Author’s response to reviews

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

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Version: 3 Date: 09 Dec 2019

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-19-00034R2

Thank you very much 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, carefully proof-read the manuscript to minimize typographical, grammatical and bibliographical errors. The amendments are highlighted in red in the revised manuscript.

Enclosed please find the revised manuscript, responses to the reviewers as well as a list of changes.

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): This paper provides useful additional data on the correlation between blood and sputum inflammatory cells during an exacerbation of COPD. Measurement of sputum is not infrequently cited as the "GOLD standard" to determine the airway inflammatory phenotype, including in this paper. However the correlation between sputum, BAL and histology data is imperfect. What is most important is to identify practical biomarkers that accurately predict treatment response. In the final paragraph the authors conclude that prediction of sputum eosinophilia from blood measurements is unreliable and therefore not helpful to inform clinical decision making. The latter statement is immediately open to challenge. In an RCT of blood eosinophil directed Prednisolone therapy for ECOPD, only patients with blood eosinophils &gt;2% showed benefit (ref 16). Other large studies have shown a clear relation between blood eosinophil level and response to ICS.

This is a retrospective study of patients during an exacerbation. This is important; eosinopenia (low blood eosinophil count) is associated with sepsis, and worse outcome in ECOPD. The current GOLD guidelines include blood eosinophils as a biomarker to guide ICS treatment. However this recommendation is based on stable blood eosinophil counts in the large studies supporting this approach. It would have been interesting to reassess this population during stable state. Whilst this was not done, in light of the above please consider acknowledging that the inflammatory state during ECOPD may differ from stable state, and whilst this may influence management of the exacerbation (larger studies are required), it should not influence long term ICS therapy.

Finally, although this a trivial point, the "A" in AECOPD is redundant.

Our answer: Thanks for your suggestions, we have revised them in my manuscript. In addition, May I acknowledge to you in my manuscript (line 236, page 23)?

Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?
No - there are major issues

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 technical rigor to allow confidence in the results?
Not sure - key details are missing from the manuscript

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?
No - there are major issues
OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?
Maybe - with major revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS:
In this manuscript entitled "Blood cells for the differentiation of AECOPD airway inflammatory phenotypes" the authors used retrospective data from COPD patients with acute exacerbation (AECOPD) to correlate the percentages of leukocytes from sputum and PBMCs. The data appear to indicate that the tested PBMCs values are poor indicators for the endotypes during AECOPD. However, major problems make it difficult to fully evaluate the study.

REQUESTED REVISIONS:

Figures: no real conclusion can be drawn from the figures, because:
- the figures have no legend, and the descriptions of the figures in the main text are not clear;
- the parts of figure 1 do not even appear in the text; so, one has to make educated guesses on what the figures might show; um
- figures A-G show one or four lines for statistical comparison, but only one number is given - and that number is, puzzling, always 0.08.

Our answer: Thanks for your suggestions, we have revised the figure 1 and the descriptions of the figures in the main text (Line 110, Page 11; Line 112, 114-118, Page 12)

* Table 1: There are no human races and I am pretty sure that 'Chinese' is a nationality.
Our answer: We have deleted the part (Line 94, Table 1, Pages 8-9).

* Table 2: it is not clear to what the p-values at the end of the rows refer to;
Our answer: We have revised the mistakes (Line 103, Table 2, Pages 10-11).

* Figure 3: the 'best' predictor in PBMCs for sputum values (%Eos) had an AUROC of 0.67, which is a value for a poor indicator - therefore, I think, one cannot claim (as the authors did in the discussion) that "blood eosinophils … were shown to distinguish patients with sputum eosinophilia". This part of the discussion and the one addressing the limitations appear to contradict each other in the usefulness of the correlation.

Our answer: Thanks for your suggestions, we have revised the mistakes and discussed the part (Line 144-145, Page 15; Line 159-163, Page 16; Line 164-175, Page 17; Line 176-187, Page 18; Line 188-198, Page 19; Line 200-202, Page 20).

* The authors highlight some limitations of their study, however, one major one is not even mentioned: namely the cause of the acute exacerbation. This is usually due to infections, and depending on the infection, changes in PBMCs might be visible that have nothing to do with the COPD. Therefore, the weak correlation they observed between the PBMCs and sputum values could be an indication for the infections, without any relevance to COPD. This is a major caveat that needs to be discussed.
Our answer: Thanks for your suggestions, we have added the part (Line 213-215, Page 21).

* Finally, the manuscript fails to adequately reference and discuss the vast literature on the topic, which largely showed for COPD what the authors report here (for example, for many others, PMID: 29696728, 29146301, 28482840, 21680942).
Our answer: Thanks for your suggestions, we have added the part in discussion and reference.