Letter to the Editor: Serum Albumin in COVID-19: A Good Example in Which Analytical and Clinical Performance of a Laboratory Test Are Strictly Intertwined

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To the Editor:

We read with interest the paper by Hundt et al. describing the behaviour of common liver tests in COVID-19 and their association with poor outcomes (1). Among presented data, we were surprised to see that serum albumin (ALB) concentrations during hospitalization did not significantly predict patient death at the multivariate analysis (MA), even if 86.6% of patients showed ALB values <35 g/L, i.e. the lower reference limit. In a similar COVID-19 population enrolled in our national reference center for infectious diseases, we recently analysed a group of common biochemistry tests, including ALB, as major predictor of COVID-19 severity (2). Although the patient rate showing an ALB <35 g/L was quite similar (89%) to that of Hundt’s study, at MA low ALB concentrations remained significantly associated (P=0.003) with higher odds of death, ALB values ≤18 g/L giving a positive likelihood ratio of 12.2 for predicting in-hospital death. In terms of absolute ALB levels in the respective populations, it is however somewhat difficult to compare our results with those of Hundt et al. as the authors do not mention the methodology used to determine ALB in their hospital network. It is known that immunoturbidimetric assays for ALB determination, such as the one in use in our institution, are specific for the ALB measurement contrary to nonspecific colorimetric methods, which are in use in the majority of U.S. healthcare institutions, also reacting with proteins other than ALB (3). The well-known lack of specificity of the latter methods, especially at low ALB and high globulin (including “acute phase reactants”) concentrations, i.e. the typical COVID-19 situation, may have influenced the Hundt’s results. Figure 1 depicts ALB distribution in our COVID-19 patients showing that even survivors displayed a median (interquartile range) [28 g/L (25-32)] quite lower that patients with severe COVID-19 enrolled by Hundt et al. Therefore, we cannot exclude that the inability of ALB to predict death in the Hundt’s study was due to spuriously higher ALB values measured with non-specific methods in the evaluated COVID-19 patients. The accuracy of ALB methods may become critical in COVID-19 cases, where ALB is decreased but acute-phase proteins are increased, and thus use of immunological assays should be preferred in this condition (4).
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Figure legend

**Figure 1.** Box and whiskers plots showing the distribution of results of serum albumin in a cohort of 390 COVID-19 patients, according to death during hospitalization (non survivors) vs. hospital discharge after clinical recovery (survivors). Adapted from ref. 2.
