Peer Review File

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Review Comments

Comment 1: Overall, an interesting study and concept building on the ideas that Light's criteria is an imperfect tool and there could be other biomarkers to assist with patient diagnostics of pleural effusions. The authors generally need to require further referencing and explanation of their patient cohort and context of the study to give better information to the reader, however the conclusion reached is an interesting one.
Response 1: We appreciate the reviewers taking the time to read our submission and offer their thoughts. We agree that Light's criteria are an imperfect tool and we hope our article contributes to the field of literature surrounding biomarkers in pleural fluid. We have attempted to address the reviewers' concerns as can be seen below.

Comment 2: 29 - Define Light's criteria and provide a reference
Response 2: We have added the following text to the body of our paragraph: "Light's criteria for determining an exudative effusion are met or fulfilled if one of the following conditions are met: 1) Pleural fluid-to-serum protein ratio greater than 0.5 2) Pleural fluid-to-serum LDH ratio greater than 0. 3)Pleural fluid LDH greater than 0.67 (ie, two-thirds) the upper limits of the laboratory's normal serum LDH.
Changes in the text: Reference added: Light RW, Macgregor MI, Luchsinger PC, Ball WC Jr. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med. 1972;77(4):507.

Comment 3: 29 This entire sentence is worded vaguely, please be more specific in these definitions.
Response 3: We have rephrased this sentence in the text as to specify the definitions more succinctly.
Changes in the text: The sentence has been reworded.

Comment 4: 43 Reference for creatinine molecular properties
Response 4: We have added a reference.
Changes in the text: Reference added: Kianoush Kashani, Mitchell H. Rosner, Marlies Ostermann, Creatinine: From physiology to clinical application,
European Journal of Internal Medicine, Volume 72, 2020, Pages 9-14, ISSN 0953-6205, https://doi.org/10.1016/j.ejim.2019.10.025.

Comment 5: 45 - I would provide more context in this instance for what a pseudoexudate is and specifics around why Light's criteria fail. What is the rate by which exudates are falsely classified and what studies have looked upon improving the failures of Light's criteria as essentially that is the point of your study, to identify a biomarker to assist with classification of pleural effusions. You have discussed vaguely the use of SPPG and BNP but what about imaging techniques i.e., ultrasound characteristics, or other biomarkers of which there are many that have been trialled in this area to further improve upon Light's. Please further discuss previous use of pleural creatinine and its characteristics. You say that it is a small molecule and has certain properties, provide a

reference for this and any previous studies examining its use in pleural pathology.
Response 5: We appreciate the reviewer's insightful comment and have elaborated further on this topic below. Certain effusions however, fail to be categorized appropriately by light's criteria. These effusions also known as pseudoexudates are typically transudates that get mischaracterized by light's criteria as exudates. The characterization of pseudo exudate often occurs in the context of a transudative effusion that has undergone volume contraction resulting in a slight increase in concentration of fluid. This subsequent volume contraction leads to a protein or LDH value that falls slightly above the cut off value for an exudate, leading the effusion to be misclassified [A]. Pseudoexudates are typically seen in a clinical context of heart failure or hepatic hydrothorax as 30% of heart failure effusions may be misclassified as an exudate [b] and 18% of hepatic hydrothorax may be misclassified as exudate [b]. These shortcomings of light's criteria have led to a search for other biomarkers such as the use of cholesterol in heffner's criteria [c] or the use SPPG and BNP [d]. Additionally, the clinical conundrum of effusion characterization has continued to pose a clinical problem such that, some have proposed the development of an ultrasound score (Duet score) to predict effusion characteristics [e].
Changes to the text: The following referenced have been added to the manuscript:
[A] Murray & Nadel's Textbook of Respiratory Medicine, 2-Volume Set, 7th Edition
[B] Porcel JM, Light RW. Pleural effusions. Dis Mon. 2013 Feb;59(2):29-57. doi: 10.1016/j.disamonth.2012.11.002. PMID: 23374395
[c] Diagnostic Value of Tests That Discriminate Between Exudative and Transudative Pleural Effusions Heffner, John E. et al CHEST, Volume 111, Issue 4, 970 - 980
[d] Tabba M, Folch EE, Slate J, eds. *The Principles and Practice of Pleural Diseases*; pp. 608-618. Lexington, MA, USA: Blossom Med Comm, 2023.
[e] Gardiner A, Ling R, Chan YH, Porcel J, Lee YCG, Teoh CM, Liew MF, Kapur J, Low SP, Lee P. DUETS for Light's in separating exudate from transudate. Respirology. 2024 Nov;29(11):976-984. doi: 10.1111/resp.14780. Epub 2024 Jul 3. PMID: 38960399.

Comment 6: 58 - Is there any information as to why these patients had pleural fluid creatinine performed? Particularly since no urinothorax was found in the cohort. Did any of them have renal pathology?
Response 6: We appreciate the reviewer's valid point. Ultimately, pleural fluid creatinine was sent as part of an order set that was submitted with any pleural fluid studies. We have added text to highlight that there there was low clinical suspicion for urinothorax in these cases
Changes in the text: Clarified that this information was available due to order set that was submitted with any pleural fluid studies.

Comment 7: 62 - I would argue that your definition of a pseudoexudate is inaccurate – did you determine what the pathology that ultimately accounted for the effusion was from the records, would that not be more accurate? Particularly given your previous reference to SPPG requiring use in combination with the clinical picture. Were there any patients with dual pathologies?
Response 7: We appreciate the reviewer's valid point. Ultimately as this was a retrospective analysis without any direct involvement in the patient care from the authors of this manuscript, we relied purely on data from chart review and with the above mentioned criteria in the literature for pseudoexudate. While it may be possible that dual pathologies were present, on the basis of this retrospective review we are unable to confirm as such.

Changes in the text: Clarified our reasoning for classifying effusions as pseudoexudate with the available data to the authors.

Comment 8: 80 - In theory – please explain why you think this? Explain the mechanism more clearly.
Response 8: Please see below for our response and changes to the text.
Changes in the text: Given the findings of this study, we suspect that this is due to creatinines ability to freely traverse the pleural space, and thus any increase in serum creatinine should reflect in increases in pleural fluid creatinine

Comment 9: 77 - The accepted specific cut off for pleural creatinine is 1.7, whilst greater than 1 is suggestive in the correct clinical context. I would rewrite this paragraph to reflect this as you are overstating the significance of your cohort.
Response 9: We agree that the wording we have originally placed has overstated the significance of the cohort. We have reworded the paragraph to clarify the accepted cutoffs in the literature as such.
Changes in the text: We have reworded the paragraph as above to include the accepted cutoff of 1.7 and to highlight the importance of clinical context

Comment 10: 115 – creatinemia, this is not a widely accepted term.
Response 10: We have acknowledged that this is not a widely used term and have thus switch the wording to creatinine level
Changes in the text: The word creatinemia has been replaced with creatinine level.

Comment 11: 130 - Your conclusion much more accurately represents your findings as opposed to the first paragraph of your discussion.
Response 11: We have edited the opening paragraph of our discussion to more similarly reflect our conclusion as per your suggestion
Changes in the text: We have adjusted our opening paragraph to more succinctly say that we do not believe (based on the results of this analysis) that pleural fluid creatinine should be routinely used to diagnose urinothorax and that its utility in pleural disease may be limited.

Comment 12: Figure 1 – This figure and those that follow are very hard to follow and poorly laid out, can it be reformatted so that each category has its own line as is usual
Response 12: we have reformatted the table as per your suggestion
Changes in the text: The figure has been reformatted so that each category has its own line

Comment 13: Why is race important in this patient group? I am not sure this is needed
Response 13: We agree that having this category does not contribute to the overall point of our paper-we have removed it from the table
Changes in the text: Race has been removed from the table.

Comment 14: How did you categorise AKI and CKD and AKI on CKD – did you review individual patient records?
Response 14: We have added text to highlight how we categorized AKI and CKD. We have categorized this according to the RIFLE criteria and AKIN criteria. These patient labels were

pulled from diagnosis codes upon individual chart review. We have added text to reflect this
Changes in the text: We have added an additional comment in the methods section to reflect this change on how these values were categorized with a subsequent reference.