



## Letter to the Editor

## Impact of convalescent and nonimmune plasma on mortality of patients with COVID-19: a potential role for antithrombin

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We read the review of treatment of coronavirus disease 2019 (COVID-19) with convalescent plasma [1] and the commentary on thromboprophylaxis in patients hospitalized for COVID-19 [2]. We believe that some considerations may link them to each other. Convalescent plasma is considered to be a potentially effective treatment for severe COVID-19 [1]. To date, there are several small studies that reported positive results on survival, especially if convalescent plasma was provided early in the course of the disease [1]. Therefore, clinical trials to assess its real effectiveness are ongoing, even if they are at high risk of bias, as correctly outlined [1].

Severe COVID-19 is characterized by a procoagulant state that can lead to fatal venous and arterial thromboembolic events, such as pulmonary embolism, disseminated intravascular coagulopathy, venous thromboembolism, stroke and myocardial ischaemia [2,3]. In other words, mortality in patients with COVID-19 is mainly attributed to thromboembolic complications [2,3]. Therefore, prophylactic or therapeutic anticoagulation is recommended in all patients hospitalized for COVID-19 [2,3]. However, despite anticoagulation, which is usually performed by treatment with heparin, mortality due to thromboembolic events

is high [2,3]. This suggests that heparin is ineffective in a significant proportion of patients with COVID-19, but the reasons remain unknown [2,3].

Several recent studies have shown that acute antithrombin deficiency is common in patients with COVID-19 [3–5]. Antithrombin deficiency may be present in at least 25% of the patients with severe COVID-19 [3–5]. The clinical efficacy of heparin is mainly due to its interaction with antithrombin, and anticoagulation may therefore be ineffective in COVID-19 patients with low antithrombin levels [3,5,6]. In addition, heparin treatment itself may further reduce antithrombin levels [3,6]. Low antithrombin levels seem to be strongly associated with mortality and the need for mechanical ventilation in patients with COVID-19 [3]. However, in patients with antithrombin deficiency, anticoagulation with heparin may become effective if antithrombin concentrate or fresh frozen plasma is administered [6,7].

These new findings suggest some considerations regarding the results obtained by the studies on the treatment of COVID-19 with convalescent plasma. Indeed, we cannot exclude the notion that some of the positive effects of convalescent plasma on patient survival may be due to the antithrombin present in the plasma when this plasma was provided to patients with unknown antithrombin deficiency. Therefore, ongoing and future trials on convalescent plasma should take into account patient antithrombin levels in order to correctly measure the impact of the treatment on outcomes. These analyses may even imply that convalescent plasma may become an elective treatment for COVID-19 patients with antithrombin deficiency, as it could act not only on the viral infection but also on the antithrombin deficiency.

## Transparency declaration

All authors report no conflicts of interest relevant to this letter.

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