Peer Review File

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Reviewer A

After this brief summary, I should include some important comments and amendments:
- Amongst the 382 patients included in the study, 144 out of them are of tuberculous origin, this supposes a "pre-test probability" >40% in the study. It is quite high and theoretically by the Bayesian analysis increases the "post-test probability" of success/accuracy of a given diagnostic tool. This should be mentioned in the manuscript.
Reply: Of the 382 included patients with PE, 144 were diagnosed with TBPE, this supposes a "pre-test probability">40%. It is quite high, 134 with MPE, 19 with PPE, 43 with empyema, 24 with transudate PE, and 18 with other types of PE of a known etiology, such as a parasite or rheumatoid arthritis.

Changes in the text: Page 5, Line 169-172.

- On the contrary and unexpectedly, ADA > 40 U/l shows in the study sample a sensitivity of 45.8% (and specificity of 81.5%) for the diagnosis of pleural TB. This data does not match at all with all the previous mata-analysis performed, accounting for many thousands of patients diagnosed with tuberculous pleural effusion: ADA showed in all of them a sensitivity and specificity of about 92% and 90% respectively for the diagnosis of pleural TB (1-4). In this sense, I would encourage the authors to analyze it and to give some convincing explanation in this regard. I would consider this a cornerstone in the manuscript, because all the following steps and calculations are based on it. I wonder if the ADA technique used by the authors might be responsible for these results, or maybe there is some other explanation not explicit in the manuscript....
Reply: The approved cut-off value for pleural fluid ADA was 40 U/L. However, our results showed that only 45.8% (66/144) of the TBPE patients had an ADA level >40 U/L (Table 1). This data does not match at all with all the previous mata-analysis performed, accounting for many thousands of patients diagnosed with tuberculous pleural effusion: ADA showed in all of them a sensitivity and specificity of about 92% and 90% respectively for the diagnosis of pleural TB. The discrepancy in sensitivity and specificity values observed in the study sample compared to previous meta-analyses could be attributed to various factors. The study sample may be smaller than the ones used in previous meta-analyses, which could have an impact on the sensitivity and specificity values. A larger sample size generally provides more accurate and reliable results. The demographics of the study population may differ from those included in previous meta-analyses. Differences in age, ethnicity, geographic location, or prevalence of co-morbidities might affect the diagnostic accuracy of ADA for TBPE. Differences in laboratory techniques and equipment used to measure ADA levels might contribute to the observed discrepancies. The study design or inclusion and statistical analysis might have affected the sensitivity and specificity values.

Changes in the text: Page 6, Line 186-201.

- The authors should include the cell count and the differential count (lymphocyte/neutrophil) in the pleural fluid; and not only regarding the relationship between the ADA value and the pleural fluid cell count, but also in the differential diagnosis between pleural TB and the rest of effusions, given that cell differential cell count is essential when differentiating pleural TB from CPPE or empyema, mostly when all of them could evolve with high ADA level….. IN MY OPINION DIFFERENTIAL CELL COUNT SHOULD BE INCLUDED IN TABLE 1.
Reply: We have added the indicator lysophocyte/eutrophil>2.53 to Table 1.

Changes in the text: Page 15.

- The authors should point out the LIMITS of the study, in my opinion:
o Its retrospective format
o Gold standard diagnosis is not reached in pleural TB patients, "clinical reaction to anti-TB therapy" is not Confirmed pleural TB, but Probable Pleural TB. I would encourage the authors to include some information in this regard.
Reply: To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) have a diagnosis of PE by ultrasonography, chest computed tomography, or X-ray; (II) have a diagnosis of malignant pleural effusion (MPE) by cytology or pleural biopsy; (III) have a diagnosis of TBPE based on a finding of chronic granulomatous inflammation in pleural tissues ; (IV) have a diagnosis of PPE based on exudative effusions related to bacterial pneumonia, lung abscesses, orbronchiectasis, and have been in remission and recovery for at least 3 months at the follow-up after antibiotic use; or (V) have a diagnosis of another type of PE of a known etiology (e.g., a parasite or rheumatoid arthritis) based on well-accepted criteria and have received the best treatment. Empyema was further diagnosed in cases of pleural frank pus.

Changes in the text: Page 5, Line 134-146.

Asymmetry in the conformation of the group of patients included: >40% out of them diagnosed with pleural TB (theoretically advantage situation for a better accuracy) whilst some other groups like Parapneumonic PE, Transudative PE and Other contribute each of them even with less than 30 patients.
If the authors do not have the data regarding the differential cell count in pleural fluid, but only the "cell count", this should be included as an important limit too. I do hope this is not the case. The sensitivity 45.8% of ADA for pleural TB in the study should be convincingly argued, and it constitutes an important limit for the results.

Reply: In addition, ADA>80 (and mostly>120) are more frequent related to empyemas and lymphomas, in which LDH levels could be proportionally higher. In this sense, the ratio ADA/LDH might gradually decrease in this scenario.
Changes in the text: Page 9, Line 289-292.

Reviewer B

The topic has been studied in the published literature and for consideration of publication the authors have to provide novelty or a relatively large robust validating cohort, of which neither was present. Shortcomings in the methods include an arbitarily selected cutoff with digital preference. A simple division between ADA and LDH would not require approximation as simple arthmetics can be expected to be performed by healthcare professionals. An exact optimum should be given, and then simple/approximated cutoffs explored.

Reviewer C

1. What is PF ADA? Please indicate its full name.

90 many patients with tuberculous pleurisy have an ADA <40 U/L. In addition, the PF
91 ADA level may increase to >40 U/L in several clinical situations, including in patients
92 with parapneumonic effusions (PPE) and empyema (7). PF ADA levels may also be
93 increased by lymphomas, solid tumors, and connective tissue diseases (7-11).

Reply: Thank you for your suggestion. We have deleted it.

Changes in the text: page 3, line 82-84.

2. In the text, there are totally 23 references cited, but there are 24 references in the references list. Please check and revise.

Reply: Thank you for your suggestion. We have revised it.

3. Please add citation of references for mentioned previous meta-analysis.

196 **(Table 1)**. This data does not match at all with all the previous mata-analysis performed,
197 accounting for many thousands of patients diagnosed with tuberculous pleural effusion: ADA
198 showed in all of them a sensitivity and specificity of about 92% and 90% respectively for the
199 diagnosis of pleural TB. The discrepancy in sensitivity and specificity values observed in
200 the study sample compared to previous meta-analyses could be attributed to various
201 factors. The study sample may be smaller than the ones used in previous meta-analyses,
202 which could have an impact on the sensitivity and specificity values. A larger sample
203 size generally provides more accurate and reliable results. The demographics of the
204 study population may differ from those included in previous meta-analyses.

Reply： Thank you for your help. We have added relevant references.

Changes in the text: page 6, line 201-214.

4. Figure 3:
Please indicate the meaning of ns in the legend.

Reply： Thank you for your help. ns: no statistical significance.

Changes in the text: page 15, line 478-479.