Peer Review File

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Reviewer A

Thank you to the author for developing good research on the patient with sepsis. The authors attempted to investigate the utility of the red blood cell distribution width (RDW) to albumin ratio as a promising biomarker to prognosticate critically ill patients with sepsis. Detailed comments about this study are as follows:

##Response:
We appreciate the reviewers' recognition of our study's contribution to sepsis research and are happy to addressing the detailed comments to further refine and clarify our findings.

--How did the authors estimate the sample size in this study? If not estimated yet, please explain why it might be exempted.

##Response:
Thank you very much for the careful review and valuable comments, we would like to clarify that the sample size for our study was determined based on previous literature in this field, particularly focusing on similar studies evaluating biomarkers in sepsis. Our approach was to ensure a sufficient sample size to detect statistically significant differences in the red blood cell distribution width (RDW) to albumin ratio between different patient outcomes. However, we acknowledge that a formal sample size calculation was not conducted prior to the study, primarily due to the retrospective nature of our analysis and the reliance on available clinical data. We believe that the sample size we utilized was adequate to draw meaningful conclusions, but we agree that future prospective studies should include a formal sample size estimation to strengthen the validity of the findings.
The following phrase has been added to the methods section (Data Source, Line: 117-120) of the paper:
"To ensure robustness of our findings, the sample size was guided by precedent in similar biomarker studies in sepsis, although a formal calculation was not performed due to the retrospective nature of our analysis and reliance on existing clinical data."

--This study used the multiple-imputation method; thus, please describe the imputation method's details, such as sequential imputation using chained equations or multivariate normal regression (mvn). Also, please provide the details

of the reasons why the authors used those methods.

##Response:

We highly agree with your valuable suggestions and further to describe the query regarding the multiple-imputation method. We acknowledge that the manuscript currently lacks specific details about the imputation technique employed. The method used was sequential imputation using chained equations (SICE), which is well-suited for handling different types of variables (continuous, binary, ordinal). We chose this method due to its flexibility and efficiency in dealing with the complex nature of our dataset, where different types of missing data were present.

To update the Methods section of the manuscript, the following text has been included:

"In this study, we addressed missing data using the Sequential Imputation using Chained Equations (SICE) method. SICE is a robust multiple imputation technique that allows for the imputation of missing values in a dataset with different types of variables, such as continuous, binary, and ordinal. The process involves imputing missing values multiple times to create several complete datasets. Each variable with missing data is imputed sequentially, with the method taking into account the distribution of the observed data. By employing this technique, we aimed to minimize bias and improve the reliability of our analysis, ensuring that the missing data did not significantly skew the results. The imputed datasets were then analyzed separately, and the results were combined to produce estimates that reflect the uncertainty due to the missing data."

--Why did this study exclude patients whose ICU stay was less than one day? Because it may be using the length of stay in decimal numbers, for example.

##Response:

Thank you very much for the careful review and valuable comments. The decision to exclude patients with an ICU stay of less than one day was made to focus on individuals with more established cases of sepsis, where clinical interventions and outcomes could be more meaningfully assessed. Shorter stays often represent either rapid clinical improvement or early mortality, both of which could introduce significant variability into the analysis. By setting this exclusion criterion, we aimed to reduce potential confounders and enhance the reliability of our findings in reflecting the prognostic value of the RDW to albumin ratio in more clinically stable sepsis patients. We acknowledge that this approach might exclude certain patient experiences and outcomes, and future studies might consider including such patients to examine the broader applicability of the RDW to albumin ratio.

--In Figure 5, please add the 95% CI for each line.

##Response:
Thank you very much for the valuable suggestion. And we have added the 95% CI for each line in the revised Figure 5.

--In Table 1, changing the p-value of 0.000 into <0.001 in the chloride variable might be considered.

##Response:
Thanks very much for the careful review and valuable comments. We have revised the p-value of 0.000 into <0.001 in the chloride variable in Table 1.

--In Figure 4, please consider changing the labels of RDW/Albumin ratio for "4.915=6.405" into "RDW/Albumin ratio>6.405"

##Response:
Thank you very much for the valuable suggestion. We are sorry for the careless mistake in the labels and we have revised the labels in Figure 4-revised.

--To date, several studies reveal that the RDW-albumin ratio is related to increased mortality of patients with heart failure and acute myocardial infarction. Please compare this issue with previous studies, especially in septic patients with concurrent or preexisting heart failure or acute myocardial infarction conditions.

##Response:
Thank you for highlighting the importance of comparing our findings with previous studies that have investigated the RDW-albumin ratio in patients with heart failure and acute myocardial infarction. It is well-established that elevated RDW-albumin ratios are associated with increased mortality in these conditions, likely reflecting the underlying systemic inflammation and oxidative stress common in these diseases. In our study focusing on septic patients, some of whom may have concurrent or preexisting heart conditions, similar mechanisms might be at play. The RDW-albumin ratio could serve as a marker of exacerbated systemic stress in these patients, potentially leading to worse outcomes. However, our study did not specifically stratify patients based on the presence of heart failure or acute myocardial infarction, which could be a limitation in directly comparing our results with those studies. We acknowledge this as an area for future research, where a more detailed analysis could be conducted to understand the prognostic value of the RDW-albumin ratio in septic patients with these

specific cardiac conditions.

Following text has be added to the discussion section (Line 355-359):

"To contextualize our findings within the broader scope of existing research, it is noteworthy that elevated RDW-albumin ratios have been associated with increased mortality in heart failure and acute myocardial infarction, suggesting potential parallels in the systemic inflammatory and stress responses observed in our septic patient cohort."

Reviewer B

Thank you for the opportunity to review this manuscript. In this paper, the authors utilize data from the MIMIC-III database to evaluate the utility of the red cell distribution width (RDW) to albumin ratio as a prognostic biomarker in septic shock. The paper is interesting and well-written, and I appreciate that it is parsimonious in its conclusions. It is interesting to note that its AUC is basically the same as that of lactate, raising the question of how useful another biomarker is in this setting. (A high RDW/albumin level may not tell me anything new in a hypotensive patient with a lactate of 6.) It would be interesting to determine if RDW/albumin would function as an independent marker of mortality when used in combination with other markers, e.g., lactate, neutrophil-to-lymphocyte ratios, or if it is just a recapitulation of other signs of disease severity. Nonetheless, the paper is clear and well-written.

##Response:

We are grateful for your encouraging feedback and appreciate your recognition of the careful analysis and presentation of our findings using data from the MIMIC-III database to assess the RDW to albumin ratio in septic shock patients. We appreciate the observation on the utility of the RDW/albumin ratio as a biomarker in sepsis and its comparison to lactate levels. Recognizing that albumin plays diverse physiological roles and its low levels in sepsis may indicate not just nonspecific inflammation but also more complex pathophysiological processes, our study gains additional relevance. The potential therapeutic role of albumin in sepsis, akin to its established use in cirrhosis, suggests that identifying albumin-related biomarkers like the RDW/albumin ratio could be crucial in stratifying patients for targeted albumin interventions. This stratification could enable a more personalized approach to sepsis management, similar to how albumin therapy is tailored in liver cirrhosis. Future research will aim to elucidate whether the RDW/albumin ratio can aid in identifying patients who might benefit most from therapeutic albumin interventions, thereby expanding its utility beyond being a mere indicator of disease severity.

Following text has be inserted into the Discussion section of the paper (Line 372-377):

" Our findings suggest that the RDW/albumin ratio, beyond reflecting disease severity, might also have potential in guiding therapeutic strategies. Specifically, it could aid in the future identification of sepsis patients who are likely to benefit from albumin supplementation, akin to the targeted use of albumin in cirrhosis. This perspective opens new approaches for personalized sepsis management, where biomarkers are not only prognostic indicators but also guide therapeutic interventions."