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.

Overcoming bleeding events related to extracorporeal membrane oxygenation in COVID-19

Matthieu Schmidt and colleagues[1] aimed to establish the clinical characteristics and outcomes of patients with COVID-19 and respiratory failure treated with extracorporeal membrane oxygenation (ECMO). Among 83 patients, 30 (36%) died, 35 (42%) had major bleeding events, and four (5%) had a haemorrhagic stroke. When discussing the effectiveness of ECMO, an essential aspect is assessing whether the associated bleeding events are adverse incidents, or events resulting from abnormal coagulation.

Bleeding symptoms generally tend to be interpreted as adverse events related to heparin dissolved in the ECMO circuit. However, the amount of anticoagulant therapy used in their cases seemed to be appropriate and is unlikely to be the main cause of bleeding. Therefore, other mechanisms should be considered as reasons for bleeding under ECMO use in patients with COVID-19. Firstly, excessive fibrinolytic activation could occur. A report by Tang and colleagues[2] showed that in the severe cases of COVID-19 leading to death, elevated fibrinogen dropped sharply to 1·0 g/L, and mildly elevated fibrin degradation products increased to 100 μg/mL in just 3 days (day 7 to 10 after admission). During this period, elevations in D-dimer were relatively gradual, leading to a large discrepancy between fibrin degradation product and D-dimer concentrations. These data suggest disseminated intravascular coagulation with enhanced fibrinolysis, indicating the development of coagulation disorders in COVID-19 that could cause major clinical bleeding.[3] Another plausible mechanism is vascular endotheliitis, given that severe COVID-19 reportedly causes severe vascular endothelial injury and vascular vulnerability.[4] Acquired von Willebrand syndrome is also a possibility. During extracorporeal circulation, such as ECMO, high shear stress is known to destroy large multimers of von Willebrand factor.[5]

In critical COVID-19 cases that require ECMO, it can be assumed that the phase of disseminated intravascular coagulation often changes from a suppressed-fibrinolytic type to an enhanced-fibrinolytic type. However, because of the rapid conversion, this change might be overlooked unless blood coagulation tests (table) are done regularly. In the report by Schmidt and colleagues,[1] although the concentration of fibrinogen was increased at 6·4 g/L, the data obtained at early stages of the disease are not representative of the actual coagulation state at the time of bleeding events.

Follow-up data, such as fibrinogen and fibrinogen degradation product concentrations, or at least those at the time of major bleeding events, would be of interest to help elucidate the underlying mechanism of bleeding events. Such information might subsequently help to improve the survival of critically ill patients receiving ECMO.

	Importance of testing	Subsequent treatment
Platelets	Decreased due to various causes*	Treatment according to cause
Prothrombin time	(1) Screening for vitamin K deficiency (2) Liver failure	(1) Vitamin K supplementation (2) FFP replenishment, as needed
Activated partial thromboplastin time	(1) UFH monitoring (2) Screening for lupus anticoagulant (3) Screening for acquired haemophilia	(1) Increase or decrease in UFH dose (2) Monitor for increased thrombotic tendency (3) Treatment of acquired haemophilia
Fibrinogen	(1) Diagnosis of DIC (particularly enhanced-fibrinolytic-type)† (2) Screening for liver failure	(1) Treatment of DIC‡ (2) Supplement with FFP or fibrinogen concentrate, as needed
FDP or D-dimer	(1) Diagnosis of DIC (particularly enhanced-fibrinolytic-type)§ (2) Reflects lung injury	(1) Treatment of DIC‡ (2) Treatment of COVID-19
VWF (antigen and activity)	Screening for acquired von Willebrand syndrome¶	Supplementation of VWF concentrate and FFP, as needed

FFP=fresh frozen plasma. UFH=unfractionated heparin, DIC=disseminated intravascular coagulation. FDP=fibrin or fibrinogen degradation products. VWF=von Willebrand factor. ECMO=extracorporeal membrane oxygenation. *Causes of platelet count reduction in COVID-19 include COVID-19 itself,[6] DIC as a complication,[2] immune thrombocytopenia, antiphospholipid syndrome, haemophagocytic syndrome, heparin-induced thrombocytopenia, pseudo-thrombocytopenia, and drug-induced myelosuppression; platelet count decrease is also associated with ECMO.[7] †Rapid decrease in a few days.[2] ‡Nafamostat, an antithrombin drug with strong antiplasmin action, is effective against DIC with enhanced fibrinolysis,[3] and also has the effect of suppressing severe acute respiratory syndrome coronavirus 2 entry into host cells;[8] during ECMO, heparin and nafamostat combination therapy is inevitable, because UFH is also administered. §Rapid increase in a few days;[2] in DIC with enhanced fibrinolysis, FDP concentrations increase significantly, but D-dimer is only mildly to moderately elevated, resulting in a discrepancy between FDP and D-dimer concentrations.[2,3] ¶In acquired von Willebrand syndrome, VWF activity is lower than the amount of VWF antigen.

***Table*: Haemostatic markers, their clinical significance, and treatment**

We declare no competing interests.

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