Original Article

Effect of statins on pulmonary function in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis of randomized controlled trials

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Background: Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease, and its treatment is still controversial. Statins have been proven to have anti-inflammatory and immunomodulatory effects, but their effectiveness in the treatment of COPD is still unclear. We conducted this meta-analysis to more accurately evaluate the therapeutic effect of statins on COPD patients.

Methods: Randomized controlled studies published in PubMed, Cochrane Library, Embase, Wiley Online Library, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang databases from inception to July 2022 were retrieved to evaluate the effect of statins on COPD patients. Two evaluators conducted literature screening based on inclusion and exclusion criteria, and conducted a bias risk assessment on them. Meta analysis was conducted using Stata17.0 statistical software.

Results: A total of 1,463 patients from 10 studies were included. After statin treatment, the percentage of predicted forced expiratory volume in the first second (FEV1%pred) of COPD patients was improved [weighted mean difference (WMD): 7.89; 95% confidence interval (CI): 7.19–8.60; P<0.05], and the level of the inflammatory factor C-reactive protein (CRP) decreased (WMD: −0.63; 95% CI: −1.84, 0.58; P<0.05). The 6-minute walking distance (6MWD) of patients in the statin treatment group demonstrated a significant benefit (WMD: 26.27; 95% CI: 24.02–28.51; P<0.05). Compared to the placebo control group, statins significantly reduced COPD Assessment Test (CAT) (WMD: −2.45; 95% CI: −3.62, −1.27).

Conclusions: Preliminary evidence suggests that statins may have a certain effect on improving lung function, reducing inflammatory factor levels, and improving clinical symptoms in COPD patients. However, due to the quality and quantity limitations of the included studies, these results need to be further verified through a larger, higher quality randomized controlled trial (RCT).

Keywords: Lung disease; chronic obstructive; statins; meta-analysis

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Introduction

Chronic obstructive pulmonary disease (COPD) is a persistent disease of the respiratory tract characterized by respiratory symptoms (dyspnea, cough, and production of sputum) and anatomical changes in airflow obstruction at different rates. With severe complications and high mortality (1), pulmonary hypertension (PH) is a serious complication that occurs at different stages of COPD. It is divided into 5 groups according to pathogenesis, and there is no clear correlation between its severity and previously reported disease severity (2). PH is defined by a mean pulmonary arterial pressure (mPAP) equal to or greater than 25 mmHg at rest, as measured by a right heart catheter (RHC) (3). However, the prevalence of PH in patients with COPD has not yet been established. In one study, the 5-year survival rate of COPD patients with mPAP >25 mmHg was only 36%, while the 5-year survival rate of patients with mPAP <25 mmHg was 62%. COPD is one of the four major causes of pathological death in humans and greatly increases the global healthcare burden (1). However, no specific vasoactive drugs are available to the general public for the treatment of COPD-related PH. Therefore, finding effective drugs or developing new strategies is crucial for long-term management of COPD-related PH. Statins are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase that have been used clinically to treat hyperlipidemia. Recent experimental studies have shown that statins have a relatively comprehensive protective effect on human blood vessels independent of lowering cholesterol levels. Therefore, statins inhibit thrombotic responses (4-6).

Highlight box

Key findings

- The results of this meta-analysis showed that statins can reduce inflammation levels and improve clinical symptoms in patients with stable chronic obstructive pulmonary disease (COPD).

What is known and what is new?

- Statins may have potential value in the treatment of many vascular disease, including pulmonary hypertension (PH).
- This study aims to investigate the efficacy of statins in the treatment of COPD, in order to provide a rational, informed basis for decision-making.

What is the implication, and what should change now?

- The study evaluated the efficacy and safety of statins in COPD patients. Statins can significantly improve lung function and clinical symptoms in COPD patients.

Statins have anti-inflammatory and immunomodulatory effects, which can reduce the levels of inflammatory markers [such as C-reactive protein (CRP)] in the serum, improve vascular endothelial function, reduce the infiltration and adhesion of inflammatory cells, and inhibit the production of inflammatory factors such as tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) (7,8). Studies have shown that statins attenuate the progression of PH in several animal models (9-11). However, statins, as a kind of drugs widely used in the treatment of cardiovascular diseases, are still controversial in the treatment of COPD. Some clinical trials have reported the potential benefits of statins in improving lung function, inflammatory factors, and clinical symptoms in COPD patients (12-18). However, other studies have failed to demonstrate this effect, and these inconsistent results can be attributed to differences in factors such as study design, sample size, type and dosage of statins (12-18). Therefore, we conducted this meta-analysis in order to provide more reliable conclusions through a comprehensive and quantitative analysis of existing evidence, integrating and analyzing data from multiple studies. We present this article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1042/rc).

Methods

Literature inclusion and exclusion criteria

Published randomized controlled studies on the therapeutic effect of statins on COPD patients were searched from PubMed, Cochrane Library, Embase, Wiley Online Library, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang databases until July 2022. The search language is limited to Chinese and English. The electronic database search yielded 3,242 publications (*Figure 1*). After excluding the ones that did not meet the inclusion criteria and the duplicate studies, this left 139 articles with subject matter related to this meta-analysis. In a more detailed review, studies were excluded due to the lack of interesting results, duplication of data, and inclusion of patients with other lung diseases. Inclusion criteria: (I) research on COPD patients, regardless of age, gender, race, or severity of COPD. (II) Intervention: the study must involve the use of statins as an intervention in the treatment of COPD, including but not limited to various statins, such as atorvastatin, simvastatin, pravastatin. The patients in the control group were treated with placebo.

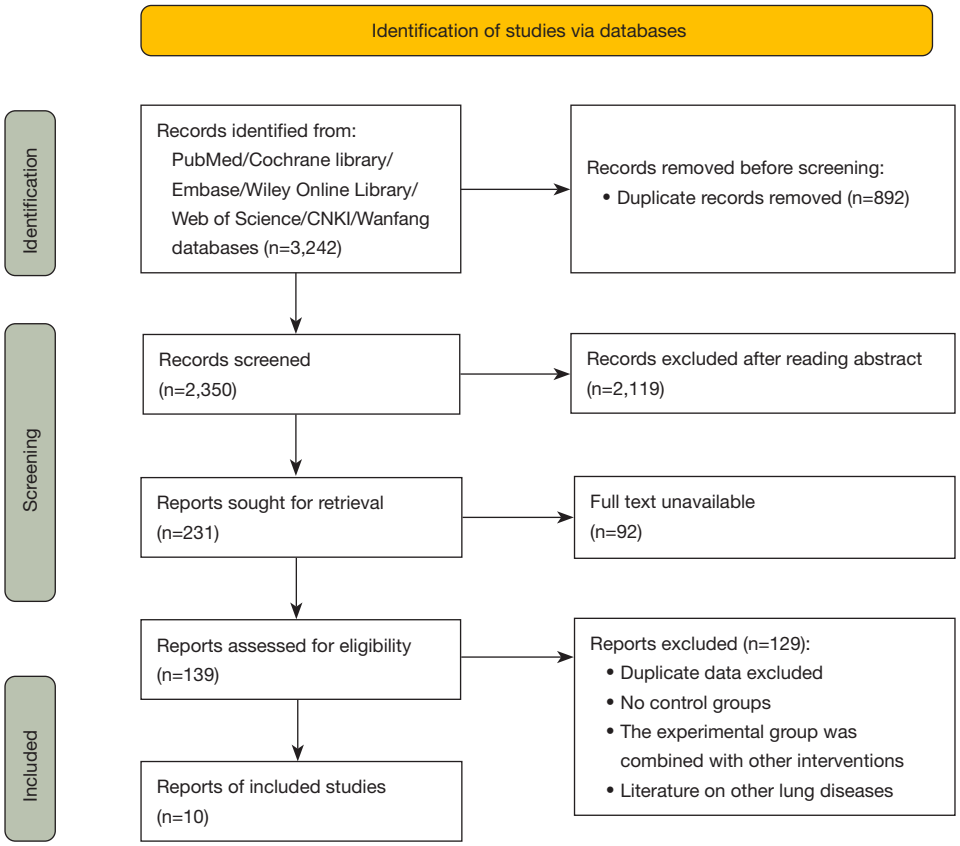

Figure 1 Flow chart of the literature inclusion process. CNKI, China National Knowledge Infrastructure.

(III) Outcome measures: improvement in lung function (such as FEV1), levels of inflammatory biomarkers (such as CRP, interleukin-6), improvement in clinical symptoms, and safety of statins. Exclusion criteria: (I) simple descriptive studies, reviews, systematic reviews, and studies without relevant research data; (II) animal experiments; (III) case/control, historical control, and uncontrolled studies; (IV) papers not written in Chinese or English; (V) repeat studies.

Data extraction and quality assessment

The reviewers were responsible for screening articles that meet the criteria. The reviewers compared the selected studies and resolved any differences in judgment through discussion. They prepared a data sheet to extract data from each text, table, and chart included in the study, year of publication, type of treatment, number and age of patients, 6-minute walking distance (6MWD), and forced expiratory volume in the first second (FEV1). The quality of the study was evaluated by the Detsky method (19).

Of the 1,023 articles that were first retrieved, 105 were read for more specific evaluation, and 10 articles were included in the study (12-18,20-22) (*Table 1*). We mainly included randomized controlled trials (RCTs), so we used Cochrane's risk bias assessment tool to assess the bias risk of each study.

Statistical analysis

Stata17.0 was used for various analyses. For continuous variables, we will use mean difference (MD) to express the results and provide a 95% confidence interval (CI). For the two categorical variables, we will use odds risk (OR) to express the results and provide a 95% CI. The Chi-square test and I^2 test were used to estimate the heterogeneity of experimental results across studies, and the analytical model was chosen accordingly (fixed effects or random effects). A cutoff of $P \leq 0.05$ and $I^2 > 50\%$ indicated high heterogeneity, in which case a random effect model was used. If $P > 0.05$ and $I^2 \leq 50\%$, we used a fixed effect model.

Table 1 Basic information of the included RCTs

First author	Year of publication	Number of cases (trial/control)	Drug usage	Drug dose, mg/d
Lee (20)	2009	27/26	Pravastatin	40
Criner (12)	2014	433/452	Simvastatin	40
Ghobadi (13)	2014	25/25	Atorvastatin	40
Maneechotesuwan (15)	2015	26/26	Simvastatin	20
Mroz (14)	2015	33/37	Atorvastatin	40
Neukamm (21)	2015	47/47	Rosuvastatin	10
Chogtu (16)	2016	32/30	Rosuvastatin	10
Liu (17)	2017	60/60	Atorvastatin	20
Patyk (18)	2019	26/24	Simvastatin	20
He (22)	2020	43/43	Atorvastatin	10

RCT, randomized controlled trial.

The research result chart and the research accuracy of each result (funnel diagram) were used to evaluate publication bias. Continuous variables are expressed as mean difference ± standard deviation (SD) and were compared according to the weighted mean difference (WMD). The results showed a significant publication bias with bilateral P<0.05.

Results

Basic information about the included studies

A total of 3,242 relevant studies were retrieved. Ten studies with 1,463 patients were included after the screening. See *Figure 1*.

Characteristics of the included studies

This meta-analysis included 10 studies (12-18,20-22) that compared the effects of simvastatin, atorvastatin, and rosuvastatin on the course of COPD patients. Four articles administered three doses of atorvastatin, 40, 20, and 10 mg. Three articles gave simvastatin at doses of 40 and 20 mg. Two articles involved rosuvastatin treatment and one article involved pravastatin treatment. *Table 1* summarizes the recent studies on the use of statins in COPD patients.

Exercise ability

A total of 4 studies, including 307 patients, reported on the 6-minute walk test. We used the random effects model to meta-analyze the change in 6MWD, and the overall evaluation was carried out in four trials. Statins had a significant benefit on the 6MWD (WMD: 26.27; 95% CI: 24.02–28.51; P>0.05, *Figure 2*). The funnel plot showed that the data points were distributed on both sides and were funnel-shaped. No significant heterogeneity difference was observed between the studies (P=0.655>0.05) (*Figure 3*).

Lung function

Data on FEV1/pred were provided in six RCTs (*Figure 4*). The improvement in FEV1% was predicted to significantly improve with statin therapy through the random effects model (WMD: 7.89; 95% CI: 7.19–8.60; P<0.05). No significant heterogeneity was observed between studies (*Figure 5*). In conclusion, our data suggest that statin therapy improves lung function.

Effects of statins on inflammation

The random effects model evaluated the effects of statins on inflammation in patients with COPD, as measured by inflammatory indicators in the plasma of patients (three trials) (*Figure 6*). The results indicated that statins improved these indicators more than placebo (WMD, –0.63; 95% CI: –1.84, 0.58; P<0.05). The heterogeneity between trials was not significant (*Figure 7*).

Effect of statin on COPD Assessment Test (CAT) score

The results of CAT were reported in three studies (70

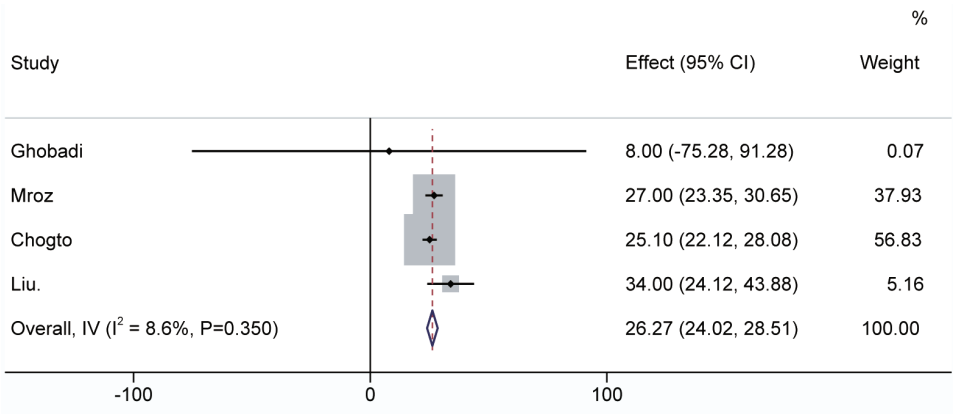

Figure 2 Forest plot of the effect of statins on 6-minute walking distance. CI, confidence interval.

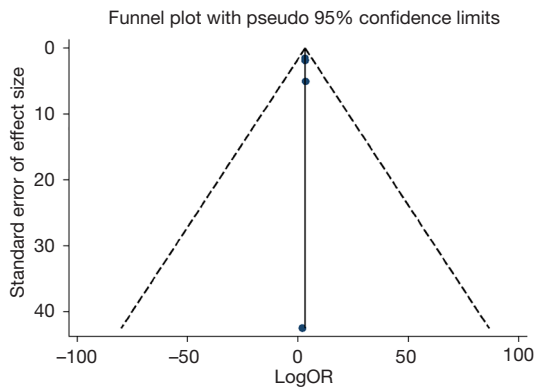

Figure 3 Funnel plot of the studies of statins and 6-minute walking distance. OR, odds risk.

patients in the statin group and 67 patients in the control group). The Chi-square test P value was <0.05 and I^2 was ≥50%, so a random effects model was selected to evaluate CAT. Compared with control, statins significantly reduced CAT (WMD: –2.45; 95% CI: –3.62, –1.27, *Figure 8*). The heterogeneity between studies is not significant (*Figure 9*).

Discussion

Statins can have beneficial effects against cardiovascular diseases. According to previous epidemiological studies, smoking in patients with COPD is the most important pathogenic factor and a factor promoting the development of coronary artery disease. Large studies have found that the most common complication in COPD patients is cardiovascular disease. A large cohort study observed a significant increase in disease (33.6% *vs.* 27.1%) among 384888 subjects with COPD (23). Moreover, for patients with mild to moderate airway obstruction, a 10% decrease in predicted forced expiratory volume in the first second (FEV1%pred) is associated with a 28% increase in cardiovascular mortality and a 20% increase in the risk of non-fatal coronary events (24). Therefore, it is particularly important to use drugs to improve the lung function of patients (14,25-27). Several observational studies have shown the potential benefits of statins as adjunctive therapy for COPD patients (12-15,20). However, there are limitations in observational study. Although some meta-analyses have reported the impact of statins on COPD. For example, Zhang *et al.* (28) reported that patients with statin therapy have elevated levels of CRP or cholesterol. Xue *et al.* reported that FEV1/forced vital capacity (FVC) and high-density lipoprotein were allowed after statin treatment (29), but there were also some other aspects, such as exercise ability, which were not reported. Therefore, this paper aims to incorporate systematic evaluation and meta-analysis methods into the latest research to explore the impact of statins on the efficacy of COPD.

In this meta-analysis, 1,463 COPD cases from 10 articles were analyzed. Meta-analysis results show that statin use can significantly improve patient function and exercise capacity, which is consistent with the results of several studies (12,14). This has been linked to the inhibition of vasculitis by statins and the stimulation of nitric oxide synthesis, which in turn relaxes pulmonary vessels, leading to improvements in pulmonary artery wedge pressure (PAWP) and mean pulmonary artery pressure (mPAP) (12,14,20,30). Furthermore, statins can regulate the balance of Th1/Th2 cells by inhibiting TH1 development and increasing TH2

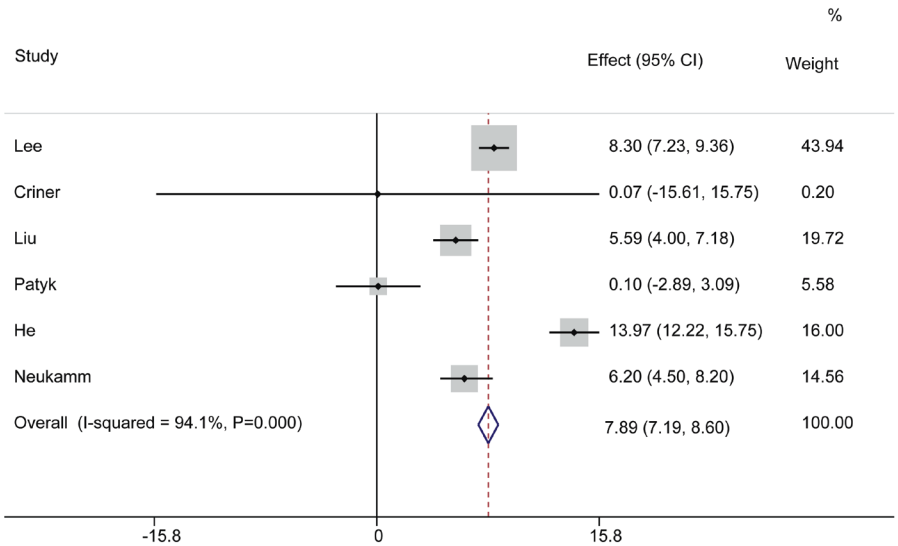

Figure 4 The effect of statins on FEV1/pred in COPD patients. CI, confidence interval; FEV1, forced expiratory volume in the first second; COPD, chronic obstructive pulmonary disease.

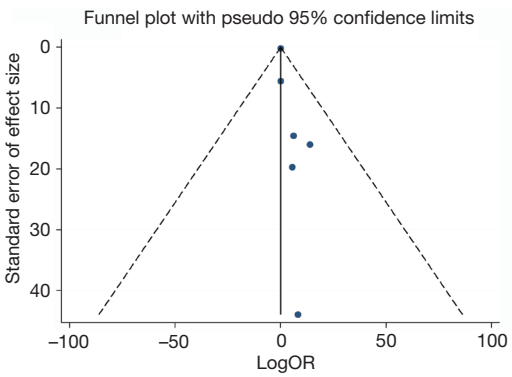

Figure 5 Funnel plot of the studies of statins and the lung function of COPD patients. OR, odds risk; COPD, chronic obstructive pulmonary disease.

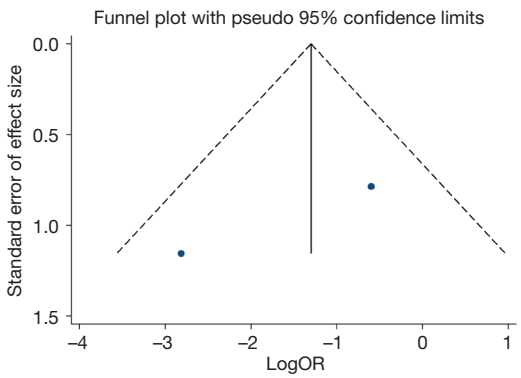

Figure 7 Funnel plot of the studies of statins and inflammatory factors in COPD patients. OR, odds risk; COPD, chronic obstructive pulmonary disease.

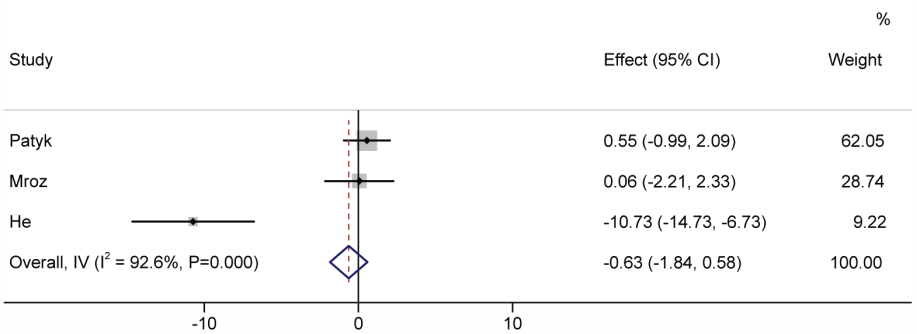

Figure 6 The effect of statins on CRP in COPD patients. CI, confidence interval; CRP, C-reactive protein; COPD, chronic obstructive pulmonary disease.

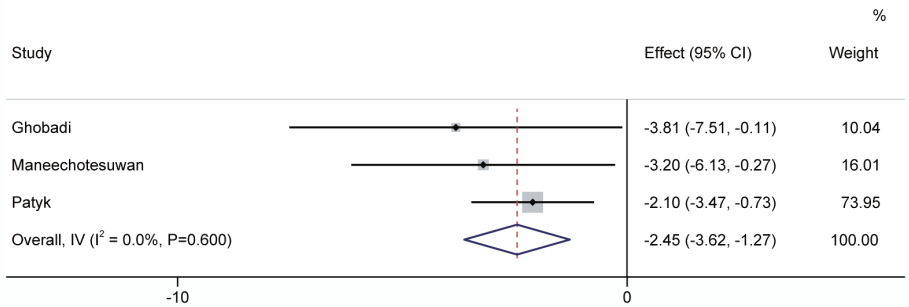

Figure 8 The effect of statins on CAT score in COPD patients. CI, confidence interval; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease.

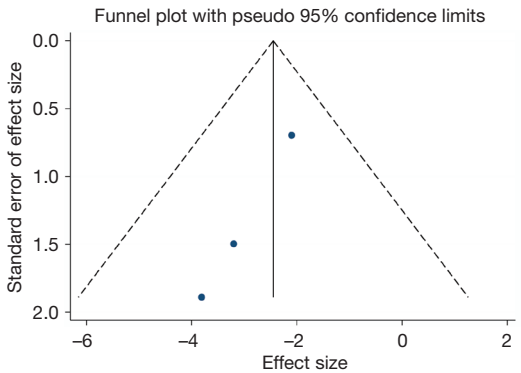

Figure 9 Funnel plot of the studies of statins and CAT score in COPD patients. CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease.

development of $CD4^+$ T cells, statins therefore have anti-inflammatory, antioxidant and antithrombotic properties. In this meta-analysis, statin use was also found to significantly improve the inflammatory response in patients. Improvement in lung hemodynamics may be another potential benefit of statins in COPD (20,30). The common complication of COPD is HP, which is characterized by short life expectancy, poor prognosis and high cost of medical treatment (25). Statins also have a positive impact on the patient's athletic ability. After treatment, the patient's 6-minute walking distance increased significantly, indicating that statins improved the patient's physical activity level (13,14). This may be due to statins improving oxygen delivery and muscle endurance by improving pulmonary hemodynamics and promoting pulmonary vasodilation. Statins were also found to reduce CAT scores, meaning that the disease had less impact on quality of life and patients' quality of life was improved in this study. This may be due to the anti-inflammatory and antioxidant effects of statins, as well as the improvement of vascular function.

There are some limitations in this study. First, although this paper does not search all the databases and the language is limited to Chinese and English, it is inevitable that there will be omissions in the search. Secondly, the number of literatures included in this paper is small, which leads to the limitation of meta-analysis, such as the inability to analyze and compare different populations, different diseases, different treatments. Finally, some of the results included in this paper are heterogeneous, which may affect the results to some extent.

Conclusions

In summary, statins can reduce inflammation levels and significantly improve lung function and clinical symptoms in COPD patients. However, considering the shortcomings of this article, more high-quality, large sample randomized controlled studies need to be included in the future to further evaluate the effectiveness of statins in treating COPD.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1042/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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