

Peer Review File

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Reviewer A

The paper titled “Meta-analysis of the effect of statins on pulmonary function in patients with chronic obstructive pulmonary disease” is interesting. Statins can reduce the level of inflammation and improve the clinical symptoms of COPD patients by improving lung function. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) The content of this study is too simplistic. Suggest increasing the analysis of the impact of different statins on pulmonary function in patients with COPD.

Reply: Thank you for your comment. Thank you for your suggestion. However, due to the relatively small number of literatures ultimately included in this article and the wide variety of statin drugs. If subgroup analysis is conducted, there may be some cases where only one article related to this type of statin cannot be analyzed, so the impact of different statin drugs on lung function in COPD patients has not been analyzed.

Changes in the text: None

2) What is the regulatory effect of statins on inflammation levels in patients with chronic obstructive pulmonary disease? It is recommended to add relevant content.

Reply: Thank you for your comment. We have added relevant content.

Changes in the text: Paragraph 2/ Introduction; Paragraph 1 / Discussion

3) There are many databases. Why did the author only select several databases in this study for searching? Please explain the reason.

Reply: Thank you for your comment. There are many domestic and foreign databases. We try our best to select data with wider coverage for representative retrieval. PubMed is the world 's largest life science literature database. Cochrane Library, Embase, Wiley Online Library and Web of Science are all global databases with wide coverage, while CNKI, Wanfang and Chinese Science and Technology Journal Database are the three most important academic literature databases in China.

Changes in the text: None

4) The quality and quantity of included studies are limited, and the conclusions need to be confirmed by more large-scale, high-quality RCTs.

Reply: Thank you for your comment. We have modified the conclusion.

Changes in the text: Paragraph 4 / Abstract

5) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Inflammatory parameters and pulmonary biomarkers in smokers with and without chronic obstructive pulmonary disease (COPD), J Thorac Dis, PMID: 34527321”. It is recommended to quote the articles.

Reply: Thank you for your comment. We have added references to relevant literature.

Changes in the text: Paragraph 2/ Introduction

6) This study is based on the analysis and summary of the literatures. It is suggested to add clinical experimental research, which may be more meaningful.

Reply: Thank you for your comment. Meta-analysis is based on the analysis and summary of existing research to draw conclusions. By increasing the sample size and statistical power, it can provide more accurate estimates. It can also be used to address inconsistencies in a single study, or to assess possible factors that may affect the outcome.

Changes in the text: None

7) It is suggested to increase the possible mechanism of this therapy in the discussion section, so as to enrich the information of this paper.

Reply: Thank you for your comment. We have increased the relevant content.

Changes in the text: Paragraph 1,2 / Discussion

Reviewer B

1) First, the title needs to indicate the outcomes of interest of this study, not a vague term “effect” and I suggest the authors to indicate “a meta-analysis of randomized controlled trials”.

Reply: Thank you for your comment. The content of the conclusion is relatively complex, and the refining summary may lead to the title summary is not comprehensive enough, so the curative effect is used instead. 'Randomized controlled trials ' have been added to the title.

Changes in the text: Paragraph 1 / Title

2) Second, the abstract needs some revisions. The background did not describe the controversy regarding the efficacy of statins for COPD and why a meta-analysis is needed to address this controversy. The methods need to clearly describe the

inclusion criteria for eligible studies according to the PICOS principles, and risk of bias assessment of included studies. The results need to describe the levels of risk of bias of included studies and the sample size in both the statins group and the control group. Please specify the treatment of control group when describing the comparative results. The current conclusion needs to tone down because of the clinical heterogeneity and risk of bias in included studies.

Reply: Thank you for your comment. We have modified the Abstract.

Changes in the text: Paragraph 1,2,3,4 / Abstract

3) Third, the introduction of the main text is poor. The authors did not describe the clinical controversy regarding the efficacy of statins for COPD, analyze the potential reasons for the controversy and explain why a meta-analysis can address this controversy. In this part, the authors described the safety outcomes but they did not analyze on this outcome in the following analysis.

Reply: Thank you for your comment. We have modified the introduction.

Changes in the text: Paragraph 2 / Introduction.

4) Fourth, in the methodology of the main text, please describe the inclusion criteria for eligible studies according to the PICOS principles, including the outcome measures and the intervention of the control groups, as well as the tool for assessing the risk of bias of included studies. Please describe the data extraction for safety outcomes and explain why inflammatory biomarkers can be an efficacy outcome. In statistics, please describe the P value for statistical significance, subgroup analysis for sources of heterogeneity, and statistical tests for publication bias.

Reply: Thank you for your comment. We have modified the methods.

Changes in the text: Paragraph 1 / Methods.

Reviewer C

1. Several meta-analysis of the effect of statins on COPD had been published (e.g., Lu Y, et al. Respiratory Research 2019; 20:17; Cao C et al. The effects of statins on COPD exacerbation and mortality: a systemic review and meta-analysis of observational research. Sci Rep 2015;5: 16461; Zhang MZ eta al. Statins may be beneficial for patients with pulmonary hypertension secondary to lung disease. Journal of Thoracic Disease 2017; 9:2437.) The present manuscript did not quote any of these meta-analysis studies.

Reply: Thank you for your comment. We have added some retrieved meta-analyses to enrich the content of this article.

Changes in the text: Paragraph 1 / Discussion

2. Introduction - The authors commented that pulmonary hypertension (PH) is an adverse factor in patients with COPD. However, no further description of effect of statins on PH was described in the Methods or Results.

Reply: Thank you for your comment. The main focus of this paper is not on PH, and many literatures only mention the existence of PH, and do not involve the outcome indicators in this regard. Therefore, this article is only mentioned as a possible potential adverse factor, and not too much interpretation in the results.

Changes in the text: None

3. Methods - the authors had not described in details of the inclusion criteria for the studies. A large number of studies were excluded (e.g., duplicate record = 892 in Fig 1, 2119 excluded after reading abstract, details not explained why so many were excluded at this stage). With remaining 139 studies, 129 were excluded for various reasons without breakdown. Some studies were excluded due to lack of interesting results. Finally, only 10 studies were included for analysis - an exceptionally low number.

Reply: Thank you for your comment. Because although the search needs to add a qualifier, but the initial search must have a large number of low correlation literature. And because the initial search browsing titles and abstracts can eliminate these documents. The remaining 129 articles were mainly based on no control group, repeated publication, intervention combination and other intervention methods (such as multi-drug combination), and the combination of other diseases.

Changes in the text: None

3. Results - only very brief discussion was made for effect of statins on exercise ability, lung function, inflammation (details of what inflammatory factors were studied was not included), CAT score. There was no description of effect of statins on COPD exacerbation, PH or mortality.

Reply: Thank you for your comment. This is where we are wrong. We have deleted the relevant content in the discussion section.

Changes in the text: Paragraph 2 / Discussion

4. Discussion - again PH related to COPD was discussed, as in Introduction section. Effect of statins on COPD exacerbation and mortality were discussed, but these were not included in the Method or Results sections.

Reply: Thank you for your comment. We have modified it.

Changes in the text: Paragraph 1,2 / Discussion