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Letter to the Editor

Potential effect of blood purification therapy in reducing cytokine storm as a late complication of critically ill COVID-19

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Dear Editor,

We described three critically ill patients with coronavirus disease 2019 (COVID-19) in Wuhan, China, featured with profound inflammation and treated with blood purification therapies, including plasma exchange and adsorption. Potential effect in managing cytokine storm and pathogenic antibodies was shown. This added to the limited therapeutic options in these patients, and more efforts are proposed to further prove the benefits.

During the ongoing outbreak of COVID-19, 5–6% of the patients need ICU admission or even mechanical ventilation due to severe respiratory failure, with the mortality increasing from 1.4% to over 60% [1,2]. Non-survivors, with profound hypoxia and inflammatory response, are more likely to develop acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome [2,3]. Additionally, reduced peripheral lymphocytes, high levels of C-reactive protein (CRP) and IL-6, and significantly abnormal coagulation parameters are hallmarks in those severe cases [4,5]. Emerging evidence indicates the potential benefits of managing cytokine storm, via using steroid or IL-6/IL-6-receptor blocking antibodies [3,6]. The capability of blood purification therapy in removing pathogenic antibodies or cytokines has been proven in multiple scenarios, but not in COVID-19 patients [7,8].

The first case was a 69-year-old man without remarkable past medical history. He felt fever and lethargy on Jan 16, and diagnosed with COVID-19 by positive IgM/IgG anti-SARS-CoV-2 antibody and bilateral ground glass shadows in chest computed tomography (CT) one week later. Treated with antibiotics and Ribavirin, his fever persisted and aggravated dyspnea developed. On February 5, endotracheal intubation was performed because of severe respiratory failure. On February 20, he was transferred to our ICU, ventilated at pressure control (PC) mode with a fraction of inspired oxygen (FiO2) of 40% and positive end-expiratory pressure (PEEP) of 8cmH_2O. Lab tests showed persistent leukopenia (0.71×10^9 /l) and elevated inflammation (CRP 105.5 mg/l [reference 0-3 mg/l], IL-6 54.57 pg/ml [reference 0-7 pg/ml]). We treated him with antibiotics, gamma globulin and other supportive therapies. Then, we observed a continuous decrease of platelet count (minimum value 32×10^9 /l on March 6), increase of D-dimer (maximum value 19.73μg/ml on March 6) and inflammatory markers (maximum CRP 192.7 mg/l, IL-6236.3 pg/ml on March 9), while his prothrombin time (PT) remained stable. On March 5, dry gangrene appeared in his right index finger. Within one week, we confirmed multiple cerebral infarction with brain CT and bilateral jugular venous thrombi with doppler ultrasound. On March 11, antiphospholipid antibodies were positive for anti-β2 glycoprotein-I (anti-β2GPI-IgG 258.1CU [reference 0-20CU] and anticardiolipin (aCL-IgG 43.2CU [reference 0-20CU]). Antiphospholipid syndrome (APS) was diagnosed and he was treated the low molecular weight heparin and aspirin. From March 14 to 16, we performed three sessions of plasma exchange, after which dramatic reduction of the titers of antiphospholipid antibodies and inflammatory marker were observed (anti-β2GPI-IgG 45.1CU, aCL-IgG 8.3CU, CRP 44.4 mg/l, IL-6 92.05 pg/ml) (Fig. 1). On March 24, this patient was successfully weaned from ventilator and remained clinically stable till now.

The second case was a 65-year-old man with hypertension. He presented fever, dyspnea and diarrhea on Jan 26, 2020. One week later, he was diagnosed with COVID-19 by reverse real-time transcriptase polymerase chain reaction. He was hospitalized with worsen dyspnea on Feb 2. Lab tests showed leukopenia (0.44×10^9 /l) and elevated inflammatory marker (CRP 67.6 mg/l, IL-6 46.76 pg/ml). He was treated with antibiotics, Arbidol, methylprednisolone and oxygen therapy. On Feb 16, his respiratory failure required endotracheal intubation and mechanical ventilation (PC mode, PC 20cmH_2O, PEEP 14cmH_2O, FiO_2 50%). And refractory respiratory acidosis and hypoxia (ABG PH 7.20, O_2 55mmHg, CO_2 69 mmHg) led to venous-venous extra corporeal membrane oxygenation (vv-ECMO) therapy. Meanwhile, we treated him with antibiotics, gamma globulin, hydrocortisone and other supportive therapy. His leukopenia and inflammatory marker elevation persisted (lymphocyte 0.16×10^9 /l, CRP 259.3 mg/l, IL-6556.3 pg/ml). On Feb 19, he experienced sudden death and was successfully resuscitated, after which continuous renal replacement therapy (CRRT) was initiated. It was performed with the oXiris® hemofilter (Baxter, Meyzieu, France), a modified AN69 surface treated membrane with adsorption capacity [9]. The hemofilter was changed every 12–24 h for 6 days, and his lab tests were improved (lymphocyte 0.43×10^9 /l, CRP 154.9 mg/l, IL-6 78.22 pg/ml) (Fig. 1). However, he experienced multiple complications, including refractory disseminated intravascular

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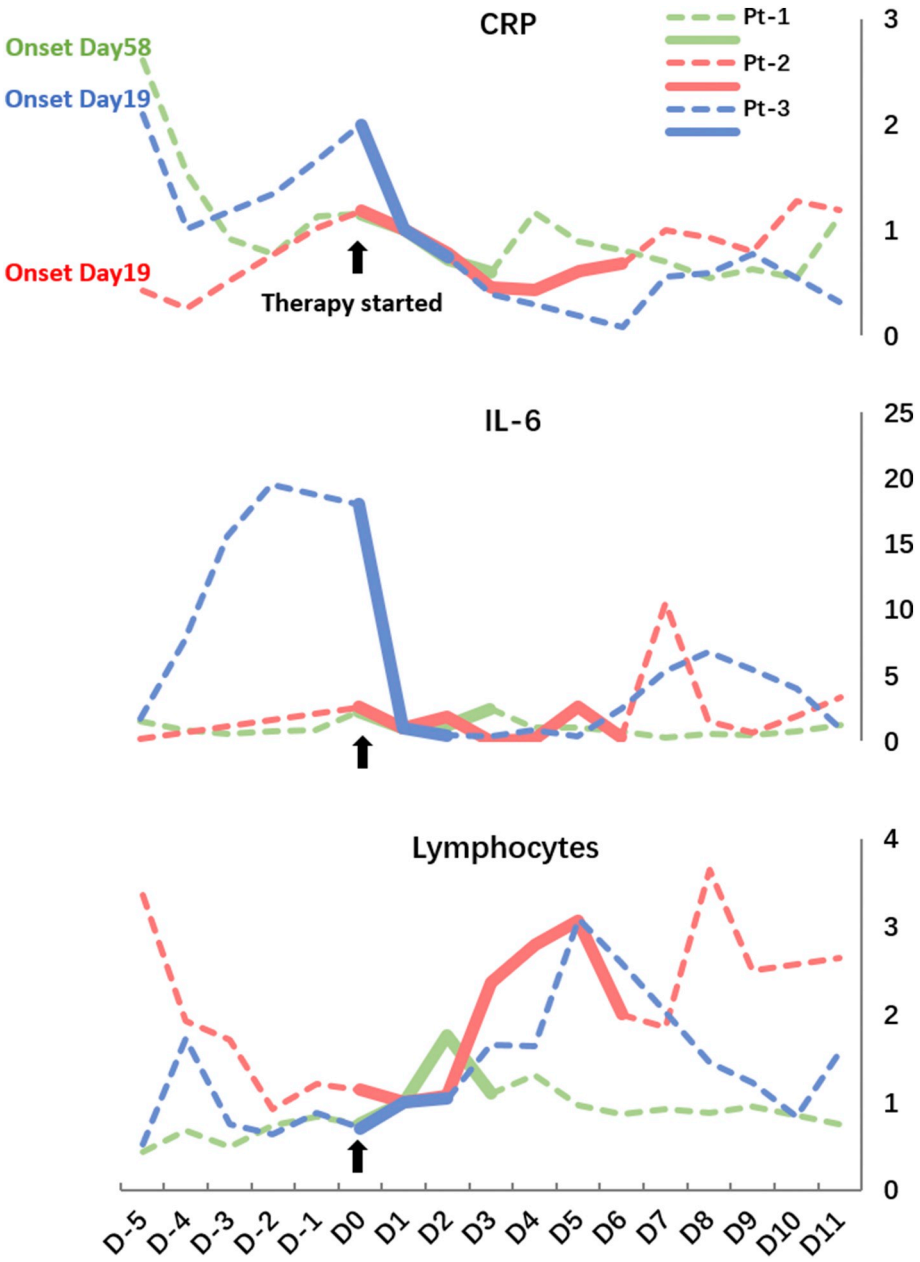

Fig. 1. The effect of blood purification therapy on inflammation markers and lymphocytes.The values of CRP, IL-6 and lymphocyte number were normalized, with reference to the first day of blood purification therapy (D1 in the figure). The dotted lines represented the data when patients were not on therapy, while the solid lines were data during the therapy.

coagulation (DIC) and right lung pneumothorax. On March 6, he had another sudden death and the resuscitation was not successful.

The third case was a 56-year-old man without any underlying disease. He was admitted to a local hospital on Feb 14, reporting fever and fatigue for one week. A diagnosis of COVID-19 was confirmed by positive IgM/IgG anti-SARS-CoV-2 antibody and chest CT. He was first treated with Lopinavir and Ritonavir, and transferred to our ICU due to respiratory failure on Feb 16. He was given endotracheal intubation and mechanical ventilation (PC mode, PC 16cmH_2O, PEEP 16cmH_2O, FiO_2 70%). Lab tests showed leukopenia (0.21 $\times$ 10^9 /l) and inflammation (CRP 144 mg/l, IL-6 29.32 pg/ml). We treated him with antibiotics, gamma globulin and other supportive therapy. His leukopenia persisted and inflammation intensified (CRP 298.4 mg/l, IL-6304.4 pg/ml) until Feb 23. We gave methylprednisolone and CRRT with oXiris® hemofilter on Feb 24. On Feb 26, we stopped CRRT because the inflammatory markers were almost normalized in two days (CRP 59.1 mg/l, IL-6 5.63 pg/ml) (Fig. 1). His ventilator's setting was quickly downregulated and the weaning was successful on March 1. He was transferred out of the ICU for rehabilitation on March 7.

Our knowledge of critically ill COVID-19 in the late phase was quite limited. These cases highlight the presence of cytokine storm or pathogenic antibodies after three weeks of COVID-19 onset (Fig. 1), which correlated with the disease severities. Monitoring inflammation and antibodies are important especially in patients infected by virus with persistent fever or abnormal coagulopathy. Expeditious control of the cytokine storm in early phase might be beneficial to selective patients, and blood purification therapy is effective in our limited experiences. The therapies are tolerable to most patients if performed with the assistance of nephrology specialists, in order to minimize risks of infection and bleeding. Although randomized trial data is lacking, we propose that multi-disciplinary efforts should be made to maximize the availability of blood purification therapy to proper patients.

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Declaration of Competing Interest

All other authors declare no competing interests.

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