PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Chronic obstructive pulmonary disease exacerbation purulence status and its association with pulmonary embolism: protocol for a systematic review with meta-analysis
AUTHORS	Mai, Vicky; Girardi, Laura; de Wit, Kerstin; Castellucci, Lana; Aaron, Shawn; Couturaud, Francis; Fergusson, Dean; Le Gal, Grégoire

VERSION 1 – REVIEW

REVIEWER	Minghang Wang Te First Afliated Hospital of Henan University of Chinese Medicine, Department of Respiratory Diseases
REVIEW RETURNED	01-May-2024

GENERAL COMMENTS	1. Clarity and Importance of Research Objectives: It is recommended to further clarify the research objectives in the introduction and provide detailed explanations on the significance of assessing the association between purulence status in Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) and the diagnosis of Pulmonary Embolism (PE). This will better explain the motivation and value of the study to the readers. 2. Transparency in Methods: In the methods section, more details regarding literature search, selection criteria, and data extraction methods are needed to ensure readers understand the overall design and implementation process of the study. Additionally, providing more information on the study design and analysis plan would enhance the methodological quality assessment of the study. It is suggested to update the literature search timeframe to cover the latest research findings, thereby improving the comprehensiveness and timeliness of the study. 3. Choice of Statistical Analysis Software: Considering the use of Reverman 5.3 for statistical analysis, it is advisable to consider using other statistical analysis software such as R or STATA, which offer broader applications and more functionalities to better support the analytical requirements of the study. 4. Reliability of Results Analysis: In the results section, a more detailed discussion on potential biases and confounding factors is needed, along with proposed methods to control for them to ensure the reliability of the results. Furthermore, caution is advised in handling subgroup analyses, with thorough explanations and discussions provided. 5. Clinical Significance and Practical Recommendations: In the conclusion section, it is essential to clearly discuss the clinical significance of the research findings and provide corresponding practical recommendations to guide clinical practice and future research directions.

REVIEWER	Zakaria Alagha
	Marshall University School of Medicine
REVIEW RETURNED	09-May-2024

| GENERAL COMMENTS | Thank you for allowing me to review such an important proposal for a systematic review. The authors' endeavor to investigate the relationship between purulence status in COPD and the risk of pulmonary embolism (PE) while developing an algorithm for prediction is commendable.

Overall, I find their approach to be quite promising. However, a few areas could benefit from further clarification to enhance the proposal's comprehensiveness and effectiveness.

In the conclusion section:
"Improving PE diagnostic algorithm for patients with AECOPD is of high importance to reduce the burden of imaging since PE and AECOPD share similar symptoms, but also to minimize the proportion of missed PE"
I suggest that the authors clarify in the methods section how they will develop such a proposed PE diagnostic algorithm for patients with acute exacerbations of COPD. It would be beneficial to include details on how the purulence status will be assessed and integrated into the algorithm and how the algorithm's efficacy will be validated to reduce the burden of imaging and minimize missed PE cases.

Developing an algorithm requires robust validation using independent datasets or external validation cohorts. Failure to adequately validate the algorithm could limit its clinical utility and predictive accuracy.

"This systematic review with meta-analysis aims at evaluating if AECOPD purulence status could be a predictor of PE in order to improve the care of patients with COPD"
Aligning the hypothesis more closely with the objectives would be helpful. A discrepancy between the stated hypothesis and the aims could lead to confusion. Ensuring coherence will enhance the overall clarity and effectiveness of the study.

By addressing these points, the authors can strengthen their proposal and provide a more comprehensive and focused approach to studying the association between purulence status in COPD and the risk of pulmonary embolism. |

VERSION 1 – AUTHOR RESPONSE

Reviewers' comments

1. Clarity and Importance of Research Objectives: It is recommended to further clarify the research objectives in the introduction and provide detailed explanations on the significance of assessing the association between purulence status in Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) and the diagnosis of Pulmonary Embolism (PE). This will better explain the motivation and value of the study to the readers.

• We further clarified the objectives in the introduction. "Thus, the main aim of this systematic review with meta-analysis is to evaluate whether purulence status in AECOPD is associated with PE. We hypothesize that the risk of PE will be lower in purulent AECOPD compared to non-purulent or unknown purulent status AECOPD, since the etiology of the exacerbation is unknown in up to 30% of the AECOPD10 and PE could thus be an explanation in those cases. As a secondary aim, we would like to evaluate the association between AECOPD purulence status and the risk of venous thromboembolism (VTE) [deep venous thrombosis (DVT) of the lower extremity and PE] and the risk

of DVT, respectively. We hypothesize that the risk of VTE and DVT, respectively, will be lower in patients with purulent AECOPD compared to non-purulent or unknown purulent status AECOPD."

• We provided further details explaining our rational in evaluating the association between AECOPD and PE by adding this sentence in the introduction: "As a matter of fact, some studies showed a lower risk of PE or VTE in patients with purulent AECOPD7-9."

2. Transparency in Methods: In the methods section, more details regarding literature search, selection criteria, and data extraction methods are needed to ensure readers understand the overall design and implementation process of the study. Additionally, providing more information on the study design and analysis plan would enhance the methodological quality assessment of the study. It is suggested to update the literature search timeframe to cover the latest research findings, thereby improving the comprehensiveness and timeliness of the study.

• The literature search timeframe has been updated to April 2024. The selection criteria have been kept broad to be more inclusive. However, to be as inclusive as possible, we added subsegmental PE in the outcome definition of PE. Details have been added in the analysis plan.

3. Choice of Statistical Analysis Software: Considering the use of Reverman 5.3 for statistical analysis, it is advisable to consider using other statistical analysis software such as R or STATA, which offer broader applications and more functionalities to better support the analytical requirements of the study.

• For the analyses we are aiming to conduct for this study, we think that Revman is an adequate statistical software to use. It is a tool proposed by Cochrane Reviews.

• We have added the possibility in evaluating pooled proportions of PE in patients with purulent AECOPD and non-purulent/unknown purulence status AECOPD, respectively, if the meta-analysis includes some studies that could not be pooled in the relative risk evaluation. Pooled proportions would be calculating using StatsDirect statistical software.

4. Reliability of Results Analysis: In the results section, a more detailed discussion on potential biases and confounding factors is needed, along with proposed methods to control for them to ensure the reliability of the results. Furthermore, caution is advised in handling subgroup analyses, with thorough explanations and discussions provided. [NOTE FROM THE EDITORS: Please rebut this comment, since there is no Results section in this protocol manuscript]

• Subgroup analyses are detailed in the Methods section to explore confounding. Subgroup analyses on the type of study (randomized trials vs prospective cohort studies vs retrospective cohort studies vs cross-sectional studies), systematic search of PE (or VTE) vs no systematic search of PE (or VTE) and localization of PE (or DVT) will be conducted. There is no Results section in the protocol manuscript, thus, we think that there is no need to add it twice in the paper.

5. Clinical Significance and Practical Recommendations: In the conclusion section, it is essential to clearly discuss the clinical significance of the research findings and provide corresponding practical recommendations to guide clinical practice and future research directions. [NOTE FROM THE EDITORS: Please rebut this comment - as noted above, the Conclusion section is not part of the BMJ Open protocol manuscript format and should be removed]

• We discussed the clinical significance of the research findings in the Discussion section. A Conclusion section is not part of the BMJ Open protocol manuscript format.

6. In the conclusion section: "Improving PE diagnostic algorithm for patients with AECOPD is of high importance to reduce the burden of imaging since PE and AECOPD share similar symptoms, but also to minimize the proportion of missed PE". I suggest that the authors clarify in the methods section how they will develop such a proposed PE diagnostic algorithm for patients with acute exacerbations of COPD. It would be beneficial to include details on how the purulence status will be assessed and integrated into the algorithm and how the algorithm's efficacy will be validated to reduce the burden of imaging and minimize missed PE cases.

• As a first step, we plan in conducting this systematic review with meta-analysis aiming in evaluating the association between AECOPD purulence status and PE. As a second step, we plan in deriving a PE diagnostic algorithm and will evaluate AECOPD purulence status as a predictor if an association between AECOPD purulence status and PE is shown in this meta-analysis. Therefore, the

methodology related to the derivation of a new PE diagnostic algorithm will not be included in this paper, but rather in the manuscript of the next project aiming in deriving a new PE diagnostic algorithm for patients with COPD.

7. This systematic review with meta-analysis aims at evaluating if AECOPD purulence status could be a predictor of PE in order to improve the care of patients with COPD"

Aligning the hypothesis more closely with the objectives would be helpful. A discrepancy between the stated hypothesis and the aims could lead to confusion. Ensuring coherence will enhance the overall clarity and effectiveness of the study.

• We made the modifications in the introduction by clarifying the main and secondary aims as well as the hypotheses related to each aim.