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Author's Reply

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Response to "Etiology and Management of Bleeding during ECMO in a COVID-19 Patient"

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We thank Yamada, Ogawa, and Asakura[1] for their interest in our case report describing the management of bleeding in a COVID-19 patient during extracorporeal membrane oxygenation (ECMO). Our report[2] focused on the development of acquired von Willebrand syndrome (AVWS) due to ECMO in a COVID-19 patient in a thrombotic state. Fortunately for us, Yamada *et al.* expanded the discussion to include disseminated intravascular coagulation (DIC), which is another important cause of bleeding during ECMO.

Our patient[2] was diagnosed with enhanced-fibrinolytic-type DIC during ECMO treatment, based on the International Society on Thrombosis and Haemostasis (ISTH) diagnostic guidelines for DIC[3]. However, levels of D-dimer, thrombin–antithrombin complex (TAT), and plasmin-α2-plasmin inhibitor complex (PIC) were already increased before starting ECMO therapy. After ECMO was initiated, platelet counts rapidly decreased from a normal level to $<50 \times 10^9$/L, and the patient met the ISTH diagnostic criteria for DIC. As discussed in our report[2], the mechanisms of thrombocytopenia during ECMO treatment are multifactorial. The cause of thrombocytopenia in our case was unclear, but it could have been COVID-19, ECMO, DIC, or other conditions. Therefore, it was difficult to determine whether DIC was due to COVID-19, ECMO, or both.

Yamada *et al.* also described the treatment of a patient with COVID-19 and enhanced-fibrinolytic-type DIC[1]. They recommended using combination therapy with heparin and nafamostat. Nafamostat is a serine protease inhibitor that inhibits thrombin, plasmin, and trypsin[4], which explains its effectiveness against enhanced-fibrinolytic-type DIC. This drug has been used for the treatment of pancreatitis and DIC for >30 years, but only in Japan. The inhibitory effect of nafamostat on the coagulation pathway is weak compared with that on the fibrinolytic pathway. Therefore, Yamada *et al.*[1] recommended combination therapy with nafamostat and heparin, because the latter inhibits the coagulation pathway. Recently, Yamamoto *et al.*[5] reported that nafamostat has a direct viral effect against SARS-CoV-2, mediated by the inhibition of viral entry into host cells. Nafamostat might be effective against COVID-19 owing to both its antiviral and anti-DIC activity. However, the dose of nafamostat in DIC treatment is 10 times higher than that in pancreatitis treatment. The optimal dose of nafamostat for treating COVID-19 in combination with heparin remains unclear. Although nafamostat does not exhibit severe hemorrhagic side effects, its optimal dosage and the screening method for its efficacy should be established for clinical use. Further analysis is required to confirm the efficacy and safety of combination therapy with heparin and nafamostat in patients with COVID-19 who are undergoing ECMO.

Bleeding has often been observed in COVID-19 patients during ECMO[6]. Management of these patients with treatments such as cryoprecipitate and the combination of nafamostat and heparin should be analyzed in large-scale studies.

Conflicts of Interests

The authors declare no conflicts of interests.

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