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.

Cytokine adsorption and ECMO in patients with COVID-19

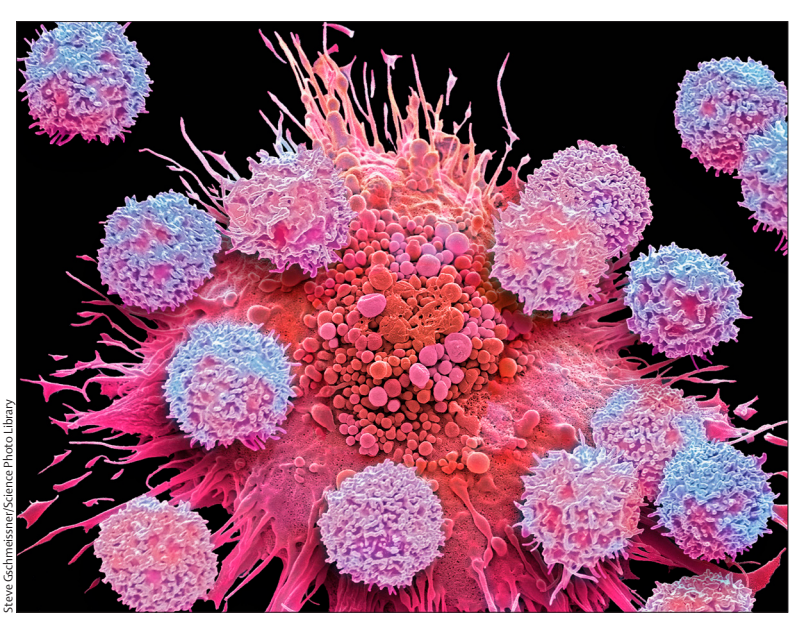
We read with interest the CYCOV trial by Alexander Supady and colleagues,[1] in which the authors describe extracorporeal membrane oxygenation (ECMO) support in patients with severe COVID-19 combined with cytokine adsorption. The authors conclude that cytokine adsorption during the first 72 h of ECMO support did not result in reduced interleukin (IL)-6 concentrations after 72 h, that cytokine adsorption was associated with an increased mortality risk within 30 days after initiation of ECMO, and that early cytokine adsorption should be avoided in patients with COVID-19 requiring venovenous ECMO support. Several comments can be made regarding these statements.

First, we suggest that the most important limitation of the trial is that the patient models were unevenly grouped, notwithstanding the randomisation. The patients in the cytokine adsorption group were sicker: there were more patients with chronic multimorbidity in this group. These patients were started on mechanical ventilation right after hospital admission (number of days from hospital admission was equal to duration of non-invasive and invasive ventilation before ECMO), which also points to them being in a poorer condition. Some of them had been ventilated for 11 days until they were started on ECMO. This approach openly contradicts the European Extracorporeal Life Support Organisation (EuroELSO) recommendations for 3 days mean mechanical ventilation time before ECMO initiation. 7 days of mechanical ventilation is a direct contraindication for ECMO according to guidelines.[2] We consider that violation of this recommendation added to poor clinical outcomes of the patients who were sicker in the cytokine adsorption group. On the contrary, mean ventilation time in the control group was 4–8 days, which is maximally close to EuroELSO ECMO initiation guidelines.[2] It is hardly a surprise that respiratory parameters were worse in the cytokine adsorption group: because these patients had lower ratio of the partial pressure of oxygen in arterial blood to the fractional concentration of oxygen in inspired air (PaO_2/FiO_2) and lower arterial PaO_2, they required 5-times more norepinephrine.

Second, ECMO is a life supporting therapy and thus all studies involving patients on ECMO support shall list the ECMO parameters. Specifically, the pressure in the circuit is responsible for the blood flow in the arteriovenous shunt, where an adsorption device is installed. The use of small diameter cannulas results in a greater pressure gradient between arterial and venous line, thus creating a greater blood flow through the adsorption device shunt, which provokes suboptimal flow in the main line and deprives the patient of adequate gas exchange. Such parameters as ECMO circuit type, ECMO flow, and ECMO duration were not described in this trial.

Third, the treatment of patients in each group was different. According to the worldwide accepted approaches for COVID-19 treatment, the use of lopinavir–ritonavir and remdesivir is not recommended for severe COVID-19 treatment;[3,4] all such patients should be prescribed glycocorticosteriods.[5] However, not all patients in both groups received an evidence-based therapy.

Fourth, the mean concentrations of IL-6 listed (357·0 pg/mL adsorption *vs* 289·0 pg/mL controls) are too low to be treated by haemoadsorption. In our understanding, cytokine storm is characterised by higher concentration of IL-6 and other cytokines in the setting of fever and normal or low C-reactive protein and procalcitonin values. Given the lack of a unifying definition of cytokine storm,[6] the extent of elevation of cytokines should be greater than 500 pg/mL for a patient with COVID-19 to be eligible for cytokine adsorption. The authors state that they sought to clarify the benefit of cytokine adsorption in patients with COVID-19 supported with venovenous ECMO, but then the adsorption should be started earlier. In previous publications, early haemoadsorption is started



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24–48 h after diagnosis,[7,8] whereas in the CYCOV trial, haemoadsorption was started much later. We feel compelled to add that haemoadsorption in patients with COVID-19 should be started at intensive care unit (ICU) admission and continued until stable improvement. Considering previous published evidence, patients with COVID-19 receiving ECMO support tend to stay in the ICU longer than 30 days, so assessing 30-day mortality might not be the optimal outcome in such a trial.

In conclusion, we agree with Kiran Shekar and colleagues' Comment[9] that future studies require better design, but stating that the intervention is associated with apparent harm as a result of one single-centre study is unreasonable. Most of the available evidence indicates a clear signal towards a positive clinical effect for cytokine adsorption in COVID-19. More studies with detailed inclusion criteria are needed to estimate issues such as haemoadsorption initiation times, its effect on mortality and survival rates, and its effects on patients with severe COVID-19.

We declare no competing interests.

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