Peer Review File

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Reviewer A

Comment 1: Authors state that LAR has been described as an independent risk factor for mortality in COVID 19 ARDS patients and the aim of this study is to evaluate the association between LAR and ARDS prognosis…. What does this study aim to add? Do the meant non-COVID ARDS? (LINE 76).

Reply 1: Thanks for your comments. To study the predictive value of LAR in general ARDS patients, the study supplemented the prognostic value of LAR in non-COVID-19 ARDS patients. We strongly agree with your comments and have refined the aims in the text (see Page 3, line 73-74).

Changes in the text: The added part about the aim on Page 3, line 73-74 of the revised manuscript is following as “This study may reveal the relationship between LAR and overall dynamics of the condition in non-COVID-19 ARDS patients”.

Comment 2: Patient selection: Regarding inclusion criteria, How are ARDS diagnosis related items register in the database? How were radiological opacities identified and recorded? (LINE 95).

Reply 2: Thanks for your comments. In fact, all of the involved patients were diagnosed with icd_codes, the exact icd_codes and disease are listed in the following: Acute onset: we defined admission to the ICU on the first day of admission as an acute onset. PaO2, FiO2 and PEEP came from arterial blood and ventilator parameters on the first day of ICU admission. Chest radiograph originated from the "IMPRESSION" in the MIMIC-CXR module. Absence of heart failure: firstly, we screened the icd_code of heart failure, including 39891, 40201, 40211, 40291, 40401, 40403, 40411, 40413, 40491, 40493, 4280, 4281, 42820, 42821, 428221, 42822, 42823, 42830, 42831, 42833, 42840, 42841, 42842, 42843, 42899, I509, I0981, I110, I130, I132, I50, I502, I5020, I5021, I5022, I5023, I5030, I5031, I5033, I504, I5040,

I5041, I5042, I5043, I508, I5081, I50810, I50811, I50812, I50813, I50814, I5082, I5083, I5084, I5089, I9713, I97130 and I97131.

There is a MIMIC-CXR module related to chest X-ray in the mimic database, including EXAMINATION, INDICATION, TECHNIQUE, IMPRESSION and so on. We used this module to identify and record chest radiation information and radiological opacities based on "IMPRESSION".

Comment 3: Almost 2/3 of ARDS patients were excluded because they lacked LDH or albumin. How do authors interpret and analyze this information?

Reply 3: Thanks for your comments. In fact, when we excluded patients, we were also very surprised to the phenomenon. After careful consideration, we thought that the reason for this phenomenon is the lack of database information. Our current research focus is on ARDS patients who meet the screening criteria. Although 2/3 of ARDS patients were excluded, this also provideds us with other research directions for future attention to these 2/3 of patients. We will further analyze the clinical characteristics of these patients and further investigate other possible predictive factors combining with laboratory test results.

Comment 4: Data extraction: lab measurements were recorded at hospital admission? ICU admission? Or ARDS onset?

Reply 4: Thanks for your comments. Lab measurements were recorded at ICU admission. Accordingly, we have added more information about the data extraction on Page 4, line 125 of the revised manuscript.

Changes in the text: The added part about the data extraction on Page 4, line 125 of the revised manuscript is following as "We collected baseline parameters such as age and gender of ICU patients at first ICU admission".

Comment 5: Statistical analysis: why are patients divided in tertiles? What is this based on? I think is not well explained.

Reply 5: Thanks for your comments. The reason for dividing in tertiles is to observe

the differences between different groups of LAR more clearly and effectively control the accuracy of the research. In addition, we found that in Nafiseh Alizadeh's (1) and Minghao Liang's (2) articles using mimic database, they also conducted research in three groups. Therefore, patients in the study are divided in tertiles rather than quantiles. We have modified our text as advised (see Page 5, line 135).

Changes in the text: The added part about the data extraction on Page 5, line 135 of the revised manuscript is following as "For clarity and effectiveness of the study, we divided participants in tertiles based on LAR".

Comment 6: Results: the reason or origin of ARDS is not specified. No inflammation marker (besides LAR) has been reported. Neither possible confounders such as AKI at admission.

Reply 6: Thanks for your comments. In fact, in the final paragraph of the Discussion, we pointed out the second limitation of this study that we did not further refine patients with ARDS into direct and indirect ARDS patients. This study is a retrospective cohort study aimed at investigating the prognostic impact of LAR on ARDS. We agree with your suggestion to remove possible confounders, but we think that there are many confounders that affect ADRS, and if we address them one by one, it will be a huge project. Therefore, we didn't address these confounders. Of course, we look forward to conducting relevant study in this area in the future.

Comment 7: Results: Table 1 shows global differences. Could authors specify where are these differences by comparing the three groups with each other?

Reply 7: Thanks for your comments. In fact, according the Table 1, we found that the higher the LAR, the lower the SBP. Respiratory, rate and heart rate increased rapidly with the increase of LAR. Older people tended to have lower LAR. Creatinine, Bilirubin, Anion gap, ALT, AST, PT, INR and SASP II score increased as LAR increases.

Comment 8: Results: Table 1 describes baseline characteristics, ICU course-related

complications and outcomes. I think it would make more sense to differentiate.

Reply 8: Thanks for your comments. Firstly, we quite agree with your point. But according to the previous research, such as the researches of Chen-Shu Wu (3), Ting Lu (4) and You-lan Gu (5), the baseline characteristic table is represented like our article. We think that this is a traditional format using the mimic database, so we followed this description.

Comment 9: Discussion: based on the results of the study, I don´t think that we can conclude that LAR shows a good predictive value (AUROR 0.6).

Reply 9: Thanks for your comments. Accordingly, we have added more information about the discussion on Page 7, line 212-213 and Page 8, line 233-239 of the revised manuscript.

Changes in the text: The added part about the data extraction on Page 7, line 212-213 of the revised manuscript is following as “Moreover, ROC curves showed that LAR may have a good predictive power for 30-day mortality in patients with ARDS”. We also added part about the data extraction on Page 8, line 233-239 of the revised manuscript is following as “In addition, we found that in Jung Wan Yoo's (21) article, the area under the ROC (AUROC) curve was 0.681 (95% CI: 0.617-0.741, $p<0.001$) for red cell distribution width/albumin ratio (RDW/albumin). In Yi Zhang's (22) article, AUROC curve was 0.6613 (95% CI: 0.6238–0.6988, $p < 0.0001$) for glucose-to-lymphocyte ratio (GLR). Both AUROCs were lower than the AUROC 0.694 (95% CI: 0.634-0.754, $p<0.001$) of LAR which may suggest that LAR may have a better predictive value than RDW/albumin and GLR. Therefore, LAR may have a good predictive power for 30-day mortality in patients with ARDS”.

Comment 10: Discussion: what does LAR added as compared with other potential prognosis markers previously reported?

Reply 10: Thanks for your comments. We selected two articles that also used mimic databases to study prognostic markers of ARDS. We found that in Jung Wan Yoo's (6) article, the area under the ROC (AUROC) curve was 0.681 (95% CI: 0.617-0.741,

p<0.001) for red cell distribution width/albumin ratio (RDW/albumin). In Yi Zhang's (7) article, AUROC curve was 0.6613 (95% CI: 0.6238–0.6988, p < 0.0001) for glucose-to-lymphocyte ratio (GLR). Both AUROCs were lower than the AUROC 0.694 (95% CI: 0.634-0.754, p<0.001) of LAR which may suggest that LAR may have a better predictive value than RDW/albumin and GLR.

Comment 11: Discussion: I think that the interpretation of LAR values in patients with liver disease should be reconsidered.

Reply 11: Thanks for your comments. I agree with your opinion. LDH and albumin both reflect liver function to varying degrees. When liver function is impaired, LDH increases and albumin decreases with LAR increasing. So when ARDS patients with liver dysfunction, LAR cannot predict the prognosis of ARDS very well. Accordingly, we have added more information about the discussion on Page 8, line 240-241 of the revised manuscript.

Changes in the text: The added part about the data extraction on Page 8, line 240-241 of the revised manuscript is following as “Due to the impact of liver disease on LDH and Albumin, we hold reservations about the outcome of this interaction. Which suggested that more attention should be taken to female patients”.

Comment 12: Limitations should include database analysis related aspects.

Reply 12: Thanks for your comments. Some data sources may have data quality issues, such as incomplete or inaccurate data. Therefore, we have added more information about the discussion on Page 8, line 250-251 of the revised manuscript.

Changes in the text: The added part about the data extraction on Page 8, line 250-251 of the revised manuscript is following as “Third, due to database research, some data sources may have data quality issues, such as incomplete or inaccurate data”.

Comment 13: Conclusion: I don´t think we can give such a strong conclusion considering the design of the study and the results.

Reply 13: Thanks for your comments. In order to conduct this study, we used

restricted cubic spline analysis, Kaplan Meier analysis, Multivariate Cox regression analysis, Receiver operating characteristic analysis, and Subgroup analysis. We can determine the prognostic value of LAR for ARDS patients, and given your above comments, we believe that this conclusion is indeed strong. So, we have revised the conclusion on Page 8, line 255-256 of the revised manuscript.

Changes in the text: The added part about the data extraction on Page 8, line 255-256 of the revised manuscript is following as "LAR is a prognostic indicator for patients with ARDS. Elevated LAR levels are associated with increased 30-day mortality, 90-day mortality and in-hospital mortality in patients with ARDS".

Comment 14: Abstract: it should be modified according to the comments on the main manuscript.

Reply 14: Thank you for your comments. We have revised the abstract on Page 2, line 38-60 of the revised manuscript.

Changes in the text: The added part about the data extraction on Page 2, line 38-60 of the revised manuscript is following as "Background: Lactic dehydrogenase (LDH) to albumin ratio (LAR) was an independent risk factor for mortality in the patients with acute respiratory distress syndrome (ARDS) due to Corona Virus Disease 2019 (COVID-19), while the relationship among LAR and short-term, long-term, in-hospital mortalities of ARDS remains unclear. The current study aims to investigate the association between LAR and significant prognosis in patients with ARDS. Methods: We conducted a retrospective cohort study and analyzed patients with ARDS on the Medical Information Mart for Intensive Care (MIMIC) IV version 2.0 database. In the current study, 30-day mortality was defined as the primary outcome, 90-day mortality and in-hospital mortality were defined as secondary outcomes. Multivariate regression analysis, Kaplan-Meier curve analysis and subgroup analysis were performed to research the association between LAR and prognosis in patients with ARDS. Results: A total of 358 critically ill patients with ARDS were enrolled in the current study. The mean age of the participants was 62.6 ± 16.0 and the median of LAR was 14.3. According to the Kaplan-Meier curve analysis, the higher LAR group

had a higher 30-, 90-day and in-hospital mortalities. We also analyzed the 30-day mortality to receiver operating characteristic curve (ROC) curves by comparing the value between LAR and LAR + simplified acute physiology score II (SAPS II). The area under the curve (AUC) of the LAR group was 0.694 (95% CI: 0.634–0.754, $p < 0.001$), and 0.661 for the LAR + SAPS II (95% CI: 0.599–0.722, $p < 0.001$). For 30-day mortality, after adjusting for covariates, hazard ratios (HRs) [95% confidence intervals (CIs)] for tertile2 (LAR 8.7–30.9) and tertile3 (LAR > 30.9) were 2.00 (1.37, 2.92) and 2.50 (1.50, 4.15), respectively. Similar results were also observed for 90-day mortality and in-hospital mortality. Conclusions: Elevated LAR levels are associated with increased 30- and 90-day mortalities, as well as in-hospital mortality in patients with ARDS, which means LAR levels may predict the mortalities of ARDS patients".

Comment 15: English should be reviewed.

Reply 15: Thank you for your comments. The manuscript has been revised based on the editor's language editing comments one by one. We also improved our manuscript under the guidance of my supervisor and there are some changes. These changes will not influence the content and framework of the work. So, we did not list the changes but marked in red color in our revised paper. We appreciate for your warm work earnestly and hope that the correction will meet with approval.

Reference

(1)Alizadeh N, Tabatabaei FS, Azimi A, Faraji N, Akbarpour S, Dianatkhah M, Moghaddas A. Lactate Dehydrogenase to Albumin ratio as a Predictive Factor of COVID-19 Patients' Outcome; a Cross-sectional Study. Arch Acad Emerg Med. 2022 Aug 15;10(1):e63. doi: 10.22037/aaem.v10i1.1646. PMID: 36033986; PMCID: PMC9397596.

(2)Liang M, Ren X, Huang D, Ruan Z, Chen X, Qiu Z. The association between lactate dehydrogenase to serum albumin ratio and the 28-day mortality in patients

with sepsis-associated acute kidney injury in intensive care: a retrospective cohort study. Ren Fail. 2023 Dec;45(1):2212080. doi: 10.1080/0886022X.2023.2212080. PMID: 37194715; PMCID: PMC10193884.

(3)Wu CS, Chen PH, Chang SH, Lee CH, Yang LY, Chen YC, Jhou HJ. Atrial Fibrillation Is Not an Independent Determinant of Mortality Among Critically Ill Acute Ischemic Stroke Patients: A Propensity Score-Matched Analysis From the MIMIC-IV Database. Front Neurol. 2022 Jan 17;12:730244. doi: 10.3389/fneur.2021.730244. PMID: 35111120; PMCID: PMC8801535.

(4)Lu T, Tan L, Xu K, Liu J, Liu C, Zhang G, Shi R, Huang Z. Outcomes of hyperlactatemia on admission in critically ill patients with acute myocardial infarction: A retrospective study from MIMIC-IV. Front Endocrinol (Lausanne). 2022 Sep 23;13:1015298. doi: 10.3389/fendo.2022.1015298. PMID: 36213274; PMCID: PMC9538672.

(5)Gu YL, Yang D, Huang ZB, Chen Y, Dai ZS. Relationship between red blood cell distribution width-to-albumin ratio and outcome of septic patients with atrial fibrillation: a retrospective cohort study. BMC Cardiovasc Disord. 2022 Dec 9;22(1):538. doi: 10.1186/s12872-022-02975-1. PMID: 36494633; PMCID: PMC9733276.

(6)Yoo JW, Ju S, Lee SJ, Cho YJ, Lee JD, Kim HC. Red cell distribution width/albumin ratio is associated with 60-day mortality in patients with acute respiratory distress syndrome. Infect Dis (Lond). 2020 Apr;52(4):266-270. doi: 10.1080/23744235.2020.1717599. Epub 2020 Jan 29. PMID: 31996066.

(7)Zhang Y, Zhang S. Prognostic value of glucose-to-lymphocyte ratio in critically ill patients with acute respiratory distress syndrome: A retrospective cohort study. J Clin Lab Anal. 2022 May;36(5):e24397. doi: 10.1002/jcla.24397. Epub 2022 Mar 31. PMID: 35358348; PMCID: PMC9102764.

Reviewer B

Comment: I would prefer MIMIC database to be better “squeazed” in terms of prognostic factors as this database can offer much more information than

LDH/albumin ratio.

Reply: Thanks for your comment. We have removed a part of introduction about MIMIC database in the first paragraph of “Methods” section on Page 4, line 97-103 of the revised manuscript. Unfortunately, we did not make better use of the database for our research but we look forward to conducting more relevant study based on the database in the future.