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Albumin Kinetics in Sepsis and COVID-19

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ABSTRACT: Hypoalbuminemia has been associated with poor outcome in critically ill population including sepsis and COVID-19. The observational study by Su et al showed a favorable albumin kinetics, with an initial downwards trend followed by recovery back to the predicted albumin levels, in survivors of COVID-19 and sepsis-induced acute respiratory distress syndrome (ARDS). However, nonsurvivors in COVID-19 group did not have an upwards recovery slope, while those in sepsis group did not follow any sort of albumin kinetics. Thus, authors concluded that the pattern of albumin kinetics may be predictive of outcome in COVID-19 and sepsis-induced ARDS. Here, we would like to highlight a few more points in this letter.

KEY WORDS: COVID-19, sepsis, acute respiratory distress syndrome, hypoalbuminemia, albumin kinetics

To the Editor:

We read with interest the article by Su et al (1), published in the recent issue of *Critical Care Explorations*, have done commendable job to assess the albumin kinetics in critically ill patients with COVID 19 and sepsis-induced acute respiratory distress syndrome (ARDS). Hypoalbuminemia has been associated with poor outcome in both sepsis (2) and COVID-19 (3), but studies on albumin kinetics are scant. In this study, albumin kinetics showed an initial downwards slope to nadir levels followed by a recovery toward predicted the baseline in survivors of both sepsis-induced ARDS and COVID-19 but no such trend was obvious in the nonsurvivors of sepsis group. However, we would like to draw attention to a few points:

First, hypoalbuminemia may have varied etiologies in critical illness. Underlying nutritional status of patients, nitrogen balance, albumin losses secondary to diuretics or renal replacement therapy, hemodilution secondary to fluid therapy, and ongoing capillary leakage are not clear from the study.

Second, besides albumin breakpoints, other important aspects of albumin kinetics (2, 4) like changes in albumin half-life, albumin synthesis (fractional synthesis rate, absolute synthesis rate), interstitial extravasation (transcapillary escape rate [TER]), intravascular albumin mass (plasma albumin × plasma volume), albumin mass flow rate (TER × intravascular albumin mass), nitrogen balance, and urinary albumin losses have not been analyzed. Thus, mechanistic association of albumin kinetics is not possible from the study.

Third, in survivors of both COVID-19 and sepsis-induced ARDS, serum albumin kinetics was found to have a favorable pattern. Patients in both these groups had an initial drop in albumin levels from baseline to the lowest noted levels, known as albumin breakpoint, followed by recovery to the predicted levels. However, albumin breakpoint levels and time to albumin breakpoint were lower in the COVID-19 group, which may be explained by

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the underlying hyper-inflammatory state of COVID-19 (cytokine storm) (5) leading to greater capillary leakage of albumin. C-reactive protein/plasma albumin (PA) ratio may have been useful in this regard to correlate the albumin kinetics with underlying inflammatory stress (6). Additionally, stratification of COVID-19 into mild, moderate, and severe categories was not done in the study to make possible any correlation of albumin kinetics with underlying severity of illness. Albumin kinetics may also vary depending upon the genotypes and phenotypes of COVID-19.

Fourth, nonsurvivors in sepsis group did not have any pattern of albumin kinetics, although albumin observations were significantly less in this group. Rather, fluctuations around the predicted albumin levels were noted throughout ICU stay. Compared with survivors, age of the population (78 vs 64 yr), underlying severity of illness (Sequential Organ Failure Assessment score: 12 vs 9), comorbidities like active hematological cancer (17% vs 6.8%) and liver disease (29% vs 14%), prevalence of pneumonia (56% vs 38%), and intra-abdominal sepsis (25% vs 18%) were significantly higher in the nonsurvivors. Thus, plausible mechanisms behind the observed albumin trends in nonsurvivors could be high protein nutrition therapy, enhanced hepatic albumin synthesis (acute phase response), and resuscitative measures like hyperoncotic albumin infusions, blood products, or fluid resuscitation leading to PA enrichment by interstitial washdown and enhanced vascular refill of albumin by lymphatics (7). Additionally, host response in sepsis is heterogeneous involving a complex interplay between pro-and anti-inflammatory pathways and may not have a uniform albumin kinetics.

Finally, questions still remain unanswered regarding hypoalbuminemia as an adaptive host response, causal association with underlying stress, and the appropriate threshold and indication for treatment in different subgroups of patients (8). This study by Su et al (1) poses more questions on the (patho)physiologic and clinical relevance of hypoalbuminemia and albumin kinetics in COVID-19 and sepsis and needs further large-scale research.

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