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Coagulation abnormalities and thrombosis in patients with COVID-19

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Although most patients with coronavirus disease 2019 (COVID-19) predominantly have a respiratory tract infection, a proportion of patients progress to a more severe and systemic disease, characterised by treatment-resistant pyrexia, acute lung injury with acute respiratory distress syndrome (ARDS), shock, and multiple organ dysfunction, associated with substantial mortality.[1] Many patients with severe COVID-19 present with coagulation abnormalities that mimic other systemic coagulopathies associated with severe infections, such as disseminated intravascular coagulation (DIC) or thrombotic microangiopathy, but COVID-19 has distinct features.[2] Coagulopathy in patients with COVID-19 is associated with an increased risk of death.[3] Furthermore, the relevance of COVID-19-coagulation abnormalities are becoming increasingly clear as a substantial proportion of patients with severe COVID-19 develop, sometimes unrecognised, venous and arterial thromboembolic complications.[4,5] In this Comment we summarise the characteristics of COVID-19 coagulopathy, coagulation laboratory findings in affected patients, the prohaemostatic state and incidence of thromboembolic events, and potential therapeutic interventions.

The most typical finding in patients with COVID-19 and coagulopathy is an increased D-dimer concentration, a relatively modest decrease in platelet count, and a prolongation of the prothrombin time. In a series[6] of 1099 patients with COVID-19 from China, elevated D-dimer (>0·5 mg/L) was found in 260 (46%) of 560 patients. In another observational study[3] in 183 patients with COVID-19 in China, a mean D-dimer concentration of 2·12 mg/L (range 0·77–5·27) was measured in patients who didn't survive compared to a concentration of 0·61 mg/L (0·35–1·29) in survivors. A third study[7] found that patients who were admitted to the intensive care unit (ICU) had significantly higher median D-dimer concentrations (2·4 mg/L, IQR 0·6–14·4) than patients who received no ICU care (0·5 mg/L, 0·3–0·8). In another study,[8] D-dimer on admission greater than 1 mg/L resulted in an 18-times increased risk of death (95% CI 2·6–128·6; p=0·0033).

The prothrombin time in patients with severe COVID-19 was shown to be mildly prolonged (15·6 s, range 14·4–16·3) in patients who died versus patients who survived (13·6 s, 13·0–14·3).[3] Of note, these subtle changes might go undetected when the prothrombin time is expressed as international normalised ratio (INR).

Studies[6,7] in consecutive patients with COVID-19 have reported that only about 5% of patients present with a platelet count of less than 100×10^9 cells per L. However, mild thrombocytopenia (a platelet count of $<150 \times 10^9$ cells per L) can be found in 70–95% of patients with severe COVID-19. Thrombocytopenia in COVID-19 has not been found to be an important predictor of disease progression or adverse outcome.[5,7]

Mean fibrinogen concentrations in patients with COVID-19 are at the upper limits of normal, presumably as an acute phase response. However, a sudden decrease in plasma fibrinogen to concentrations less than 1·0 g/L was observed shortly before death in a number of patients with COVID-19 in China.[3] Plasma concentrations of antithrombin are lower in COVID-19 non-survivors than in survivors (84% of normal in non-survivors *vs* 91% in survivors); however, plasma concentrations rarely drop below 80% of normal.[3]

The combination of thrombocytopenia, prolonged prothrombin time, and increased D-dimer is suggestive of DIC, although the pattern is distinctively different to DIC seen in sepsis.[2] In sepsis, thrombocytopenia is usually more profound, and D-dimer concentrations do not reach the high values seen in patients with COVID-19. In fact, most patients with COVID-19 would not be classified as having DIC according to the DIC score of the International Society on Thrombosis and Haemostasis.[2,3]

Other laboratory abnormalities in COVID-19 that might be relevant for the coagulopathy are increased lactate dehydrogenase (LDH), and in some patients, strikingly high ferritin concentrations reminiscent of findings in thrombotic microangiopathy.[8] Post-mortem findings in patients with COVID-19 show typical microvascular platelet-rich thrombotic depositions in small vessels of the lungs and other organs. However, there are no signs of haemolysis or schistocytes in the blood film and the platelet count is higher than would be expected in case of thrombotic microangiopathy (preprint reference; appendix).

See Online for appendix

Taken together, available evidence suggests that the coagulopathy associated with COVID-19 is a combination of low-grade DIC and localised pulmonary thrombotic microangiopathy, which could have a substantial impact on organ dysfunction in the most severely affected patients.

Severe COVID-19 is also associated with increased concentrations of proinflammatory cytokines, such as tumour necrosis factor-α (TNF-α) and interleukins (IL), including IL-1 and IL-6.[7] IL-6 can induce tissue factor expression on mononuclear cells, which subsequently initiates coagulation activation and thrombin generation. TNF-α and IL-1 are the main mediators driving a suppression of endogenous anticoagulant pathways. In a subset of patients most severely affected by COVID-19, a cytokine storm profile can be found, characterised by high concentrations of proinflammatory cytokines and chemokines.[9]

Coronavirus infections are also associated with a remarkable activation of the fibrinolytic system. Observations in urokinase-type plasminogen activator knock-out mice pointed to a urokinase-driven pathway stimulating fibrinolysis and being an important factor in lethality. In addition, plasma concentrations of tissue-type plasminogen activator (t-PA) were 6-times higher in patients infected with human severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) than in patients with no infection (appendix). Inflammation-induced endothelial cell injury could result in massive release of plasminogen activators, which could explain the high concentrations of D-dimer and fibrin degradation products in patients with severe COVID-19.

Thrombotic microangiopathy is typically caused by pathologically enhanced platelet-vessel wall interaction due to ultra-large von Willebrand factor multimers. These multimers are released from perturbed endothelial cells and are under normal circumstances cleaved by ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13). In many severe inflammatory states, upon systemic infection a secondary deficiency of ADAMTS13 has been established. Currently, there are no data on ADAMTS13 concentrations in patients with severe COVID-19 infection.

The coagulation changes associated with COVID-19 suggest the presence of a hypercoagulable state that might increase the risk of thromboembolic complications. Immobilisation and vascular damage are other factors that can increase the risk of thrombosis. Patients with COVID-19 have anecdotally been reported to have had pulmonary embolism, suggesting that there could be a disproportionately high incidence of venous thromboembolism and possibly arterial thrombosis in patients with COVID-19. In critically ill patients, the incidence of thromboembolic complications ranges from 5% to 15% (appendix). Initial cohort studies show that the incidence of thromboembolic complications in patients with COVID-19 is 35–45% (appendix).[10] Some people have also suggested that pulmonary embolism could be involved in the rapid respiratory deterioration seen in some patients,[10] but for practical reasons, doing adequate objective diagnostic testing is not always possible (eg, CT-angiography).

A retrospective study[4] done in China that included 449 patients admitted to hospital with severe COVID-19 infection showed a lower mortality in patients with COVID-19-associated coagulopathy who received prophylactic heparin than in patients not receiving anticoagulant treatment (40 [40%] of 99 patients *vs* 224 [64%] of 350 patients, p=0·029) in the subgroup of patients with a high sepsis-induced coagulopathy score. In particular, in patients with increased concentrations of D-dimer (6 times the upper limit of normal), mortality was lower in heparin-treated

Panel: **Management of coagulopathy in patients with severe COVID-19**

Diagnostic approach

- Repeated (every 2–3 days) assessment of:
  - D-dimer
  - Prothrombin time
  - Platelet counts

Therapeutic management

- Subcutaneous low molecular weight heparin for all patients hospitalised
- Consider venous thromboembolism in patients with rapid respiratory deterioration and high D-dimer concentrations
  - Do CT angiography or ultrasound of the venous system of the lower extremities
  - If diagnostic testing is not possible and there are no bleeding risk factors, consider therapeutic anticoagulation
- Other interventions (such as plasma exchange, or administration of other anticoagulants or anti-inflammatory drugs) are experimental and should be considered in a clinical trial setting only

patients than those not treated with heparin. These results need to be interpreted with caution, as heparin treatment was not random and the conclusions were drawn from multiple post-hoc, subgroup analyses. A prospective randomised controlled trial testing the effectiveness of prophylactic heparin for the prevention of COVID-19-assocated coagulopathy is warranted to confirm these results.

Using the available evidence, we suggest monitoring coagulopathy in patients with severe COVID-19 by measuring prothrombin time, platelet count, and D-dimer concentrations every 2–3 days (panel).[5] There is evidence supporting the use of prophylactic dose low molecular weight heparin (LMWH) as prophylaxis for venous thromboembolism in critically ill patients. In view of the hypercoagulable state of patients with severe COVID-19, and the potential increased risk of thrombosis, we suggest that all patients with COVID-19 that are admitted to hospital should receive this prophylactic treatment in the absence of medical contraindications. If LMWH is not available, unfractionated heparin could be used, although this requires more frequent injections; an alternative is fondaparinux, but whether this drug has the postulated anti-inflammatory benefits of heparin is unclear. Patients with severe COVID-19 might need higher-dose thromboprophylaxis than is generally given because of their hypercoagulable state, and this hypothesis will be tested in several multicentre, randomised, controlled trials (NCT04372589, NCT04367831, NCT04345848, and NCT04366960).

Preliminary observations suggest that in patients with high D-dimer concentrations and a sudden deterioration of respiratory insufficiency, pulmonary embolism should be part of the differential diagnosis. This diagnosis should be confirmed by imaging, although in some very unstable patients this might be difficult. Alternatively, venous ultrasound of the legs can be helpful to identify lower extremity thrombosis. In patients with a strong suspicion of pulmonary embolism in whom no objective diagnosis can be obtained, therapeutic anticoagulation could be started, particularly in the absence of risk factors for bleeding or other contraindications for anticoagulation. Of note, the incidence of haemorrhagic complications in patients with COVID-19, even those with severe coagulopathy, appear to be low.[4]

Other anticoagulant modalities have not yet been systematically studied in patients with COVID-19 and cannot be advocated at this point. Plasma exchange could be helpful as a treatment of thrombotic microangiopathy by delivering high volumes of plasma, replenishing missing factors (eg, ADAMTS-13 or complement proteins) and removing excess inflammatory mediators; however, this treatment needs to be further evaluated in a controlled trial setting.

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*Marcel Levi, Jecko Thachil, Toshiaki Iba, Jerrold H Levy
marcel.levi@nhs.net

Cardiometabolic Programme, National Institute for Health Research University College London Hospitals (UCLH) Biomedical Research Centre, London, UK (ML); Department of Medicine, UCLH National Health Service Foundation Trust, London, NW1 2PG, UK (ML); Department of Haematology, Manchester Royal Infirmary, Manchester, UK (JT); Department of Emergency and Disaster Medicine, Jutendo University Graduate School of Medicine, Tokyo, Japan (TI); and Department of Anesthesiology, Critical Care, and Surgery, Duke University School of Medicine, Durham, NC, USA (JHL)

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