

Peer Review File

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Reviewer A

Comment 1: Authors performed a systematic review and meta-analysis to evaluate the diagnostic accuracy of pleural fluid CA72-4 for MPE. The PubMed and Web of Science databases were searched to verify potential studies investigating the diagnostic accuracy of pleural fluid carbohydrate antigen 72-4 for malignant pleural effusion. The pooled sensitivity and specificity were 0.47 (95%CI: 0.39–0.55) and 0.98 (95%CI: 0.95–0.99). The area under sROC curves was 0.77 (95% CI: 0.73–0.80). Conclusion is that pleural fluid carbohydrate antigen 72-4 has a moderate diagnostic value for malignant pleural effusion. The paper is well written and logically organized.

Reply: Thank you for your positive comments.

Comment 2: Several papers are missing in the body of references and have to be added
PMID: 34478240, PMID: 33465294

Reply: We have reviewed the references and confirmed that they are not relevant to this study. Therefore, we did not cite them.

Reviewer B

Comment 1: The systematic review and meta-analysis evaluated the diagnostic accuracy of pleural fluid carbohydrate antigen 72-4 (CA72-4) for malignant pleural effusion (MPE) and included eight studies with 1791 patients. The pooled sensitivity and specificity of pleural fluid CA72-4 for MPE were 0.47 (95% CI: 0.39–0.55) and 0.98 (95% CI: 0.95–0.99), respectively. The area under the summary receiver operating characteristic curve was 0.77 (95% CI: 0.73–0.80), indicating “moderate diagnostic accuracy”. However, a significant publication bias was observed across the eligible studies, suggesting potential overestimation of CA72-4's diagnostic accuracy. My major concern is the poor sensitivity of this diagnostic biomarker and the detected publication bias, suggesting that CA72-4 is poorer and cannot be used as a “moderate

diagnostic biomarker". The authors need to reconsider to adjust for the publication bias and tone down the current conclusion.

Reply: We appreciate your suggestion. The diagnostic accuracy of CA72-4 might be overestimated because of publication bias. We have revised the manuscript accordingly.

Changes in the text: Page 2, line 46-47.

Comment 2: In the abstract, the authors need to describe the numbers of subjects in the MPE and BPE groups, and the results of quality assessment of included studies in the methods.

Reply: We have added these issued in the abstract.

Changes in the text: Page 2, line 39. Page 2, line 34-35.

Comment 3: In the introduction, the authors need to analyze the potential reasons for the controversy regarding the diagnostic accuracy of CA72-4 and explain why a meta-analysis is suitable to address this controversy.

Reply: We have revised it accordingly.

Changes in the text: Page 5, lines 103-106.

Comment 4: In the methodology, please consider the potential language bias due to no literature search in non-English language databases. The inclusion criteria were not defined according to the PICOS principles. It is necessary to clarify whether the BPE subjects of included studies included patients with tuberculous pleurisy, heart failure, and pneumonia. More details of the QUADAS-2 are needed such as the criteria for high-quality studies. It is also necessary to indicate P value for statistical significance.

Reply: (1) We acknowledge that language bias is a limitation of our study, which we have now addressed in the discussion section. (2) This meta-analysis focuses on diagnostic test accuracy rather than an interventional study. Therefore, the PICOS principles are not applicable. Instead, we have utilized the PIDTA framework (Ann Transl Med 2019;7:788) and revised our manuscript accordingly. (3) We have clarified the composition of the BPE participants. (4) There is currently no widely accepted

criterion for defining high-quality studies. The impact of bias in each domain of the QUADAS-2 tool on the reliability of a diagnostic accuracy test study varies, depending on the degree of bias and the clinical settings involved. (5) We have indicated the P-value for statistical significance.

Changes in the text: (1) Page 9, lines 262-263. (2) Page 6, lines 121-124. (3) Page 6, line 124-126. (5) Page 6, line 155-156.

Comment 5: Please consider to cite several related papers: 1. Ge T, Song S, Li S, Yu X, Shao L, Tong J. Serum levels of carbohydrate antigen 125 in patients with heart failure and obstructive sleep apnea syndrome: a retrospective analysis. *Cardiovasc Diagn Ther* 2023;13 (6):994-1002. doi: 10.21037/cdt-23-323.

Reply 5: I have read the manuscript and found it was irrelevant to this study. Therefore, we did not cite it.