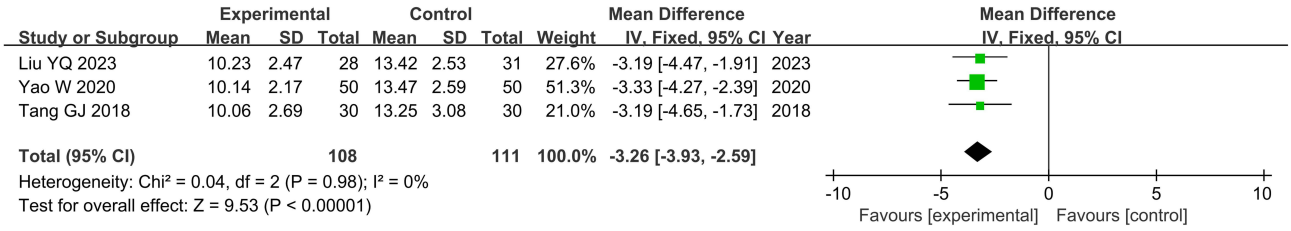

Figure 9 NE Forest plot.

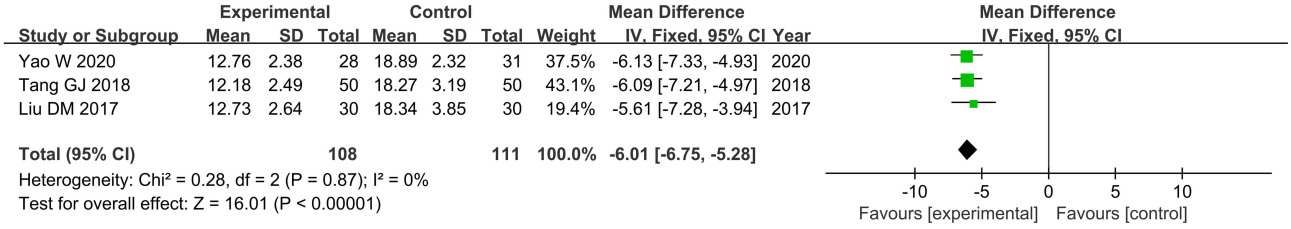

Figure 10 Gal-3 Forest plot.

compared to the group with pulmonary hypertension. However, the difference between the two subgroups was not statistically significant (P = 0.44, I^2 = 0%), as illustrated in Figure 11. This suggests that the presence of pulmonary hypertension exerts minimal impact on the outcomes of rosuvastatin as an adjunct treatment for acute exacerbations of chronic obstructive pulmonary disease, indicating good data stability.

The included studies provided only general descriptions of standard treatment protocols and optional medications, without clearly specifying whether all patients in each study received the complete standard regimen or only certain components of the treatment. Moreover, the original studies did not stratify patients according to the presence of respiratory failure or the severity of COPD, nor did they supply sufficient data to enable subgroup analyses based on disease severity. Consequently, subgroup analyses according to the severity of AECOPD were not performed in the present study.

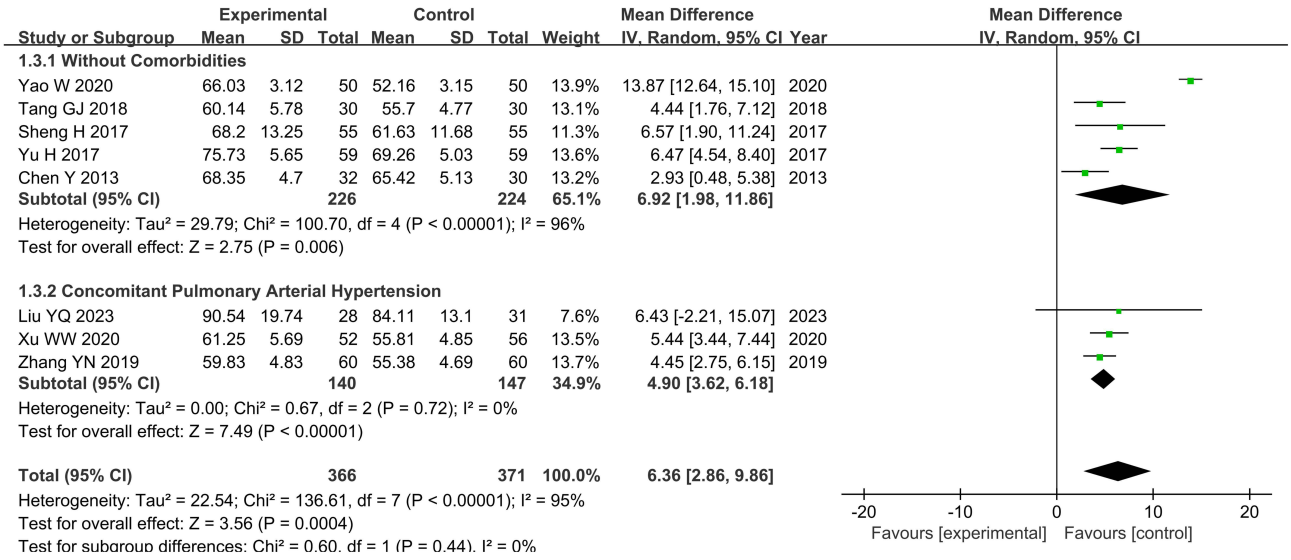

Figure 11 Subgroup Analysis.
Notes: This subgroup analysis was stratified based on the presence or absence of pulmonary hypertension.

Sensitivity Analysis

Sensitivity analysis indicated that the study by Yao[23] had a significant influence on the results, potentially contributing to heterogeneity, as shown in Figure 12. Nevertheless, after excluding this study and re-conducting the meta-analysis, the results did not reverse, suggesting that the findings remain stable and continue to support the benefits of adjunctive therapy.

Publication Bias Analysis

A publication bias test was conducted for the FEV1/FVC outcome measure, with the funnel plot results shown in Figure 13. Egger's test results (z = 2.88, P = 0.0040) indicated the presence of publication bias, necessitating consideration of regional limitations and potential biases arising from study methodologies and reporting objectives. Additionally, it is important to consider that the limited number of included studies may result in reduced detection power.

Discussion

Currently, although numerous studies have investigated the potential effects of statins in the treatment of COPD, the majority of these studies have focused on stable-phase patients and other types of statins. However, patients with AECOPD often experience acute disease progression accompanied by severe cardiovascular and cerebrovascular complications, as well as significantly elevated levels of inflammation, which collectively increase the risk of treatment. Therefore, evaluating the applicability of statins in AECOPD patients is of significant clinical importance. In addition to their lipid-lowering effects, statins exhibit significant anti-inflammatory and immunomodulatory properties, which may contribute to the control of systemic inflammation in AECOPD patients. However, as the pharmacokinetics and pharmacodynamics of drugs in acute-phase patients may differ significantly from those in stable-phase patients, it is crucial to analyze the efficacy and safety of statins in this population to provide a scientific basis for individualized treatment.[5,6]

Compared with other statins, rosuvastatin demonstrates superior cholesterol-lowering efficacy, a longer half-life, and reduced dependency on CYP3A4 metabolism, thereby minimizing the risk of drug–drug interactions. However, variations in efficacy, safety, and pharmacological characteristics exist among different statins, and disease-specific conditions significantly influence drug selection.[10–12] The findings of this study demonstrate that adjunctive therapy with rosuvastatin in patients with AECOPD significantly improves pulmonary function parameters, including FVC, FEV1, FEV1/FVC, and PEF. This outcome is closely aligned with the primary therapeutic goals of pharmacological intervention,

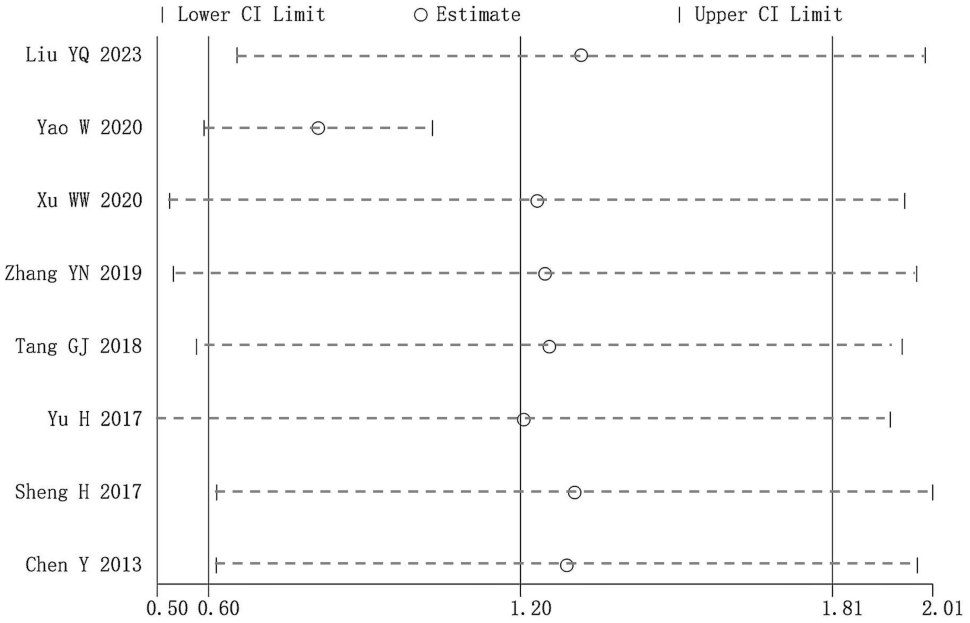

Figure 12 Sensitivity Analysis.
Notes: The sensitivity analysis was conducted with respect to the outcome measure of FEV1/FVC.

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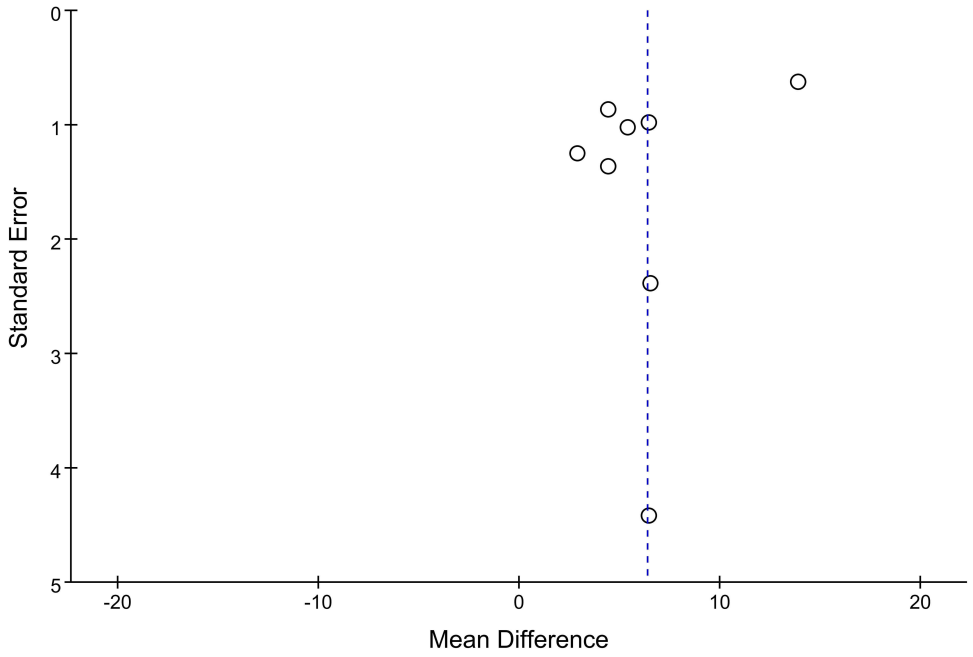

Figure 13 Publication Bias Analysis.
Notes: The publication bias analysis was performed with regard to the outcome measure of FEV1/FVC.

namely the enhancement of lung function and the promotion of patient recovery. Improved pulmonary function not only alleviates symptoms such as dyspnea but also contributes to reducing hospitalization rates and slowing disease progression. Moreover, rosuvastatin was found to markedly decrease several systemic inflammatory markers, including hs-CRP, IL-6, IL-8, TNF-α, NE, and Gal-3, indicating its beneficial role in attenuating airway and systemic inflammation and in modulating disease activity. Effective control of inflammatory responses is essential for preventing further deterioration of AECOPD and minimizing the risk of complications. In addition, the incidence of adverse events in the rosuvastatin group was low and comparable to that observed in the control group, further supporting the safety profile of rosuvastatin as an adjunctive therapy in AECOPD. These findings provide a rationale for the clinical use of rosuvastatin to achieve therapeutic efficacy while ensuring patient safety.

Although the pooled results of the meta-analysis revealed statistically significant overall differences in these outcomes, discrepancies among individual studies should be noted. For instance, the study by Liu YQ 2023 did not observe a significant improvement in FEV1 with rosuvastatin. Sensitivity analyses further indicated that the study by Yao W 2020 had a notable impact on the meta-analytic results for FEV1 and FEV1/FVC. These inconsistencies may be attributed to variations in disease severity, comorbidities, prior statin use, and standard treatment regimens across the included studies.

It is noteworthy that most included studies did not provide detailed information regarding patients' standard treatment regimens or pulmonary function classification, which limited further analysis of the impact of disease severity on the adjunctive effect of rosuvastatin. Nevertheless, heterogeneity analyses preliminarily suggest that rosuvastatin may be beneficial across AECOPD patients with varying degrees of severity. Consequently, there is a pressing need for additional high-quality, large-scale, multicenter studies to further elucidate the efficacy of rosuvastatin in different subgroups of AECOPD patients, thereby providing stronger evidence to support precision medicine in clinical practice.

Sensitivity analyses, including subgroup analyses based on the presence or absence of pulmonary hypertension, revealed no significant deviations in our findings, indicating a high level of result stability. However, during the synthesis of results, the limited number of included studies and the lack of detailed study protocols and procedural information in some research prevented a comprehensive assessment of the risk of bias. Therefore, the widespread application of rosuvastatin in the acute-phase treatment of AECOPD should be approached with caution. It is recommended that its use in clinical practice be rationally guided by specific national healthcare policies and guidelines.

Limitations

However, the randomized controlled trials (RCTs) included in this study were predominantly conducted in China, which may introduce regional bias. The healthcare infrastructure, patient demographics, and prescribing practices in China may differ from those in other regions, necessitating caution when generalizing these findings to broader populations. Additionally, only 911 participants were included across the 11 RCTs analyzed in this study, with fewer than 100 subjects included in certain outcome analyses. Consequently, the overall risk of bias among the included studies remains uncertain, which limits the ability to reliably synthesize effect sizes from the available evidence. Furthermore, due to the limited sample size and methodological constraints of the included clinical trials, it was not possible to further evaluate whether the therapeutic efficacy of rosuvastatin is consistent across different severities of AECOPD. Therefore, it is of critical importance to conduct more high-quality, multicenter RCTs in the future. Despite the potential risk of bias, the overall findings suggest that statins may have a beneficial effect on inflammation control and disease stabilization in patients with AECOPD. This trend underscores the potential value of statins in the management of AECOPD.

Conclusion

Rosuvastatin effectively improves lung function and alleviates inflammatory responses, thereby achieving adjunctive therapeutic effects, consistent with findings from remission phase and comprehensive studies, supporting its therapeutic advantages. However, due to certain biases in AECOPD-related RCTs, interpretation of the results should remain cautious.

Acknowledgments

We want to thank all the authors who participated in this study.

Funding

This study was funded by the National Natural Science Foundation of China (Grant No. 82360012).

Disclosure

The authors declare that they have no relevant affiliations or financial ties to any organization or entity that could be perceived as having a financial interest or conflict of interest related to the subject matter or materials presented in this manuscript.

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