

## Comment on Hu et al: The cytokine storm and COVID-19

To the Editor,

We read with interest the excellent review by Hu et al<sup>1</sup> published in the recent issue of the *Journal of Medical Virology*. The authors outlined the main pathophysiologic features of the cytokine storm, which was linked to fulminant severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (coronavirus disease 2019 [COVID-19]) and its putative therapies, in the absence of effective vaccines and antiviral treatment. The strict biological diagnosis of cytokine release syndrome (CRS) related to COVID-19 remains poorly defined.<sup>2</sup> In clinical studies, a growing amount of evidence suggests that a minority of patients with COVID-19 can develop the life-threatening disease, which is characterized by acute respiratory distress syndrome (ARDS), multisystem organ failure, thromboembolic disease, neurological manifestations, and CRS.<sup>3-8</sup> Hu et al shared various putative therapies in treating COVID-19 associated CRS such as the monoclonal antibody (tocilizumab) against interleukin-6 (IL-6), corticosteroids, and convalescent plasma transfusion (CPT), which showed promise although their results are either still debatable or pending.<sup>9,10</sup> Herein, we wish to outline another treatment option that we feel was not adequately addressed.

Our group applied therapeutic plasma exchange (TPE), without protective antibodies, to treat patients with life-threatening COVID-19 and associated CRS. We defined the latter by using pertinent inflammation biomarkers such as C-reactive protein, lactate dehydrogenase, ferritin, and IL-6 amongst others.<sup>11,12</sup> Our clinical observation was that a minority of critically ill COVID-19 patients can present with a fulminant disease, which is associated with high sequential organ failure assessment (SOFA) scores, and increased levels of inflammatory biomarkers. Hence, we performed TPE, during the early stages of fulminant COVID-19, using the Spectra Optia Apheresis System, which operates with acid-citrate dextrose anticoagulant as per kidney disease improving global outcomes 2019 guidelines.<sup>11,13</sup> TPE can remove significant proportions of interferon-gamma, IL-3, IL-10, IL-1B, IL-6, IL-8, and tumor necrosis factor- $\alpha$ .<sup>11</sup> Our feasibility study showed a putative beneficial effect on the survival of these critically ill COVID-19 patients. Moreover, we found that TPE can significantly reduce the levels of inflammatory biomarkers in patients with life-threatening COVID-19. No side effects of TPE such as allergies, infections, coagulopathy, and deterioration of renal or cardiac function were observed.

The exaggerated inflammatory immune response and microthrombosis in COVID-19 results in multisystem organ failure with fatal outcomes.<sup>1-11</sup> Unlike several immunomodulatory therapies, there is no immunosuppression associated with plasma exchange. In our study, the decrease in inflammatory markers was associated with a sustained

increase of lymphocytes counts as others also observed.<sup>11,14</sup> Whether the drop in proinflammatory cytokine levels following TPE might be caused by the increments in lymphocyte counts, and not due to the reduction of these cytokines per se remains to be elucidated in future studies. We did not measure any specific subtypes of lymphocytes as this was not one of the study endpoints. However, we observed that after TPE, the decrease in inflammatory biomarkers was associated with a concomitant amelioration of oxygenation and SOFA scores.<sup>11</sup> No side effects of therapy such as allergies, infections, coagulopathy, and deterioration of renal or cardiac function were observed.

CPT was previously described as rescue therapy in severe COVID-19.<sup>15</sup> However, this therapy is more technically demanding, and time-consuming compared to TPE.<sup>16</sup> Moreover, the overall benefit of CPT on survival in critically ill patients with COVID-19 remains debatable as a recent randomized control trial suggested.<sup>17</sup> Another issue with CPT, but not TPE, is the putative risk of antibody-dependent infection enhancement.<sup>18</sup> This might suppress innate immunity, and, thus, facilitate intracellular viral growth. Hence, TPE might be an alternative rescue therapy for life-threatening COVID-19 compared to CPT, especially if natural immunity after SARS-CoV-2 infection does not arise.<sup>17,19</sup> Also, the natural course of SARS-CoV-2 viremia is still undetermined as reinfections and/or recurrently positive reverse transcriptase-polymerase chain reaction results were reported.<sup>20,21</sup>

TPE and other extracorporeal blood purification modalities were utilized in the treatment of sepsis in clinical trials.<sup>22</sup> In contrast, the role of TPE in treating refractory ARDS with associated CRS was partially explored in the previous SARS-CoV outbreak.<sup>23</sup> In this pandemic, we are facing a respiratory virus, SARS-CoV-2, which showed a versatile organotropism for extrapulmonary targets nevertheless.<sup>24</sup> SARS-CoV-2 can bind to the angiotensin-converting enzyme 2 receptor promoting endothelial injury, and thromboinflammation, on the grounds of dysregulated renin-angiotensin-aldosterone and immune systems' responses. We agree with Hu et al that the reduction of pivotal cytokines such as IL-6 and/or the generalized suppression of the ensuing dysregulated inflammatory response in rapidly evolving severe COVID-19 may be indeed a key therapeutic approach in a subset of critically ill patients. In our study, we employed TPE early in the course of fulminant COVID-19 to suppress the development of a full-blown CRS. Presumably, at this stage of COVID-19, hyperinflammation and dysregulated immune system response may be more important than viral replication per se. This theory was also suggested in the RECOVERY trial, which showed a beneficial effect on survival in critically ill patients with COVID-19 due to the administration of low-dose dexamethasone.<sup>25</sup>

The use of TPE, which is a relatively safe and accessible therapeutic modality, could enrich our therapeutic arsenal in the fight against life-threatening COVID-19. Surely, the availability of TPE equipment and trained staff varies worldwide; moreover, the application of TPE requires close monitoring, preferably in a high-dependence unit. TPE still carries the risk of exposure to a highly transmissible virus; hence, proper application of personal protective equipment by the staff, careful handling of the TPE devices, and utilization of the pertinent disposables as biohazardous materials are deemed to be necessary as should be the case for all extracorporeal blood purification therapies used in patients with COVID-19. Obviously, TPE is not superior to other immunomodulatory therapies that were previously used in COVID-19, instead it should be considered as an adjunctive safe therapeutic strategy in life-threatening disease. Larger prospective studies are necessary to investigate the role of potential immunomodulatory therapies against life-threatening COVID-19 with associated CRS.

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#### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

#### AUTHOR CONTRIBUTIONS

All authors have equally contributed in drafting this manuscript.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

#### ETHICS STATEMENT

This study was approved by our Institutional Review Board (protocol/serial numbers: H-01-R-053, IORG0010374, and H1R1-29-20-01). Written informed consent was obtained by the patients or their legal representatives. Also, the study is registered at ISRCTN21363594; <https://doi.org/10.1186/ISRCTN21363594>.

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