JIM Letter to the Editor

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# Regarding: Hypoalbuminemia in COVID-19

Dear Editor,

I read with interest the paper by Wu et al. [1] dealing with the issue of hypoalbuminemia in patients with COVID-19. The authors reported that hypoalbuminemia, expression of disease severity, may be due to pulmonary capillary leakage of albumin. Such capillary leak syndrome of COVID-19 is the result of injury of the alveolar epithelial–endothelial barrier leading to lung proteinaceous edema [1]. However, the authors did not consider at all relevant pathogenetic aspects of hypoalbuminemia occurring during acute inflammation, and, expectedly, COVID-19, namely decreased hepatic synthesis of albumin and its increased catabolism after oxidation. Regarding decreased synthesis of albumin, it has been shown that as a result of acute inflammation plasma albumin levels fall markedly, that is, by about 50%, associated with a considerable decline in liver albumin mRNA and hepatic secretion of albumin [2]. The reduction in albumin mRNA concentration, caused by a decrease in gene transcription, is due to the acute-phase reaction mediated by cytokines such as interleukin-6 and tumour necrosis factor-$\alpha$ [3], which are involved in the inflammatory status of COVID-19. Regarding increased albumin catabolism, it is worth considering that albumin is the major plasma antioxidant, circulating at relatively high concentrations (about 0.6 mM) and capable of reacting with free radicals/oxidant species and of binding-inactivating harmful prooxidant metals [3,4]. The antioxidant properties of albumin are basically related to its free cysteine residue thiol group (Cys-34), reactive with oxygen radicals, chlorinating and nitrating oxidants, and electrophiles including cytotoxic reactive aldehydes [3,4]. As a consequence of reaction with oxidant species, native reduced albumin, dubbed mercapto-albumin, undergoes oxidative denaturation turning into non-mercapto-albumin [3]. The oxidative stress-induced denatured albumin is degraded via gp18- and gp30-mediated and caveolae-related endocytosis in endothelial cells followed by lysosomal metabolism [3,5]. Oxidative stress, which occurs in COVID-19, results in generation of oxidized dysfunctional albumin and its enhanced rapid degradation, leading to hypoalbuminemia together with inflammation-related decreased hepatic synthesis of albumin and its extravasation; thus, high-dose albumin may be required for albumin replacement therapy. The study by Wu et al. has specific therapeutic implications; the authors invoked indeed a more responsible treatment of COVID-19, using agents (nevertheless still under investigation) able to activate alveolar fluid clearance, namely solnatide, or to stabilize the endothelial barrier, avoiding useless and potentially harmful administration of albumin, which might extravasate possibly impairing lung function [1]. However, in a recent preliminary report, Violi et al. [6] provided evidence that high-dose (400 g/week) albumin administration for 7 days not only dampens hypercoagulability in patients with COVID-19, but also strikingly reduces mortality, with no fatal outcome in the albumin-treated group; notably, average serum albumin levels rose from 2.7 to 3.6 g/dl after 7 days of albumin treatment [6]. In this context, conceivably only high-dose albumin administration can maintain or even increase albumin levels in the clinical setting of acute inflammation and COVID-19; associated with albumin, it is worth considering administration of *N*-acetylcysteine, which regenerates albumin Cys-34 [4], exerts antioxidant/anti-inflammatory effects, and decreases endothelial leakage of albumin [7], thus improving therapeutic effects. Such issues warrant further clinical investigation.

### Author contribution

The author had access to any data and a sole role in the manuscript. The author alone is responsible for the content and writing the manuscript.

### Conflict of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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