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.

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Does adjunctive hemoadsorption with CytoSorb affect survival of COVID-19 patients on ECMO? Authors' response

We thank Thomas Köhler and co-authors for critically discussing the results of the "Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation" (CYCOV) trial that were recently published in *The Lancet Respiratory Medicine* [1,2]. We would like to take the opportunity to respond to the authors' concerns regarding the interpretation of the results of the CYCOV trial and add some clarification. We have discussed similar questions before and, in particular, have rebutted concerns that the higher mortality of patients treated with cytokine adsorption could be explained by the fact that these patients had been sicker at study inclusion [3].

Köhler et al. questioned the validity of the results by suggesting that it "seems implausible the CytoSorb should be the only difference in between the groups". We strongly reject this concern. As described in the manuscript, patients were properly randomized and treated in both groups according to the specifications of the study protocol. Indeed, the only treatment difference was the use of CytoSorb (CytoSorbents Corporation, Monmouth Junction, NJ, USA) in the treatment group.

Furthermore, the indication for CytoSorb in the CYCOV trial was challenged. We would like to point out that currently there are no generally accepted criteria for the indication of CytoSorb or other hemoadsorption procedures [4]. We set out to examine this in the prospectively planned randomized controlled CYCOV trial. Inclusion criteria in our trial were thoroughly defined. The rationale for the use cytokine adsorption in the CYCOV trial was not only inflammation due to coronavirus disease 2019 (COVID-19), but also additional activation of inflammatory response by the initiation of extracorporeal membrane oxygenation [5,6].

Additional concern relates to the reporting of the dose of cytokine adsorption administered to each patient. Köhler et al. suggest to report the amount-of-blood-purified (ABP) as introduced previously [7]. We understand the rationale for describing the applied dose, however, we doubt that there is sufficient evidence to promote the use of ABP. So far, ABP was only described in a small single-center analysis and was not validated externally. The relationship between CytoSorb dose determined by ABP and survival requires further investigation, particularly because of the retrospective design of the analysis and the lack of a control group [7].

We agree that comparably low interleukin (IL)-6 levels in the CYCOV trial cohort could potentially explain the missing positive effect of cytokine adsorption. It is also true that IL-6 may not be the optimal parameter for assessing the effectiveness of therapy with CytoSorb, as previously discussed [7]. This consideration is consistent with observations from another retrospective analysis [8]. However, this cannot explain the association of cytokine adsorption with mortality in the CYCOV trial. Survival of patients treated with cytokine adsorption was significantly lower than survial in the control group (18% vs. 76%). Our observation should be taken seriously and requires that further use be carefully reviewed and monitored. We propose that additional randomized trials are required to assess hemoadsorption in patients requiring extracorporeal membrane oxygenation for severe COVID-19 acute respiratory distress syndrome. These patients should not be treated with hemoadsorption outside of clinical trials.

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Contributors

AS wrote the first draft of the manuscript, DD revised the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

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References

[1] Supady A, Weber E, Rieder M, Lother A, Niklaus T, Zahn T, et al. Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation (CYCOV): a single Centre, open-label, randomised, controlled trial. Lancet Respir Med. 2021;9(7):755–62.

[2] Köhler T, Schwier E, Henzler D, Eickmeyer C. Does adjunctive hemoadsorption with CytoSorb affect survival of COVID-19 patients on ECMO? A critical statement. J Crit Care. 2021.

[3] Supady A. Cytokine adsorption and ECMO in patients with COVID-19 - Author's reply. Lancet Respir Med. 2021;9(8):e72–4.

[4] Badulak J, Antonini MV, Stead CM, Shekerdemian L, Raman L, Paden ML, et al. Extracorporeal membrane oxygenation for COVID-19: updated 2021 guidelines from the extracorporeal life support organization. ASAIO J. 2021;67(5):485–95.

[5] Cho HJ, Kayumov M, Kim D, Lee K, Onyekachi FO, Jeung KW, et al. Acute immune response in Venoarterial and Venovenous extracorporeal membrane oxygenation models of rats. ASAIO J. 2021;67(5):546–53.

[6] Millar JE, Fanning JP, McDonald CI, McAuley DF, Fraser JF. The inflammatory response to extracorporeal membrane oxygenation (ECMO): a review of the pathophysiology. Crit Care. 2016;20(1):387.

[7] Schultz P, Schwier E, Eickmeyer C, Henzler D, Köhler T. High-dose CytoSorb hemoadsorption is associated with improved survival in patients with septic shock: a retrospective cohort study. J Crit Care. 2021;64:184–92.

[8] Scharf C, Schroeder I, Paal M, Winkels M, Irlbeck M, Zoller M, et al. Can the cytokine adsorber CytoSorb(®) help to mitigate cytokine storm and reduce mortality in critically ill patients? A propensity score matching analysis. Ann Intensive Care. 2021;11(1):115.

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