Author’s response to reviews

Title: Blood cells for the differentiation of airway inflammatory phenotypes in COPD exacerbations

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Author’s response to reviews:

Dear PhD Anna Melidoni,

Title: Blood cells for the differentiation of AECOPD airway inflammatory phenotypes
Journal: BMC Pulmonary Medicine
Submission ID: PULM-D-19-00034R3

Thank you for your advice and the reviewers’ valuable comments on the paper. We have revised the manuscript in accordance the reviewers’ comments, and would like to re-submit it for your consideration.

We have addressed the comments raised by the reviewers. The amendments are highlighted in red in the revised manuscript.

We acknowledge the reviewer’s comments and suggestions very much, which are valuable in improving the quality of our manuscript. Thank you and all the reviewers for the kind advice.

I sincerely hope this manuscript will be finally acceptable to be published. I look forward to hearing from you soon.

Yours sincerely
Dr Gao

Reviewer reports:

Stephen Bourke, PhD (Reviewer 1): The authors have addressed most concerns.

1. I have reservations about stating that measurement of inflammatory cells in sputum is the "Gold Standard" to determine airway inflammatory phenotype. A poor correlation between blood and sputum results may lead to a false conclusion that measurement of blood inflammatory cells is not useful. This
is clearly incorrect as blood eosinophil count has been shown to be a reliable predictor of response to inhaled corticosteroids when stable and oral steroids during acute exacerbation (acknowledged in the paper). Instead, I regard both sputum and blood eosinophils as surrogate markers of airway inflammation; the correlation between both of these biomarkers and airway histology is imperfect. What is most important is that the biomarker accurately predicts steroid treatment response. The biomarker in question must also be easy to measure in routine clinical practice; clearly not true of airway histology, and debatable in the case of sputum. I suggest either replace the statement on "Gold Standard" with the above, or at least follow it with this important caveat.

Our answer: Thank you very much for your comments. Those comments are all valuable and very helpful for improving our researches. We have revised the paper again which we hope meet with approval. However, if there is more question, we are willing to revise it again.

We have revised the statement. (Line 187 Pages 18).

2. The authors have acknowledged that inflammatory cells during exacerbation are likely to differ from stable state and now highlight that blood eosinophil counts during exacerbation should not influence long term ICS decisions - thank you. In the discussion the authors mention eosinophils may be increased if there is overlap with asthma, but in pure COPD approx. 30% of patients have an eosinophilic component to their airway inflammation. Moreover, during sepsis and many severe exacerbations of COPD, blood eosinophils may fall to very low levels (transient eosinopenia) - this latter point is worth acknowledging.
Our answer: Thanks for your suggestions. We have added the point. (Line 170-171, Pages 17).

3. All figures should be interpretable without reference to the text; a clear legend is required.
Our answer: We have revised the errors (Line 109-113, Pages 11-12; Line 146-150, Pages 14-15; Line 154, Pages 16).

4. Thank you for offering to include an acknowledgement in the paper. As this is an open review process; additional formal recognition is not required (I'm happy either way).
Our answer: We have revised the part (Line 251, Pages 24).

5. Use of English: some further attention is required - perhaps by the copy editor if accepted for publication.
Our answer: Thanks for your suggestions, I will wait for their decision.

Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses one or several testable research questions? (Brief or other article types: is there a clear objective?)

Yes - there is a clear objective
DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with sufficient technical rigor to allow confidence in the results?

Yes - experiments and analyses were performed appropriately

STATISTICS - Is the use of statistics in the manuscript appropriate?

Not sure - I am not able to assess the statistics in this study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

Yes - the author's interpretation is reasonable

OVERALL MANUSCRIPT POTENTIAL - Has the author addressed your concerns sufficiently for you to now recommend the work as a technically sound contribution? If not, can further revisions be made to make the work technically sound?

Yes - current version is technically sound

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: The revision of the manuscript entitled "Blood cells for the differentiation of AECOPD airway inflammatory phenotypes" clearly improved on the previous text. However, a few problems remained unaddressed in regard to the figures/tables.

ADDITIONAL REQUESTS/SUGGESTIONS:

- The text still does not contain figure legends,

Our answer: Thank you very much for your comments. Those comments are all valuable and very helpful for improving our researches. I hope you are satisfied with the revised manuscript. However, if there is more question, we are willing to revise it again.

We have revised the errors (Line 109-113, Pages 11-12; Line 146-150, Pages 14-15; Line 154, Pages 16).
- It is still not clear in table 2 to what the p-values at the end of the rows refer to (what is compared here?).

Our answer: Dear Professor, we had showed the Mixed granulocytic group vs Neutrophilic group (p < 0.001) and Paucigranulocytic group vs Neutrophilic group (p = 0.004). Eosinophilic group vs Neutrophilic group (p = 0.413); Mixed granulocytic group vs Paucigranulocytic group (p = 0.485); Eosinophilic group vs Paucigranulocytic group (p = 0.437); Eosinophilic group vs Mixed granulocytic group (p = 0.653). And if it is still not clear, I will revise it again.