COVID-19 is Associated with an Acquired Factor XIII Deficiency

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Coronavirus disease 2019 (COVID-19) is associated with an increased risk of thrombotic complications.[1] Multiple lines of evidence support the existence of a hypercoagulable state in hospitalized COVID-19 patients. Enhanced platelet activation,[2] enhanced in vivo thrombin generation and ex vivo thrombin-generating capacity,[3,4] hyperfibrinogenaemia,[5] and ex vivo resistance to fibrinolysis[3,4,6,7] have all been demonstrated. Despite a marked ex vivo hypofibrinolytic state, erroneously referred to as 'fibrinolytic shutdown' by some researchers, patients with COVID-19 demonstrate fibrinolytic activity in vivo, as evidenced by elevated plasma levels of plasmin–antiplasmin complexes, and high plasma levels of D-dimer.[3] The hypercoagulable state in COVID-19 persists even in the presence of anticoagulant therapy, as evidenced by elevated plasma levels of thrombin–antithrombin complexes and by ex vivo whole blood viscoelastic tests.[3,5,8] Nevertheless, patients with COVID-19 on anticoagulant therapy may experience both bleeding and thrombotic complications.[9]

We have recently reported on the haemostatic status in a large cohort of COVID-19 patients and showed profound hypercoagulable changes.[10] In a continuation of our systematic assessment of haemostatic changes in COVID-19 patients, we unexpectedly detected a substantial decrease in plasma factor XIII (FXIII) activity.

Of a single-centre cohort of 102 patients with COVID-19, we had plasma of 97 patients available for FXIII assays. The majority of patients were admitted to general wards with 'mild' disease, and specifics on this cohort are described elsewhere.[10] Of the 97 patients included in this study, 54 and 23 patients received low-molecular-weight heparin once and twice daily, respectively, at the time of blood sampling. Four patients received oral anticoagulants, and 16 patients were not on any anticoagulation. We also studied 28 healthy controls to establish FXIII reference values. We measured FXIII activity as described previously.[11] Importantly, there is no interference of our FXIII activity assay by low-molecular-weight heparin levels up to 1 U/mL (data not shown). FXIII levels were substantially decreased in patients compared with controls. The decrease in FXIII levels was more pronounced in patients admitted to a high care facility compared with patients admitted to general wards. FXIII levels decreased proportionally with the level of respiratory support. FXIII levels were numerically lower in patients who died within 30 days of hospitalization compared with those who survived, although this difference was not statistically significant (►**Table 1**).

FXIII, after activation by thrombin, stabilizes the fibrin clot by cross-linking adjacent fibrin fibres and further increases resistance to fibrinolysis by cross-linking α-2 antiplasmin to the fibrin network.[12] In addition, FXIII mediates red blood cell retention within clots, which has been shown to facilitate venous thrombogenesis.[13] In the general population, acquired FXIII deficiency is a rare bleeding disorder that may be associated with life-threatening bleeding. Causes of acquired

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Table 1 Factor XIII levels in COVID-19 patients related to disease severity and 30-day mortality

	Factor XIII (%)
Healthy controls ($n = 28$)	103 [73–152]
COVID-19 patients ($n = 97$)	49 [34–78]
p-value	<0.0001
Based on location	
General ward ($n = 85$)	54 [37–81]
High care[a] ($n = 12$)	35 [31–42]
p-value	0.009
Based on level of respiratory support	
No respiratory support ($n = 36$)	57 [39–97]
Nasal cannula/mask $\leq$5 L O_2 ($n = 45$)	47 [32–79]
Higher respiratory support[b] ($n = 17$)	39 [32–63]
p-value	0.147
Based on 30-d survival	
Survivors ($n = 87$)	51 [35–79]
Non-survivors ($n = 10$)	38 [32–67]
p-value	0.204

Note: The results are presented as median [interquartile range]. Comparisons were made using the Mann–Whitney *U* test or Kruskal–Wallis test, as appropriate. *p*-values <0.05 were considered statistically significant.
[a]Three patients were admitted to the intensive care unit and nine patients were admitted to the intermediate care unit.
[b]Respiratory support in this group comprised >5 L O_2 by nasal cannula/mask ($n = 13$), non-invasive ventilation ($n = 2$), and intubation ($n = 2$).

FXIII deficiency include neutralization of FXIII by (auto)antibodies, consumption, and decreased synthesis.[14] Importantly, immune-mediated FXIII deficiency is associated with bleeding.[14] It is unclear whether FXIII deficiency associated with consumption (e.g., during major surgery) or decreased synthesis (e.g., in liver disease) is associated with bleeding and may benefit from FXIII replacement.[15] The mechanism underlying acquired FXIII deficiency in COVID-19 patients remains uncertain, but a consumptive mechanism seems likely. Even in patients receiving anticoagulation, there is continuing generation of thrombin (as evidence by elevated thrombin–antithrombin complex levels), with subsequent breakdown by the fibrinolytic system (evidenced by elevated plasmin–antiplasmin complexes and D-dimer levels). As D-dimers are derived from FXIIIa-mediated cross-linked fibrin, it seems likely that FXIII is consumed in this process of ongoing activation of coagulation. Indeed, both FXIII and D-dimer levels are related to COVID-19 disease severity.

We have identified a profound decrease in FXIII plasma levels in patients with COVID-19. Whether these decreased FXIII levels in part compensate for the hypofibrinolytic state of COVID-19, and perhaps even contribute to COVID-19-related bleeding, is an intriguing hypothesis that requires additional study.

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Conflict of Interest
None declared.

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