Peer Review File

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Reviewer A:

The authors derived a new scoring system to predict in-hospital mortality in patients receiving ECMO in their institute. Several concerns have been raised.

Comment 1: Overall, the format might not be appropriate for the academic paper. For example, the title is too long and redundant.

Reply A/1: Thank you for your comment. We rewrite our title to make it shorter. It became "**Extracorporeal Membrane Oxygenation (ECMO) Support for Acute Hypoxemic Respiratory Failure Patients: Outcomes and Predictive Factors**"

Comment 2: There are already various scoring systems to predict clinical outcomes following the initiation of ECMO. The novelty of this study is unclear.

Reply A/2: Our study provides data on outcomes and prediction score for in-hospital mortality of patients treated with ECMO support in a low ECMO volume center from a developing country, which may be different from the prior reported prediction scores mostly reported from the developed countries with high ECMO volume center. We mentioned this issue in our introduction. We also mentioned this in discussion line

235-241. It be “During the current COVID-19 pandemic, several new ECMO centers have been established in both developed and developing countries for rescue therapy to treat patients with severe COVID-19 and acute severe respiratory failure[16,17]. The newly developed SHOP score could be used to select candidate patients and for prognostic determination at new ECMO centers. This could provide a more accurate score than other scores developed at centers with high ECMO experience.”

Comment 3: One of the critical limitations of this study is a lack of validation study. It is not surprising that the new score had the highest predictability among others in their derivation cohort.

Reply A/3: We agree with your comment. So we describe this concern in our limitation, line 246-248. It is “We plan to perform both internal validation by using data from new ECMO cases and securing external validation by use of ECMO case data from other hospitals in the future.”

Comment 4: Could the authors explain the reasons why these variables were included in the univariate analyses in table 4?

Reply A/4: We selected variables included in table 4 by clinical reasoning and p-value <0.05 in table 1 and 2. All baseline clinical parameters that showed significant different between survived and died patients were performed an univariate analysis. For the continuous variables, we performed ROC curve analysis to identify cut-off value, as

mentioned above, before performed univariate analysis. We explained this in method, line 106-109.

Comment 5: What does p-value in Table 5 indicate?

Reply A/5: p-value in Table 5 is the *p*-value of the area under the ROC curve (AUC). If $p<0.05$, it indicated that the AUC is significantly different from 0.5, therefore there is evidence that the mortality predicting score has an ability to distinguish between the survivor and non-survivor. If $p>0.05$, it indicated that the AUC is no different from 0.5, therefore, the mortality predicting score has no ability to distinguish between the survivor and non-survivor. We mentioned this at the end of Table 5.

Comment 6: The implication of their new score should be discussed in the discussion section.

Reply A/6: The SHOP mortality prediction score can be used together with clinical assessment for appropriate patient selection to initiate ECMO support in developing countries. We added "During the current COVID-19 pandemic, several new ECMO centers have been established in both developed and developing countries for rescue therapy to treat patients with severe COVID-19 and acute severe respiratory failure[16,17]. The newly developed SHOP score could be used to select candidate patients and for prognostic determination at new ECMO centers. This could provide a more accurate score than other scores developed at centers with high ECMO experience."

Reviewer B:

Thank you for an opportunity to review this paper. This is a single-centered study including

65 patients who received ECMO support over 10.5 years for hypoxemic respiratory failure. The cohort included 43 patients on V-V ECMO and 22 patients V-A ECMO, with an in-hospital mortality of 69%. The authors found that: SOFA score >14, hospitalization >72 hours before ECMO, PF ratio <60, and pH <7.2 were associated with worse hospital survival. The proposed SHOP score performed better than other ECMO risk scores such as PRESERVE, RESP and PRESET.

On the whole, the manuscript was well-written and easy to follow. It was a pleasure to witness the outcomes of an ECMO system in a developing country. I sincerely congratulate the authors for their work.

Reply to reviewer B: Thank you for your comment.

Major comments:

Comment 1: The study is aimed to examine mortality in acute hypoxemic respiratory failure, for which V-V ECMO is the default modality of support. However, up to 37% patients in this cohort received V-A ECMO. As we know, the mortality rates of V-A ECMO are generally much higher than V-V ECMO, hence, it is inappropriate to pool these patients together in the development of a prediction scoring system without accounting for the underlying differences.

Reply B/1: We agree with your concern. We added our explanation in discussion, line 217-228. It became “This study enrolled

patients who presented with acute hypoxemic respiratory failure, which is a unique underlying pathophysiologic condition that typically requires VV-ECMO support. However, in severe cases prolonged hypoxemia causes hemodynamic compromise and circulatory collapse, which requires VA-ECMO. The difference in mortality rates of VA-ECMO and VV-ECMO patients from previous reports may be influenced by underlying conditions. In the previously reported study, VA-ECMO was mainly used in ECMO assisted CPR, in which those patients had acute coronary syndrome as an underlying condition.[15] In this case, the mortality rates of VA-ECMO were generally much higher than VV-ECMO. In the present study, the mortality rate of VA-ECMO supported patients was 72.7% (n=22), which similar with 67.4% (n=43) among VV-ECMO supported patients. This could be explained by the similarity of acute hypoxemic respiratory failure among the patients due to underlying conditions."

Comment 2: Although the proposed SHOP score only has 4 parameters, it is prudent to remark that the SOFA score itself consists of 6 components. For centers who do not routinely calculate the SOFA during clinical care, this adds an extra layer of complexity before application of the SHOP score.

Reply B/2: We agree with your concern. We mentioned our Reply in the limitation, line 249-258. It is "Although the proposed SHOP score

only has four parameters, it is prudent to remark that the SOFA score itself consists of six components. For centers who do not routinely calculate the SOFA score during clinical care, this may increase complexity prior to SHOP score application. However, the SOFA score evaluates the function of six main organs. In order to calculate the SOFA score, two parameters must be evaluated: mean arterial blood pressure and the Glasgow Coma Scale score. Additionally, four essential laboratory investigations (creatinine, platelet count, bilirubin level and PaO_2/FiO_2 ratio) must be examined, especially among the critically ill that are candidates for ECMO support. Furthermore, the SOFA score is currently a part of the SEPSIS-3 definition for diagnosis of sepsis and septic shock, which promotes its use worldwide."

Comment 3: Results, lines 173-177: Given that the odds ratios of the 4 predictors of in-hospital mortality range from 8.77 to 14.99, please give reasons why each of these predictors were equally weighted with a numerical score of 1 point in the composite SHOP score.

Reply B/3: The odds ratios of the 4 predictors for in-hospital mortality were all within 10+/-5, which actually in the narrow range. We would like to create an easy-to-use prediction score, thus we assigned a score of 1 to all parameters with statistical significance in multivariate analysis.

Comment 4: Discussion: Like the authors pointed out, the real value of this paper is its presentation of a cohort that is different from most

cohorts from large ECMO centers in developed countries. Please consider discussing, with reference to published literature, the underlying differences and difficulties encountered in such a healthcare system in contrast to others.

Reply B/4: Thank you for your suggestion. We add "During the current COVID-19 pandemic, several new ECMO centers have been established in both developed and developing countries for rescue therapy to treat patients with severe COVID-19 and acute severe respiratory failure[16,17]. The newly developed SHOP score could be used to select candidate patients and for prognostic determination at new ECMO centers. This could provide a more accurate score than other scores developed at centers with high ECMO experience." in the discussion.

Minor comments:

Comment 5: Results, lines 137-138: While acknowledging that patients on ECMO could have more than one of the diagnoses mentioned, for the purposes of the study, it may be more helpful to present the primary diagnosis necessitating ECMO support (one per patient). Please also provide detailed breakdown of the causes of ARDS.

Reply B/5: We provided the primary diagnosis of each patients in Table 1. We also provide the detail causes of ARDS as well.

Comment 6: Results, lines 140-141: It is interesting that the incidence of pulmonary embolism was higher in survivors compared with non-survivors, which is in contrast to the usually reported poor outcomes with pulmonary embolism. Following on the discussion, whether ECMO was indicated in these patients with PE for respiratory or circulatory failure,

and therefore whether they received V-V or V-A ECMO was not clear.
Reply B/6: All PE patients in this study presented with refractory hypoxemia, following with low blood pressure, then they received V-A ECMO support for circulatory failure and refractory hypoxemia. We mentioned this in our result. We mentioned this in the result, line 129-131.

Comment 7: Results, lines 153-154: Can the authors clarify how these "indications" differ from the "diagnoses" stated in lines 137-138?
Reply B/7: The diagnosis described the disease that cause severe hypoxemia in each patient. For the indication for ECMO, it described the condition that initiate ECMO support.

Comment 8: Results, lines 186-189: It would be useful to provide the AUC for the proposed SHOP score in predicting mortality in the different cohorts. Given the modest size of the score development cohort, it is important to try to externally validate the performance of the SHOP score.
Reply B/8: We agree with the reviewer comment. We have acknowledged the lack of external validation of the SHOP score in the limitation, line 246-248. We plan to perform both internal validation by using data of our new ECMO cases and external validation by using data of ECMO cases from another hospitals, in the future.

Comment 9: Limitations, lines 247-248: The number of 6 patients with PE is different from that in the Results section line 141.
Reply B/9: Thank you. The result in line 141 was a typing error, we have corrected this to "4/20 (20%) vs 2/45 (4.4%), p=0.046"

Comment 10: Table 1, diagnosis: As mentioned above, please consider

simplifying to one diagnosis per patient.

Reply B/10: We rewrite the principle diagnosis in Table 1 and make it to be one per patient.