Hypoalbuminaemia in COVID-19 infection: A predictor of severity or a potential therapeutic target?

To the Editor,

We read with interest the findings of Huang et al’s retrospective study which revealed an association between hypoalbuminaemia and mortality in COVID-19. In response to their findings, we have synthesized a structured summary of the literature to date to discuss conclusions that could be drawn collectively (Table 1). Furthermore, the authors also discuss a potential therapeutic role for correction of this hypoalbuminaemia. We would like to draw attention to the existing literature concerning albumin infusion in acute respiratory distress syndrome (ARDS) and severe sepsis, the principal causes of mortality in COVID-19.\(^2\,^3\)

We note the majority of studies in Table 1 report a lower serum albumin on admission than in the authors’ cohort. This may be explained by the measurement of serum albumin at a median of 3 days from symptom onset, perhaps representing an earlier stage of disease progression than in the other studies. The Zhang et al\(^7\) cohort included a temporal dimension to their study where they identified a significant, continual decrease in albumin from triage to intensive care unit admission. Thus, serial albumin trends may serve as a predictive tool beyond values taken at an isolated time point. For example, it has been suggested that a decrease in albumin to below 20 g/L in addition to decline over a week may be of more value than C-reactive protein in predicting and monitoring the severity of ARDS.\(^1\) We also note the considerable variability in mortality in Table 1, which may relate to differences in inclusion criteria and follow-up period.

Whilst the authors have identified the serum albumin level as an independent predictor of outcome, we wish to highlight the non-specific nature of hypoalbuminaemia in COVID-19 infection. Indeed, Zhang et al\(^7\) reported a greater incidence of hypoalbuminaemia in a matched pneumonia cohort \((n = 114)\) when compared to their COVID-19 cohort \((n = 115)\).\(^7\) The typical time course of severe COVID-19 illness has been characterized by an initial sepsis at a median 10 days from symptom onset, followed by ARDS at 12 days with later septic shock and end-organ failure.\(^2\) It follows that there is relevance in reviewing the existing efficacy of albumin therapy in other non-COVID diseases that result in the same final common pathway of ARDS and septic shock with haemodynamic compromise.

As the authors cite, a systematic review found albumin treatment to improve oxygenation in ARDS.\(^12\) While this trend was identified in two of the three trials part of this review there was, however, no evidence of reduction in mortality. It has been hypothesized the reduction in colloid pressure from hypoalbuminaemia contributes to the development of pulmonary oedema in ARDS, though a link between cause and effect has not yet been fully established. In respect to haemodynamic compromise, routine correction of albumin in severe sepsis or septic shock has shown no significant benefit in mortality across three large multicentre trials.\(^13\)

This may pertain to the increased microvascular permeability and consequent redistribution of albumin into extravascular compartments, rendering albumin supplementation ineffective in raising intravascular colloid pressure. Whilst the current research is equivocal in ARDS and septic shock, we do acknowledge there may be mechanisms not yet elucidated in COVID-19 that prove receptive to the correction of hypoalbuminaemia. For example, there is evidence that albumin downregulates the expression of ACE2, the target receptor of COVID-19.\(^14\)

We thank the authors for demonstrating the predictive value of hypoalbuminemia and highlighting the need to explore the therapeutic potential of albumin therapy in patients with COVID-19. Whilst related studies have described similar findings, the considerable interstudy variation is likely explained by heterogenous patient populations. Finally, despite the paucity of research into the use of albumin infusion in COVID-19, the existing evidence base in ARDS and sepsis suggests there will be limited benefit. Nonetheless, without further investigation, we cannot exclude the possibility that albumin therapy may be beneficial in COVID-19 through alternative mechanisms.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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TABLE 1  

| Study           | Study size | Cohort mortality, at end of follow-up period | Mean (or median) albumin level (g/L) | Comparison of albumin level between defined outcomes* (g/L) | Median time from onset of symptoms to laboratory sample |
|-----------------|------------|--------------------------------------------|-------------------------------------|-----------------------------------------------------------------|--------------------------------------------------------|
| Huang et al1    | N = 299    | 5%                                         | 37.3                                | Survivors: 37.6 (n = 283) Nonsurvivors: 30.5 (n = 16)            | 3 d                                                    |
| Chen et al3     | N = 274    | 41%                                        | 33.9                                | Survivors: 36.3 (n = 161) Nonsurvivors: 30.1 (n = 113)          | 10 d                                                  |
| Wu et al4       | N = 201    | 22%                                        | 32.8                                | Without ARDS: 33.7 (n = 117) With ARDS: 30.4 (n = 84)           | No data                                                |
| Mo et al5       | N = 155    | 14%                                        | 38.0                                | Improvement: 39.0 (n = 70) Refractory cases: 36.0 (n = 85)       | No data                                                |
| Wan et al6      | N = 135    | <1%                                        | 40.5                                | Mild-moderate cases: 49.9 (n = 95) Severe cases: 36.0 (n = 40)  | No data                                                |
| Zhang et al7    | N = 115    | <1%: Study excluded cases that were critical on admission | 33.9                                | Mild-moderate cases: 40.4 (n = 84) Severe cases: 34.4 (n = 31)  | No data                                                |
| Rica et al8     | N = 48     | 21%                                        | 34.7                                | Without ARDS = 39.2 (n = 27) With ARDS = 29.0 (n = 21)         | No data                                                |
| Huang et al7    | N = 41     | 15%                                        | 31.4                                | Non-ICU care: 34.7 (n = 28) ICU care: 27.9 (n = 13)             | 7 d                                                    |
| Chen et al10    | N = 21     | 19%                                        | 33.7                                | Mild-moderate cases = 37.2 (n = 10) Severe cases = 29.6 (n = 11) | 7-8 d                                                  |

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

*All studies reported statistical significance between their defined outcomes of interest.

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