Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editors-in-Chief

Targeting raised von Willebrand factor levels and macrophage activation in severe COVID-19: Consider low volume plasma exchange and low dose steroid

We read with interest the case report by *Escher* [1] et al. highlighting marked endothelial activation in a COVID-19 patient with multi-organ failure. In view of raised plasma von Willebrand factor (VWF) antigen levels (4.1 fold above upper limit of normal [ULN]) and 40 fold increase in D-dimers on Day 27, he was switched from prophylactic Dalteparin to therapeutic dose unfractionated heparin with reversal of multi-organ failure. The International Society for Thrombosis and Haemostasis recommends COVID-19 patients with 3–4 fold increase in D-dimers be administered prophylactic low molecular weight heparin [2]. *Escher* et al. suggest therapeutic anticoagulation in severe COVID-19 patients with endothelial activation [1].

VWF is a platelet - adhesive protein and the carrier of coagulation factor VIII synthesized by endothelial cells and megakaryocytes. Baseline VWF antigen levels were raised 3.2–4.7 fold above ULN and predicted poor outcome over the next 7–8 days in patients with acute liver injury/failure [3] and acute on chronic liver failure [4]. The large sized high molecular weight VWF multimers (5000–10,000 kDa in size), the main circulating form in health, cannot be removed on hemodialysis, which removes molecules < 60 kDa in size [5]. Plasma exchange removes molecules regardless of size. We demonstrated VWF-pheresis during plasma exchange in patients with liver failure [6]. Plasma VWF levels reduce after plasma exchange in patients with early septic shock [7].

Rising serum ferritin levels (which indicate macrophage activation/secondary hemophagocytic lymphohisticytosis) predict death in COVID-19 patients [8]. As VWF molecules are cleared by macrophages, it is possible that endothelial activation (reflected by raised VWF levels) contribute to macrophage activation in COVID-19.

Lung capillary congestion noted in all COVID-19 patients at post mortem, was probably secondary to pulmonary arterial platelet – fibrin microthrombi (seen in 33 of 38 patients) [9]. The main locations of macrophages in the body are in liver sinusoids and lung capillaries. It is likely that the enlarged activated macrophages and raised VWF multimer levels may contribute to sludging within the lumen of lung capillaries and impede oxygenation in COVID-19 patients [10].

In our preliminary experience, a treatment protocol of low volume plasma exchange and low dose steroid improved survival in patients with acute liver injury, probably by ameliorating macrophage activation and reducing VWF levels [10]. This treatment worked best in patients identified and treated early in the illness [2,3]. We propose that this protocol be studied in patients with acute lung injury due to severe COVID-19 in the setting of endothelial and/or macrophage activation.

Declaration of competing interest

None.

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