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Response to 'Inaccurate conclusions by Tang and colleagues'

We appreciate the opportunity to respond to the letter from Dr Greenstein. It's true that most of the heparin users just received a prophylaxis dose in our study, due to lack of evidence of arterial or venous thromboembolism (VTE), and typical signs of disseminated intravascular coagulation (DIC) in the majority of the patients; in addition, some of them were also too unstable to transport for imaging examinations. Therapeutic doses of heparin had been used in patients with definite thrombosis but were not specifically mentioned in our paper.

According to a recent report about VTE prophylaxis in the management of COVID-19,[1] 40% of the patients were considered at high risk of VTE on the basis of the Padua Prediction Score[2] in a Chinese cohort with COVID-19; however, only 7% of all patients received anticoagulant drugs during hospitalization. In a previous Chinese multicenter study,[3] 36.6% of medical patients and 53.4% of surgical patients had a high risk of VTE during hospitalization, and only 6.0% and 11.8% of them, respectively, received an appropriate prophylactic. We have to say that routine thromboprophylaxis has not been routinely practiced in China.

Even so, our study has highlighted the importance of appropriate anticoagulant treatment for COVID-19 patients with coagulopathy. Close monitoring of coagulation markers and early intervention are critical. Further prospective studies are required to elucidate whether higher doses of anticoagulants will provide more benefits in COVID-19 patients with coagulopathy.

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CONFLICTS OF INTEREST

None declared.

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DIC in COVID-19: Implications for prognosis and treatment?

The ongoing COVID-19 pandemic is an exceptional challenge for health systems throughout the world. So far, no causative therapy nor protective vaccine are available. In several countries, the capacities for intensive care and for support for cases of acute respiratory distress syndrome (ARDS) are overstretched, and mortality is considerable. In this situation, useful prognostic parameters and targeted supportive treatment are urgently needed.

Recently, Tang et al[1] reported about the frequent occurrence of disseminated intravascular coagulation (DIC) in COVID-19 patients with serious respiratory failure. DIC, as diagnosed according to the validated International Society on Thrombosis and Haemostasis (ISTH) criteria,[2] was much more frequent in non-survivors (71.4%) than in survivors (0.6%). This suggests that establishing the diagnosis of DIC by the validated and recognized ISTH tool[2] might be useful as readily assessable prognostic parameter, warranting enhanced vigilance[3] and further research into pathophysiology and clinical impact of DIC in severe COVID-19.

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Moreover, it appears reasonable to formulate the hypothesis that DIC might not only be a concomitant finding, but even a pathophysiological process contributing to circulatory and organ failure, in COVID-19 particularly pulmonary damage. As well know from DIC, eg, in bacterial sepsis, disseminated fibrin deposits occur in the microvasculature, impairing the perfusion and thus performance of vital organs. In this context, it is of interest that in three patients with severe COVID-19 pneumonia induced ARDS tissue plasminogen activator (tPA) treatment resulted in documented but transient improvement of pulmonary function parameters.[4.] This would be compatible with the assumption that during tPA infusion the pulmonary microvasculature was partially reopened, but after terminating tPA the microthrombi increased again, due to the ongoing inflammatory stimulus perpetuating DIC.

If the above hypothesis is correct, it might be warranted to think about possible interventions to attenuate DIC and prevent further obstruction of organ microvasculature by fibrin deposits. The key player in the generation of fibrin deposits is thrombin. Thus, for decades several approaches of anticoagulation have been evaluated for beneficial effects in DIC, particularly in sepsis. These trials have been admittedly so far frustrating. For none of the approaches could a clear and proven survival benefit be demonstrated, as shown in a recent meta-analysis.[5] However, some of the clinical studies conducted so far had considerable flaws. For instance, the large randomized multicenter KyberSept trial[6] used exceedingly high antithrombin III (AT) doses, in many patients accompanied by effective heparin doses, resulting in excessive bleeding. In their meta-analysis,[5] Umemura et al showed that AT nevertheless did show a small reduction of mortality (risk ratio 0.63; 95% confidence interval [CI] 0.45; 0.90) in the subgroup of sepsis patients with DIC. Also, a recent summary[7] of systematic reviews found some evidence, albeit with low certainty, for a beneficial effect in sepsis-induced DIC, and mentioned that the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock weakly recommended the use of antithrombin for DIC patients with reduced antithrombin activities.

Thus, it might be time for reconsidering the interaction and modulating of different connected systems, eg, coagulation, fibrinolysis, kallikrein-kinin, complement, and immunity (cytokine storm), in order to elaborate a rationale for developing strategies for attenuating DIC in COVID-19. If such efforts are successful, it might have immense benefit also for intensive care patients far beyond the current crisis.

CONFLICTS OF INTEREST

Both authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Rainer Seitz wrote the manuscript; both authors contributed to the concept, literature search, and conclusions.

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Hereditary haemorrhagic telangiectasia: A disease not to be forgotten during the COVID-19 pandemic

Dear Editor,

From November 2019 to date, almost six thousand papers have been published on COVID-19, the disease caused by SARS-CoV-2 infection. As physicians working in a multidisciplinary center for the cure of hereditary haemorrhagic telangiectasia (HHT) in a country (Italy) that has been severely affected by COVID-19, we are surprised that, among this impressive amount of publications, there is none on HHT. Indeed, we performed our last PubMed search on

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