Re-Prealbumin: A New Biomarker for Predicting Prognosis in Patients with Severe COVID-19

We read with great interest the article titled "Prealbumin: A new biomarker for predicting prognosis in patients with severe COVID-19" by Issever *et al*.[1] We thank the authors for this informative and useful article. We would like to mention a few important points about the interpretation of the statistical tests performed in the study.

In statistical analysis, firstly, non-parametric comparison tests were used to determine the relationship between prealbumin and mortality. Mortality was significantly higher in patients with prealbumin levels lower than 0.085 g/L than the higher.[1] A second analysis was performed based on the receiver operating characteristic curve (ROC) to test prealbumin's ability to predict whether a patient died or survived. As a rule of thumb, a perfect predictor test tends to have area under curve (AUC) of 1.0.[2] AUC value <0.5 is considered as indistinguishable from random, while those close to 1 are evaluated as close to the perfect predictor.[2] It has been reported that AUC value >0.9 has high predictability, while AUC in the range of 0.9 - 0.7 has moderate predictability, and in the range of 0.7 - 0.5 lower predictability.[2] In the discriminatory power analysis, authors determined the AUC value of prealbumin as 0.656, which shows that prealbumin's ability to predict mortality is close to random. A further analysis was performed by using odds ratios (OR) to examine predictive ability of prealbumin for mortality. As a rule of thumb for ORs, a useful predictor/diagnostic test has ORs greater than 20.[3] In the aforementioned study, OR for significant cut-off value of prealbumin was 2.193.[1] Although the results of Issever *et al*.'s study show that prealbumin predicts mortality significantly better than random, we think that it is not clinically significant because its predictive ability is too close to random.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
All authors participated in the design, execution and analysis of the paper and approved the final version to be.

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AUTHOR'S REPLY

Sir,

First of all, we thank the authors of this letter for showing interest in our manuscript and their comments on it. We think that such evaluations and contributions improve researches.

In our analysis, the median prealbumin levels were 0.08 g/L (0.04 - 0.1) for non-survivors and 0.09 g/L (0.07 - 0.13) for survivors and the p-value was 0.002. Sensitivity and specificity were 59.8% and 59.6%, respectively; and the area under curve (AUC) was 0.656. All these values statistically prove that prealbumin levels were lower in mortal patients and this test can be used as a predictor for mortality in patients with severe COVID-19. Congruently, in the discussion and conclusion parts of our article, we mentioned that "Prealbumin levels, that were studied at the time of admission to ICU, were found significantly lower for non-survivor patients in this study". The randomised controlled, prospective, meta-analysis, and review studies conducted with higher numbers of patients in the literature revealed similar results to our study so far.[1-5] Even in one of these studies, for predicting the prognosis of COVID-19, the performance of prealbumin was found to be better than most routine laboratory indicators, such as albumin, hypersensitive C-reactive protein, d-dimer, and lactate dehydrogenase.[2] We were already aware of and agree that, with p=0.002 and AUC of 0.656, prealbumin can not be stated as a "very very strong" indicator for mortality in patients with severe COVID-19 in our study. Accordingly, we did not claim that the relationship between low serum prealbumin levels and mortality was "very very strong" in our study. However, this situation might be caused by the limitations of our study, which were of its retrospective nature and a small study group (47 survivors *vs*. 102 non-survivors). Another reason for this result might be that the

study was conducted only with the patients treated in the intensive care unit (ICU). All patients were severely ill irrespective of their outcomes and we can estimate that prealbumin levels were lower than normal in most of them, since it is a well known negative acute phase reactant. In contrast to the authors of the subject letter, we can interpret that prealbumin could still show its predictive ability in this study group, all of which consists of severely ill patients.

As a result, despite the limitations of our study, not only the statistically significant results of our study; but also the clinical studies claiming similar results regarding the association of prealbumin with mortality in the literature, support our opinion that this biomarker can be a predictor for mortality in patients with severe COVID-19.

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