Author's response to reviews

Title: Pleural Fluid Soluble Triggering Receptor Expressed on Myeloid Cells-1 as a Marker of bacterial infection: a Meta-analysis.

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Author's response to reviews: see over
Dear Editor,

We appreciate the suggestions and comments from the two reviewers and editors. Those comments have definitely helped us in improving our manuscript. We have seriously considered those comments and suggestions and made substantial revision in the manuscript accordingly. The reply to the comments of the two reviewers in a point-to-point manner will be described in the enclosed sheets. Thank you once again for the constructive comments and suggestions.

Kind regards,

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Response to Dr Giamarellos-Bourboulis:

We are very grateful to Dr Giamarellos-Bourboulis for his suggestions and we have altered the manuscript as required:

1) We appreciate Dr Giamarellos-Bourboulis comments about us having failed to make it clear in the manuscript whether we are reporting data for pleural fluid sTREM-1. We have reviewed the whole manuscript and made it clear that it concerns pleural fluid sTREM-1.

2) As Dr Giamarellos-Bourboulis correctly pointed out that both sTREM-1 and TREM-1 cannot be used in the analysis, we have made changes to the materials and methods section by deleting the terms TREM-1 and triggering receptor expressed on myeloid cells-1. Dr Giamarellos-Bourboulis also advised us to mention any study which used fluid cytometry and the method for pleural fluid sTREM-1 measurement. The study by Chan et al. reported measurement by flow cytometry and ELISA was used for pleural fluid sTREM-1 measurements in all 7 studies. We have included these data in the manuscript.

3) Dr Giamarellos-Bourboulis expressed his concerns about the variability in the cut-off values. The reported values are all for pleural fluid sTREM-1. Even though the cut-off values varied greatly for each study, all the studies had good scores when assessed with the QUADAS score and STARD checklist. We believe that the variability was due to parapneumonic effusions and empyemas being included together in the studies. However, we were unable to extract data separately for these two entities.

4) Dr Giamarellos-Bourboulis enquired about studies reporting both serum and fluid sTREM-1. There is in fact, one of the 7 studies (Chan et al.) which investigated both serum and pleural fluid sTREM-1. This study showed that pleural fluid sTREM-1 greatly exceeds that in serum, suggesting that sTREM-1 is produced locally by recruited inflammatory cells in the pleural space, and that sTREM-1 released into pleural effusion does not evade into serum. Moreover, the main aim of our meta-analysis was to determine whether pleural fluid sTREM-1 alone could be used for the diagnosis of pleural infection.

5) Dr Giamarellos-Bourboulis brought our attention to the fact that instead of The reporting the small number of patients in the studies and the changes of sTREM-1 by therapy as two main limitations, we should have mentioned that i) for situations like pleural effusions the numbers of enrolled patients are satisfactory and ii) sTREM-1 was estimated before start of any treatment in these studies. We thank Dr Giamarellos-Bourboulis for this advice and we have made the necessary changes in the discussion section.
6) Dr Giamarellos-Bourboulis advised that the type of bacteria involved in bacterial pleuritis in the individual studies and their impact on sTREM-1 should be provided. Hence we added the following paragraph in the discussion section “The studies carried out by Determann et al. and Bishara et al. were the only two studies to provide details of the isolated pathogens from pleural effusions. However, they did not mention which organism cultured had the greatest impact on pleural fluid sTREM-1. Moreover, one patient from the study of Determann et al. and four patients from the study of Bishara et al. with macroscopic empyema had negative culture results and high pleural fluid sTREM-1 levels, thereby showing that even though organisms fail to be cultured, pleural fluid sTREM-1 is still high in pleural infection.”

Response to Dr Sebastien Gibot:

We thank Dr Gibot for his constructive remarks and suggestions and we have made the following changes accordingly:

1) Dr Gibot pointed out that we searched the databases as from 1990 when TREM-1 was known only after 2000. We thank him for this comment. We only wanted to increase the search so that we do not miss any article and thus we chose the earliest possible date which was offered by the databases.

2) Dr Gibot also expressed some concern about the 2 articles which were retrieved from the reference lists of the other articles. These 2 articles were not found during the database search and it was only when going through the reference lists of the other articles that we found them.

3) Moreover, Dr Gibot asked about the heterogeneity when the study by Porcel et al. is censored. We carried out investigation of heterogeneity excluding this study. Statistical heterogeneity and inconsistency were found for positive LR (p= 0.016, $\chi^2 = 13.91$, $I^2 = 64.0\%$), negative LR (p= 0.025, $\chi^2 = 12.81$, $I^2 = 61\%$), and DOR (p= 0.011, $\chi^2 = 14.91$, $I^2 = 66.5\%$), but not for sensitivity (p= 0.090, $\chi^2 = 9.52$, $I^2 = 47.5\%$) and specificity (p= 0.080, $\chi^2 = 9.52$, $I^2 = 47.5\%$).

Even though statistical heterogeneity was not found for sensitivity and specificity when the study by Porcel et al. was excluded, statistical heterogeneity was still found for DOR, which is a single indicator of test accuracy, combining data from sensitivity and specificity into a single number.

4) Dr Gibot advised us to moment on the usefulness of sTREM-1 as compared to usual markers. We thank Dr Gibot for this advice and we have made the necessary inclusion in the discussion section where we have stated that Chan et al. proved that pleural fluid sTREM-1 has a better diagnostic accuracy than traditional parameters.
5) Dr Gibot also pointed out that there are too many abbreviations in the abstract. We are very grateful to Dr Gibot to have brought this drawback to our attention. In this respect, we have removed the abbreviations and replaced them by the terms in full.

6) In the introduction, following Dr Gibot’s comment, we have changed the sentence “The triggering receptor expressed in myeloid cells-1 (TREM-1), belonging to the immunoglobin superfamily, modulates the innate response either by amplifying or dampening Toll-like receptor-induced signals, and thus plays a crucial role in fine-tuning of the inflammatory response” to “The triggering receptor expressed in myeloid cells-1 (TREM-1) belongs to the immunoglobin superfamily and is involved in inflammatory response”.

7) Dr Gibot expressed his concerns about the study carried out by Huang et al. whereby the cut value was 768.1ng/L (which is equal to 768.1pg/mL). We agree that the cut-off value reported in this study was higher than those reported in other studies. However, when assessed using the QUADAS score, the study score 12.5 out of 14, and when assessed by STARD checklist, a score of 18 out of 25 was obtained. Also, when heterogeneity in the meta-analysis was investigated excluding this study, statistical heterogeneity and inconsistency was still found for sensitivity (p= 0.011, $\chi^2 = 14.87$, $I^2 = 66.4\%$), specificity (p= 0.001, $\chi^2 = 21.12$, $I^2 = 76.3\%$), positive LR (p= 0.000, $\chi^2 = 23.91$, $I^2 = 79.1\%$), negative LR (p= 0.014, $\chi^2 = 14.26$, $I^2 = 64.9\%$), and DOR (p= 0.001, $\chi^2 = 21.57$, $I^2 = 76.8\%$).

8) Dr Gibot further advised us to explain the abbreviations in Table 2 and we have done so. We are very grateful to Dr Gibot for having pointed out our mistakes.

Additional editorial comments:

1) We have included a conclusions section as advised.

2) The abbreviation section has been moved under the conclusion section.

3) The author’s names and other supplementary data have been mentioned on the first page of this letter.

4) A list of figures and their respective legend has been included after the reference list.

5) An Authors’ Contributions section has been included.

6) Appropriate changes have been made to the manuscript so that it conforms to the journal style.