Author's response to reviews

Title: Factors affecting pleural fluid adenosine deaminase level and the implication on the diagnosis of tuberculous pleural effusion: a retrospective cohort study

Authors:

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Author's response to reviews: see over
Dear Editor-in-Chief

We thank the reviewers for their invaluable comments. We have attempted to address the issues raised in the revised manuscript and will describe our responses to their comments in this letter.

**Reviewer: Rafal Krenke**

**Major compulsory revisions:** The relationship between the age and pleural fluid ADA should be analysed in separate groups of patients with different pleural fluid causes rather than in patients with pleural effusions as a whole.

*Response:* We agree with the reviewer’s comment and analysed the data for the whole study group as well as individually for the TPE and non TPE groups (page 7 lines 14-21 and presented in Table 2). This would therefore eliminate the confounding effect of the proportion of TPE patients in the various groups analysed e.g. according to race, gender.

**Minor essential revisions:**

1.1: The first reviewer would like a broader discussion on the relationship between age and pleural fluid ADA and wondered if the results of the studies mentioned by him consistent with our findings.

*Response:* We did find an article published by Yeon et al from Korea with the abstract in English which reported similar relationship of age and pleural fluid ADA as our study (page 9 lines 14-19). The very high pleural fluid ADA reported by Valdes in his study population does suggest that ADA is expected to be quite markedly raised in young patients with TPE (page 9 lines 19-21). However the study on a paediatric population did not report a mean ADA level even higher than what was reported by Valdes. Therefore we postulated that the negative correlation between age and ADA may not be present in the paediatric age group and only evident at a later age.

1.2: The reviewer wanted to find out whether we considered the TB category (primary vs reactivation) as a potential factor affecting pleural fluid ADA.

*Response:* We found this to be an interesting point raised but felt that because the relationship between ADA and age was also evident in non TPE patients, the reason for this age-ADA relationship is probably not restricted to underlying TB-related pathogenesis or the type of TB. We did, however offer possible explanation for the weaker correlation between ADA and age noted in the TPE group (page 9 lines 12-14; page 10 lines 19-22).

**Minor issues not for publication**

1.1: The reviewer would like to see the method of ADA measurement in our paper

*Response:*
The pleural fluid ADA in our study subjects were measured by spectrophotometry method described by Giusti and Galanti (page 4, lines 20-21).

1.2: To provide definition of neutrophilic effusion
Response:
We have added this to our manuscript (page 5, lines 10-11)

1.3: Improve the clarity of data presentation in Table 2
Response:
We presented Table 2 under categories of ‘whole group’, ‘TPE’ and ‘non TPE group’. We believe it will be easier to read the data for the whole group as well as for the 2 main subgroups.

**Reviewer: Oya Kayacan**
**Major compulsory revisions:** The reviewer suggested review of the manuscript by a biostatistician
Response:
The statistics in our study were reviewed by two biostatisticians Dr Tina Xu and Miss Rachel Phillips from the Singapore Clinical Research Institute.

**Minor essential revisions**
1.1: Mean values and SD should appear in the summary
Response:
This has been reflected in our revised manuscript

1.2: Numbers should be written as they are read at the beginning of the sentences
Response:
This was presented as suggest by the reviewer in our abstract. However we felt it would be acceptable to keep the numerical format for the rest of the manuscript.

**Reviewer: Haruki Komatsu**
**Major revisions:**
1.1: The reviewer commented on the need for clarification of weak correlation between age and ADA
Response:
A significant correlation was found for age and ADA for effusions both TB related and non TB related. However the relationship was weaker in the TPE group. This similar point was brought up by the first reviewer Dr Rafal Krenke. We offered possible explanations in our discussion (page 9 lines 12-14; page 10 lines 19-22).

1.2: The reviewer suggested the subjects be divided into TB and on TB groups and also evaluate relationships between ADA and other factors
Response:
We have analysed the patients according to the subgroups of TPE and non TPE shown in Table 2. Other variables e.g. gender, race and fluid biochemistry were analysed in the above subgroups as well.

We hope we have addressed the issues raised by the reviewers adequately and we look forward to hearing from BMC Infectious Diseases favourably.

Sincerely yours,
Tunn Ren Tay, MBBS, MRCP