

The Need for a Multidimensional Approach to Mortality Prediction in COVID-19: A Critical Review of Recent Findings

Sir,

We have enthusiastically read the study titled 'Prediction of mortality using SOFA score in critically ill COVID-19 patients' by Khan *et al.*¹ published recently in the Journal of College of Physicians and Surgeons Pakistan. Authors have made a commendable effort to prove the utility of the SOFA score in predicting mortality among patients with COVID-19. While having said so, we wanted to highlight our concerns about a few shortcomings in their methodology as well as conclusions that might prove to be beneficial in making their findings more suitable to be applied clinically.

Firstly, we think that the study design opted by the authors is not well-suited to the nature of the study as it limits the capability to draw casual relationships among findings. As per our understanding, a prospective cohort study would have been better in evaluating the predictive power of the SOFA score because it gives room for dynamic changes during the ongoing study, such as changes in clinical status and interventions over time. As we know, such changes are very crucial in the intensive care unit (ICU) settings for patients suffering from COVID-19.²

Secondly, we have found this study deficient in control for factors capable of individually altering the outcomes regarding mortality as calculated using SOFA scores, such as the use of some medications (e.g. antivirals and corticosteroids), previous ICU admissions, and comorbidities other than hypertension and diabetes.^{3,4} We suggest the use of more efficient statistical methods such as multivariable adjustment or propensity score matching to minimise the effect of such confounders.

We would also like to comment on the logistic regression model used in this study. Utilising the SOFA score at 48 hours as a predictor may introduce circular reasoning, as it is already well-established that worsening organ function is associated with increased mortality.^{5,6} The wide confidence intervals and reports of infinity for some odds ratios suggest instability in the model, potentially due to inadequate sample size or over-fitting.⁷

The authors also highlighted hypertension as a significant predictor of mortality. However, this conclusion lacks adequate justification, particularly given the inconsistent findings across various studies.⁷ The mention of an unproven hypothesis regarding angiotensin-converting enzyme (ACE) inhibitors and

ACE2 receptor upregulation is speculative and requires stronger evidence and better contextualisation within the existing scientific literature.^{8,9} While the SOFA score is a valuable tool in ICU settings, relying on it exclusively for mortality prediction in COVID-19 patients may be insufficient. A more comprehensive approach integrating clinical assessments, laboratory markers (e.g., D-dimer, ferritin, and C-reactive protein), and imaging findings could offer a more accurate assessment of a patient's prognosis.¹⁰ The lack of discussion on this integrative approach limits the study's practical applicability.

In conclusion, while the study by Khan *et al.* provides valuable insights into the potential use of the SOFA score in COVID-19 patients, the limitations outlined raise questions about the robustness of their findings. We encourage the authors to consider these points and conduct further research to substantiate their conclusions, potentially through a more comprehensive and methodologically rigorous approach.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

MKHG: Manuscript writing, review, and submission.

MKS: Reviewing and submission.

Both authors approved the final version of the manuscript to be published.

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AUTHOR'S REPLY:

We thank the authors for their thoughtful comments and kind consideration of our study. We appreciate the opportunity to address their observations.

The authors are correct in noting that the outcome of our study was observed over time. Therefore, we agree that a prospective cohort study would have been a more appropriate design. However, given the circumstances and data availability, the current design was chosen as the most feasible approach.

We appreciate the suggestion regarding multivariable adjustment to control for confounders. It seems, however, that this

aspect of our analysis may have been overlooked. We would like to clarify that we have already conducted a multivariable analysis, and the results are presented in Table III of the article.

We have already performed a bivariate (stratification) analysis in Table II of the article to illustrate the differences in mortality rates based on the mode of ventilation and the severity status of COVID-19. The statistical tests revealed significant differences, with no mortality recorded in some categories, which the reader can review for associations. The same variables are presented in the results section of the Table II for univariable analysis.

When examining Table III, the univariable analysis (crude odds ratio, OR) demonstrates that each variable maintains its own OR, independent of others. This reflects the dataset's nature, including rare events or complete separation. Such cases, while sometimes producing infinite OR values, provide valuable insights, indicating a strong predictor-outcome association. This is not a flaw in the analysis but rather a true representation of the data characteristics. In cases where the ORs or 95% confidence intervals (CIs) cannot be estimated due to the data's nature, 'NA' is often used, as seen in numerous studies published in well-reputed journals. For example, study by Woo et al. in *JAMA Network Open*,¹ Table IV, under the variable treatment required.¹

We appreciate the authors' insightful feedback and the opportunity to clarify our methods and results. We are confident that the analysis provided, including the multivariable adjustment and stratification analysis, accurately reflects the data and offers valuable insights into the study's outcomes. We thank the authors again for their valuable feedback, and we hope this clarifies our approach and findings.

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