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Review

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Application of extracorporeal therapies in critically ill COVID-19 patients

Zhifeng ZHOU[1]✉, Huang KUANG[2], Yuexian MA[3], Ling ZHANG[1]✉

[1]*Department of Nephrology, Kidney Research Institute, West China Hospital, Sichuan University, Chengdu 610041, China*
[2]*Renal Division, Peking University First Hospital, Peking University Institute of Nephrology, Key Laboratory of Renal Disease, Ministry of Health of China, Beijing 100034, China*
[3]*Department of Nephrology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu 610072, China*

Abstract: The coronavirus disease 2019 (COVID-19) pandemic is a major public health event caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 has spread widely all over the world. A high proportion of patients become severely or critically ill, and suffer high mortality due to respiratory failure and multiple organ dysfunction. Therefore, providing timely and effective treatment for critically ill patients is essential to reduce overall mortality. Convalescent plasma therapy and pharmacological treatments, such as aerosol inhalation of interferon-α (IFN-α), corticosteroids, and tocilizumab, have all been applied in clinical practice; however, their effects remain controversial. Recent studies have shown that extracorporeal therapies might have a potential role in treating critically ill COVID-19 patients. In this review, we examine the application of continuous renal replacement therapy (CRRT), therapeutic plasma exchange (TPE), hemoadsorption (HA), extracorporeal membrane oxygenation (ECMO), and extracorporeal carbon dioxide removal ($ECCO_2R$) in critically ill COVID-19 patients to provide support for the further diagnosis and treatment of COVID-19.

Key words: Coronavirus disease 2019 (COVID-19); Critical illness; Cytokine release syndrome (CRS); Acute kidney injury (AKI); Extracorporeal therapy

1 Introduction

At the end of 2019, a new type of coronavirus pneumonia with unknown etiology spread rapidly throughout the world and presented a major threat to public health (Din and Boppana, 2020; Li L et al., 2020; Rothan and Byrareddy, 2020; Velavan and Meyer, 2020). On February 11, 2020, the World Health Organization (WHO) officially named this disease "coronavirus disease 2019 (COVID-19)." It was confirmed that it is caused by a new type of β coronavirus (currently known as "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)") (Lu et al., 2020; Shi et al., 2020). COVID-19 is a respiratory disease not only characterized by viral pneumonia, but in critically ill patients, also often associated with injury to multiple organs, such as the kidney, heart, blood, and nervous system (Azoulay et al., 2020). A large proportion of COVID-19 patients become severely or critically ill, and these patients have high mortality. A summary of 72 314 cases of COVID-19 from China reported 14% severely ill and 5% critically ill patients, with a high fatality rate of 49% in the critical cases (Wu and McGoogan, 2020). In a multicenter retrospective study of 119 middle-aged COVID-19 patients, 18 (15.1%) patients developed severe illness (Wang P et al., 2020). In a larger study of 1099 patients with COVID-19, Guan et al. (2020) reported 173 (15.7%) severely and critically ill patients. In a retrospective cohort study (Nachtigall et al., 2020), 399/1860 (21.4%) of COVID-19 patients were admitted to the intensive care unit (ICU), and 250/1850 (13.5%) required invasive mechanical ventilation (IMV). Moreover, in some early reports of COVID-19 from China, the fatality rate of critically ill COVID-19 patients reached 52%–62% (Wu CM et al.,

✉ Ling ZHANG, zhangling_crrt@163.com
Zhifeng ZHOU, zhouzf97@163.com
Ling ZHANG, https://orcid.org/0000-0003-1155-4802
Zhifeng ZHOU, https://orcid.org/0000-0003-3160-589X

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2020; Yang XB et al., 2020; Zhou et al., 2020). Recent data from the USA show a fatality rate of 50%−67% among such patients (Bhatraju et al., 2020; Capone et al., 2020). Such high fatality rates seriously threaten human life and health. Therefore, there is an urgent need to find effective therapeutic strategies to reduce the mortality of critically ill COVID-19 patients.

Currently, there are many treatments for COVID-19 patients. Aerosol inhalation of interferon-α (IFN-α) can be used for antiviral treatment (Jin et al., 2020). The early application of convalescent plasma therapy can reduce mortality (Mair-Jenkins et al., 2015). Immunosuppressants like tocilizumab can bind to both soluble interleukin-6 receptor (sIL-6R) and membrane-bound interleukin-6 receptor (mIL-6R) to inhibit the release of interleukin-6 (IL-6). This may reduce the degree of inflammation in the body, thereby improving the clinical symptoms of patients (Zhao et al., 2020). However, these treatments are controversial and may not be effective when treating critically ill patients.

Recently, extracorporeal therapies have played a particularly important role in the treatment of critically ill COVID-19 patients. As adjuvant therapies for sepsis, extracorporeal therapies, such as therapeutic plasma exchange (TPE) and immunoadsorption (IA), can target cytokines and/or endotoxins and protect organ functions, and have been successively used in the treatment of critically ill patients (Yiğenoğlu et al., 2020). Extracorporeal therapies have also achieved certain effects in the treatment of COVID-19 patients, especially those who are critically ill. They are an effective measure to prevent organ failure and improve the survival rate of COVID-19 patients (Ronco et al., 2021). In this review, we discuss the application of extracorporeal therapies in critically ill COVID-19 patients to provide assistance for the further treatment of COVID-19.

2 Characteristics of critical COVID-19

When SARS-CoV-2 enters the nasal epithelial cells in the upper respiratory tract via angiotensin-converting enzyme 2 (ACE2), viral replication and local propagation occur, accompanied by a limited immune response (Hoffmann et al., 2020). Then, the virus invades and enters the type II pulmonary alveolar epithelial cells via ACE2, thereby causing a greater immune response with the release of inflammatory markers and many different cytokines (Wu et al., 2021). Continuing viral replication and infection of pulmonary alveolar epithelial cells leads to acute respiratory distress syndrome (ARDS) (Parasher, 2021). After viral infection, some patients progress to severe or critical illness. The WHO estimates that about 14% of COVID-19 patients develop severe illness, and 5% critical illness. The progression of disease in severe COVID-19 patients is usually rapid and there is no clear distinction between severe and critical illness. Combining these two classes might be helpful to diagnose and treat patients with intensive care in the early stages of critical illness (Li Q et al., 2020). According to diagnosis and treatment guidelines, severe patients manifest dyspnea, a respiratory rate of ≥30 min^{-1}, blood oxygen saturation of ≤93%, ratio of arterial oxygen partial pressure (PaO_2) to fractional inspired oxygen (FiO_2) of <300, and/or lung infiltrates of >50% within 24 to 48 h. Critical patients may present signs of respiratory failure requiring mechanical ventilation, septic shock, and/or multiple organ dysfunction or failure, requiring admission to ICUs (Wu and McGoogan, 2020).

3 Cytokine release syndrome in COVID-19 patients

Cytokine release syndrome (CRS), also known as a cytokine storm, is an excessive immune response of the host to viruses, bacteria, or other external stimuli, which is manifested by the uncontrolled release of inflammatory factors (Diamanti et al., 2020). CRS can transform COVID-19 patients from mild to severe, and from single organ damage to multiple organ dysfunction syndrome (MODS), which plays an important role in the pathological process of COVID-19 patients (Huang et al., 2020). However, some researchers now believe that COVID-19 patients do not have the characteristics of CRS. They have observed that the circulating cytokine levels of critically ill COVID-19 patients are lower than those of patients with bacterial sepsis or of other critically ill patients, which is not high enough to be regarded as a cytokine storm (Kox et al., 2020). However, SARS-CoV-2 infection can certainly lead to an uncontrolled immune function and a significant elevation of inflammatory cytokines such as C-reactive protein (CRP), IL-6, IL-10, monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor-α (TNF-α). This may cause hemodynamic

instability, shock, disseminated intravascular coagulation (DIC), and even MODS (García, 2020), all of which have obvious adverse effects on the healing of critically ill COVID-19 patients.

4 Kidney damages in COVID-19 patients

Variable degrees of kidney damage have been observed in substantial studies of critically ill COVID-19 patients. Acute kidney injury (AKI), hematuria, and proteinuria are common in COVID-19 patients (Smolander and Bruchfeld, 2020). Among 66 COVID-19 patients analyzed by Na et al. (2020), AKI patients accounted for 4.5% (3/66) of cases, and in the critically ill patients the serum creatinine, urine albumin to creatinine ratio (ACR), and urine protein to creatinine ratio (PCR) were significantly increased. In addition, Cheng et al. (2020) observed a prevalence of 5.1% for AKI, 13.1% for elevated blood urea nitrogen, and 14.4% for elevated serum creatinine. Compared with patients with mild COVID-19, critically ill COVID-19 patients are more likely to develop AKI and have a significantly elevated serum creatinine (Na et al., 2020), which undoubtedly increases their mortality. Thus, we urgently need some effective treatment methods such as blood purification to reduce mortality.

However, the potential mechanisms by which kidney damage is induced by SARS-CoV-2 infection are still unclear. Based on most evidence, the following factors may be involved. First, the transmembrane protease serine 2 (TMPRSS2) expressed in renal tissue primes the spike (S) protein of SARS-CoV-2. This can promote the fusion of SARS-CoV-2 with renal cells (Dong et al., 2020), especially with proximal tubular epithelial cells (PTECs), by binding to the ACE2, thereby promoting the local replication of SARS-COV-2 and causing kidney damage (Menon et al., 2020). Second, immune activation and cytokine release can be induced by viral infection. Significantly elevated levels of CRP, TNF-α, IFN-α, IL-1, IL-6, and IL-12 in critically ill COVID-19 patients can lead to an uncontrolled systemic inflammatory response, which can cause increased renal vascular permeability and decreased effective circulation capacity, ultimately leading to kidney injury (Wu CM et al., 2020). Third, dehydration can lead to kidney insufficiency and contribute to acute tubular necrosis (Post et al., 2020). In addition, a genetic predisposition has been found to play a key role in the development of kidney damage. Collapsing glomerulopathy was found to be associated with high-risk apolipoprotein L1 (APOL1) variants in COVID-19 patients. Renal biopsy specimens from COVID-19 patients with a high-risk genotype APOL1 revealed glomerular collapse, extensive disappearance of foot processes, and focal/diffuse acute tubular injury (Wu HJ et al., 2020).

In critically ill COVID-19 patients, the levels of inflammatory cytokines are significantly increased, and the development of kidney damage is also common. Treatment with corticosteroids can alleviate the systemic inflammatory response in critically ill COVID-19 patients, thereby reducing the length of hospitalization and increasing the survival rate (Wang Y et al., 2020). However, high doses and/or long-term use of corticosteroids can have a variety of adverse effects such as an increased risk of infection and metabolic disorders (Fardet and Fève, 2014). By targeting both sIL-6R and mIL-6R, tocilizumab can inhibit the IL-6 signaling pathway to reduce the inflammatory response, improve oxygenation, and reduce mortality. Despite these positive effects, the efficacy of treatment of COVID-19 with tocilizumab has not yet been fully established (Izda et al., 2021). However, as adjuvant therapies for sepsis, extracorporeal therapies might play a multifaceted role in improving this situation, and have been successfully applied in the treatment of critically ill COVID-19 patients and their complications.

5 Continuous renal replacement therapy

Continuous renal replacement therapy (CRRT) is a new type of blood purification technology that has been proven to be effective in the treatment of patients with severe Middle East respiratory syndrome (MERS) (Cha et al., 2015). Studies have shown that CRRT can treat critically ill COVID-19 patients by removing potentially damaging toxins and stabilizing their metabolic and hemodynamic status (Tandukar and Palevsky, 2019; Fu et al., 2020). In a retrospective case-series, the levels of CRP, IL-6 and D-dimer of 50 critically ill COVID-19 patients who underwent 2±1 sessions of CRRT treatment significantly decreased, while their PaO_2/FiO_2 ratios and lymphocyte counts increased (Alharthy et al., 2021). Katagiri et al. (2021a) suggested that CRRT should also be considered for critically ill patients with severe AKI. They recommend CRRT

treatment for patients in the acute phase of COVID-19 with AKI or MODS. Currently, various modalities of CRRT are available in the treatment of critically ill patients, including continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), and continuous veno-venous hemodiafiltration (CVVHDF). CVVHD or CVVHDF is the preferred modality. CVVHD and CVVHDF modalities can both decrease the filtration fraction and reduce the risk of circuit clotting (Nadim et al., 2020). Different CRRT modes should be selected according to the purpose of the treatment. For example, when patients are in a hypercoagulable state or not undergo anticoagulation treatment, CVVHD or CVVHDF can be applied (Fayad et al., 2016). CVVHD is effective for solutes with small molecular weights such as urea, creatinine, and potassium. However, when it comes to the clearance of higher-molecular-weight solutes such as pro-inflammatory cytokines, CVVH could be a better choice than CVVHD (Tandukar and Palevsky, 2019). In addition, there is evidence indicating that CVVHD might be the preferred method to treat severe intoxications in hemodynamically unstable patients (Kade et al., 2020).

High-flux (HF) and high-cut-off (HCO) membranes have been combined with CRRT for cytokine removal in critically ill patients. A reduction of inflammatory response mediators can be observed with the use of HF and HCO membranes, thus improving oxygenation and reducing non-cardiogenic pulmonary edema in critically ill patients. In addition to small toxins, HF membranes have high clearance capacity for middle-sized molecules such as β2-microglobulin to prevent dialysis-related amyloidosis, which makes it a more efficient treatment than low-flow (LF) membranes (Weidhase et al., 2019). Compared with standard CRRT, some studies indicated that HCO membranes can decrease the length of stay in ICU, vasopressor days, and ICU mortality, and attenuate plasma levels of inflammatory mediators such as IL-6, IL-8, and TNF-α (Haase et al., 2007; Villa et al., 2017). However, the efficacy of HCO membranes remains controversial. Some researchers are skeptical about the roles of HCO membranes in critically ill patients, as they have not observed additional beneficial effects in reducing hospital duration or mortality in these patients (Atan et al., 2018). In addition, whether HCO membranes could achieve greater success than HF membranes in treating critical patients is still unclear. Therefore, it is vitally important to design more high-quality studies to evaluate the safety and efficacy of HCO membranes in treating critically ill patients.

It is equally critical to establish the timing and treatment dose of CRRT in critically ill COVID-19 patients, which is relevant to their prognosis. Currently, there is no uniform standard for the timing of CRRT treatment in critically ill COVID-19 patients. Some clinical studies showed that the early application of CRRT is conducive to improving the prognosis and reducing mortality. The timing of early CRRT treatment was defined to be within 72 h of the onset of the disease. Beyond 72 h, the cytokine cascade reaction begins, which makes it difficult to block the inflammatory response and improve the prognosis (Pan et al., 2020). The ELAIN randomized clinical trial (RCT) also indicated that early implementation of CRRT in critically ill patients with AKI showed a significantly lower mortality rate within 90 d (Zarbock et al., 2016). However, in COVID-19 patients with AKI, some researchers considered that the timing of initiating CRRT should be individualized, considering the stage of AKI, the degree of kidney function, and the clinical context. In terms of treatment dose, an early prospective randomized study claimed that a high-volume hemofiltration (ultrafiltration rate of 45 mL/(kg·h)) can improve the prognosis of patients with severe AKI (Ronco et al., 2002). In a recent RCT including 82 patients, early high-volume hemofiltration (ultrafiltration rate of 65 mL/(kg·h)) decreased the incidence of sepsis and mortality in patients with severe burns (You et al., 2018). However, in a multi-center RCT involving septic patients, high-volume hemofiltration (ultrafiltration rate of 70 mL/(kg·h)) did not improve the prognosis in patients with severe AKI compared with conventional volume hemofiltration (ultrafiltration rate of 35 mL/(kg·h)). Moreover, the 28-d mortality in patients with sepsis could not be improved with an ultrafiltration rate of 70 mL/(kg·h) (Joannes-Boyau et al., 2013). Several prospective RCTs involving patients with sepsis also showed no advantages of a higher dose (ultrafiltration rates of 35–40 mL/(kg·h)) (The VA/NIH Acute Renal Failure Trial Network, 2008; The RENAL Replacement Therapy Study Investigators, 2009). Therefore, better large multicenter RCTs are still needed to determine the optimal treatment dose of CRRT for critically ill COVID-19 patients.

In addition to conventional CRRT treatment, combination with other treatment modalities can provide

better multi-organ support in the treatment of critically ill COVID-19 patients. Extracorporeal membrane oxygenation (ECMO) is a last line of defense for critically ill COVID-19 patients with severe hypoxia; however, evidence has shown that it may promote the release of cytokines and aggravate the inflammatory state of patients (Al-Fares et al., 2019). As mentioned above, CRRT can remove inflammatory factors. Thus, combined ECMO/CRRT support may be an effective therapy for these patients. In several critically ill COVID-19 patients treated with combined ECMO/CRRT support, the levels of inflammatory factors were significantly reduced, and computed tomography (CT) scans showed a significant decrease in ground-glass opacity (Zou and Li, 2020). This also indicated that the option of combined ECMO/CRRT support might be promising for the treatment of critically ill COVID-19 patients. CRRT combined with plasma exchange (Lin et al., 2020) or hemoperfusion (HP) (Dastan et al., 2020) can also provide life support to COVID-19 patients.

CRRT is the most common treatment for COVID-19 patients, but in many hospitals CRRT resources are in short supply. Therefore, making more effective use of limited CRRT resources will become particularly important. The use of increased doses of unfractionated heparin (UFH) or the combination of regional citrate anticoagulation (RCA) and heparin can prevent premature filter clotting, thereby prolonging filter life (Attallah et al., 2021; Deep et al., 2021). Recently, a prospective observational cohort study demonstrated that the combination of RCA and heparin may be better than the application of heparin or citrate alone. In this study, an increase of at least 165% in the median circuit survival was observed when applying the combination of RCA and heparin, which greatly improved the survival rate of the filter (Volbeda et al., 2020). Optimizing vascular access can conserve resources by minimizing the risk of catheter-related infection and thrombosis, and providing sufficient uninterrupted blood flow for CRRT (Chua et al., 2020). In addition, CRRT resources can be made more efficient by reducing the intensity of CRRT to conserve fluid, and lowering the blood flow to reduce the consumption of citrate (Adapa et al., 2020). Some studies have shown that prolonged intermittent renal replacement therapy (PIRRT) in the treatment of some critically ill COVID-19 patients can also prolong their survival rate (Yang Y et al., 2020; Ramirez-Sandoval et al., 2021). Although transitory intradialytic hypotension might occur, this treatment can greatly increase patients' coverage of CRRT machines (Yessayan et al., 2021).

In conclusion, CRRT might have the potential to improve the symptoms and prognosis of critically ill COVID-19 patients. However, there are some conflicting opinions and limitations. The determination of the optimal timing and dosing of CRRT in treating critically ill patients is still controversial, and large multicenter RCTs with better designs are urgently needed to address this problem. CRRT resources are in short supply, and therefore finding strategies to make the consumption of CRRT resources more effective is particularly important. The combination of RCA and heparin anticoagulation, optimizing vascular access, lowering the blood flow, and the use of PIRRT can all increase the coverage of CRRT.

6 Therapeutic plasma exchange

Plasma exchange is an extracorporeal blood purification technology that separates and removes the pathological plasma from the patient's blood, and simultaneously infuses a certain amount of solution or normal human plasma to eliminate pathogenic substances and reduce pathological damage (Grazioli et al., 2020). A growing number of studies have indicated that TPE might have potential benefits for some critically ill COVID-19 patients. Khamis et al. (2020) reported a study of 31 cases of COVID-19 patients. Among them, 11 patients were treated with TPE and compared with a non-TPE group. Patients on TPE had a higher extubation rate and lower all-cause mortality. Faqihi et al. (2020) enrolled ten ICU COVID-19 patients presenting with ARDS plus MODS. After TPE completion, the levels of CRP and IL-6 and organ function assessment scores tended to be normal. Moreover, following TPE treatment, all 14 critically ill COVID-19 patients requiring IMV showed improvement in symptoms and a decrease of inflammatory markers such as CRP and IL-6. Finally, ten patients were successfully liberated from IMV (Jaiswal et al., 2021).

TPE can remove inflammatory cytokines (Fernandez et al., 2020), stabilize the endothelial membrane, and reset the hypercoagulable state (Yiğenoğlu et al., 2020), and might have a unique role in the treatment of critically ill COVID-19 patients. Activation of the cytokine cascade plays an important role in the

development of ARDS. TPE can decrease or even eliminate cytokines and inflammatory mediators to help reduce the inflammatory state of patients (Adeli et al., 2020). After receiving TPE treatment, the levels of IL-6 and CRP were significantly decreased, and clinical condition was obviously improved (Luo et al., 2020). However, while reducing the inflammatory state, TPE can also remove the neutralizing antibodies against SARS-CoV-2, which is unfavorable (Honore et al., 2020). There are some methods that may possibly solve this problem. Convalescent plasma carries specific neutralizing antibodies, and using TPE combined with convalescent plasma may be an effective and safe method (Shen et al., 2020; Stahl et al., 2020b; Jaiswal et al., 2021). However, a randomized controlled, open-label, platform trial including 11 558 COVID-19 patients showed no significant difference in improving survival rate or other clinical outcomes (RECOVERY Collaborative Group, 2021). Timely intravenous immunoglobulin (IVIG) treatment can also improve adverse clinical outcomes in critically ill COVID-19 patients after TPE treatment, and may be an effective therapeutic strategy (Pourahmad et al., 2020; Shi et al., 2020). Factors such as SARS-CoV-2-induced endothelial dysfunction, and microvascular and macrovascular thromboses are also critical in determining the clinical outcomes of COVID-19 patients (Varga et al., 2020). Obvious endothelial activation and blood hypercoagulability can be observed in critically ill COVID-19 patients, and are reflected by significantly increased von Willebrand factor (VWF) antigen and D-dimers levels. TPE can reduce the levels of both VWF and D-dimers, thereby improving the survival rate of the critically ill patients (Zachariah et al., 2020). Therefore, TPE could be used for the treatment of critically ill COVID-19 patients, especially those with marked endothelial activation and a high risk of thrombosis (Gucyetmez et al., 2020). Another advantage of TPE is that it can replace the protective factors consumed in the host's immune response against the virus, such as protein C, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13) (Stahl et al., 2020a), and angiopoietin-1 (Stahl et al., 2020b). These factors play a critical role in preventing vascular leakage and maintaining the microcirculatory flow.

However, TPE might also have some potential limitations in the treatment of critically ill COVID-19 patients. After TPE treatment, the production of cytokines continues, which could subsequently cause organ damage within a few minutes (Daoud et al., 2021). At this point, a strategy for blocking cytokines for a long time becomes particularly important. In addition, TPE treatment may cause hypocalcemia when replacing fluids, which will cause adverse reactions such as twitching of hands and feet and arrhythmia. Also, the reaction between the red blood cells of patients and the plasma of donors might cause anaphylactic shock (Adeli et al., 2020). Both hypocalcemia and anaphylactic shock can lead to death. Therefore, strict attention should be paid to these problems during the treatment of critically ill COVID-19 patients with TPE, and solutions should be actively sought in subsequent studies and practice.

In summary, TPE might be able to stabilize critically ill or rapidly deteriorating patients to reduce mortality by removing inflammatory cytokines, stabilizing the endothelial membrane, and resetting the hypercoagulable state. Future clinical studies should be designed to determine if TPE could be an alternative treatment to reduce hyperinflammation, hyper-viscosity, and hypercoagulability in critically ill COVID-19 patients. In addition, more effective strategies should be designed to address the negative consequences and limitations of TPE, such as the removal of potentially beneficial molecules.

7 Hemoadsorption

HP and continuous plasma filtration absorption (CPFA) are widely used in clinical practice for patients with critical illness. HP can remove cytokines, endotoxins, and other circulating inflammatory mediators to delay the hyper inflammation process, and has shown encouraging results in the treatment of septic shock (Berhés et al., 2020). Thus, HP might be another important treatment option for critically ill COVID-19 patients (Safari et al., 2020). Several case reports have reported COVID-19 patients who were hospitalized in ICUs and developed ARDS during their hospitalization, but whose clinical condition was improved significantly after HP treatment (Moradi and Abbasi, 2020; Rampino et al., 2020; Vardanjani et al., 2021). After HP treatment of some COVID-19 patients with PaO_2/FiO_2 ratio of <300, their respiratory symptoms improved and the severity of the disease decreased significantly (Katagiri et al., 2021b). Liver impairment has been reported in some

critically ill COVID-19 patients. HP can eliminate the toxins associated with acute liver failure and has become an attractive treatment option for these patients (Colaneri et al., 2020). Punctual and early HP treatments can prevent the occurrence and development of ARDS, AKI, liver failure, and MODS, thereby stabilizing the patient's condition and reducing mortality (Vardanjani et al., 2021). IA is a well-tolerated and safe plasma adsorption therapy that can selectively remove endogenous medium and large molecular pathogenic substances such as cytokines, endotoxins, and activated neutrophils from the blood (Schefold et al., 2007). Although the theoretical basis for using IA in critically ill COVID-19 patients is still limited, many such patients have received IA treatment and achieved certain effects. The clinical application of IA was also pointed out by the expert consensus on the treatment of critically ill COVID-19 patients in China (Chinese Society of Nephrology, Professional Committee of Nephrology, 2020). CPFA is a new type of blood purification therapy, which can effectively remove cytokines from the blood and at the same time regulate the balance of volume and stabilize the body environment (Hazzard et al., 2015). Thus, CPFA may also be an effective method to improve the clinical symptoms of COVID-19 patients.

To summarize, hemoadsorption (HA) is applied to the adsorption and removal of inflammatory cytokines, and has achieved certain curative effects. HP has the potential to remove inflammatory cytokines, endotoxins, danger-associated molecular patterns (DAMPs), and pathogen-associated molecular patterns (PAMPs), and eliminate the toxins associated with acute liver failure. In addition to endotoxins and cytokines, IA could adsorb leukocytes, but evidence of its function in the treatment of critically ill COVID-19 patients is still limited. CPFA may also be an effective method for treating critically ill COVID-19 patients because of its ability to clear cytokines and stabilize the body environment.

8 Extracorporeal membrane oxygenation

As a technology providing effective circulation and respiratory support for critically ill patients, ECMO is helpful in improving blood perfusion, and gaining valuable time for the recovery of the cardiopulmonary system. Currently, venous to arterial (VA)-ECMO, venous to venous (VV)-ECMO, and venous to arterial and venous (VAV)-ECMO are the main modes (Napp et al., 2016). When there is respiratory failure, the VV-ECMO mode is preferred. VA-ECMO and VAV-ECMO modes can be used when both respiratory support and circulatory support are required (Camboni et al., 2019). ECMO plays a crucial role in life support for critically ill COVID-19 patients with cardiopulmonary failure. In the COVID-19 treatment guidelines of the National Health Commission of China (NHCC) and the National Institutes for Health (NIH), the use of ECMO can be regarded as a salvage treatment of respiratory support for severely and critically ill patients when conventional treatments fail (Ma et al., 2020). When IMV cannot solve hypoxemia, and measures such as muscle relaxants and prone position ventilation are still not effective, ECMO can be used in hospitals with conditions. However, there are some limitations in the current use of ECMO in COVID-19 patients. The benefits and risks of using ECMO in COVID-19 patients are still unclear. There have been successful cases of ECMO treatment of critically ill COVID-19 patients; however, the overall effect is not ideal, and the fatality rate can be as high as 82.3% (14/17) or 83.3% (5/6) (Ñamendys-Silva, 2020; Yang XB et al., 2020). Relevant clinical evidence on the use of ECMO in COVID-19 patients is scarce, and the timing, indications, management, benefits, and risks of ECMO are still controversial. Hence, high-quality RCTs are urgently needed to elaborate the efficacy and validity of using ECMO in critically ill COVID-19 patients.

9 Extracorporeal carbon dioxide removal

Extracorporeal carbon dioxide removal ($ECCO_2R$) is a rescue therapy for critically ill COVID-19 patients. It can reduce the tidal volume and respiratory frequency to decrease the high peak airway pressure to limit ventilator-induced lung injury (VILI), and can also correct CO_2 retention caused by ventilation defects (Combes et al., 2020). After receiving $ECCO_2R$ treatment, some critically ill COVID-19 patients with hypercapnia who were difficult to cure with conventional treatments were significantly improved to the extent that the extracorporeal life support (ECLS) was able to be weaned, and all were discharged from the ICU without any treatment-related adverse events (Husain-Syed et al., 2020; Tully et al., 2020). $ECCO_2R$ combined with CRRT may also be safe and feasible

for COVID-19 patients with ARDS or AKI. Although CRRT alone may have the ability to remove CO_2 (Jonckheer et al., 2019), the combination can remove the excess CO_2 and at the same time compensate for respiratory acidosis, thereby further limiting respiratory pressure and promoting protective lung ventilation. Chen et al. (2021) reported two critical COVID-19 patients receiving $ECCO_2R$ combined with CRRT. After the treatment, their ventilator parameters such as tidal volume and positive end-expiratory pressure (PEEP) were down-regulated, and the incidence of VILI had decreased. Anticoagulation is necessary in this treatment. Heparin appears to be the anticoagulant most frequently used, but patients with heparin-infusion anticoagulation might experience membrane clotting before the end of the treatment. However, compared with heparin anticoagulation, the combination of regional citrate with a heparin anticoagulation strategy has the effect of enhancing membrane duration (Schmidt et al., 2018). Moreover, it is recommended to use CVVHD or CVVHDF for CRRT modalities, which can also reduce the filtration fraction and has a low risk of circuit clotting (Husain-Syed et al., 2020). However, the application of $ECCO_2R$ to treat patients with COVID-19 is still limited, and it is necessary to conduct more multi-center randomized trials to evaluate the impact of $ECCO_2R$ on the clinical outcomes of critically ill patients. Overall, the $ECCO_2R$ system makes it possible to obtain metabolic removal of CO_2 to facilitate more protective ventilation. The combination of $ECCO_2R$ and CRRT might also be an option to efficiently treat critically ill COVID-19 patients. However, further high-quality studies are needed due to the lack of relevant clinical evidence.

10 Conclusions

Critically ill COVID-19 patients can experience a high-inflammation status and variable degrees of kidney damage and even MODS. Based on the recent literature, extracorporeal therapies have a potential role in the treatment of critically ill COVID-19 patients (Table 1). Extracorporeal therapies can remove inflammatory cytokines and toxins, and provide support for multiple organs, which can significantly improve the clinical symptoms and reduce mortality. However, limitations still exist when treating critically ill COVID-19 patients (Table 2), and there is a lack of large-scale multicenter clinical studies to guide clinicians in the treatment of these patients. More studies are needed to clarify the roles of various types of extracorporeal therapies in the treatment of these patients. Currently, medical workers are required to formulate individualized extracorporeal treatment plans based on the specific clinical conditions of each patient (Fig. 1), so that extracorporeal therapies can become an effective and safe treatment method.

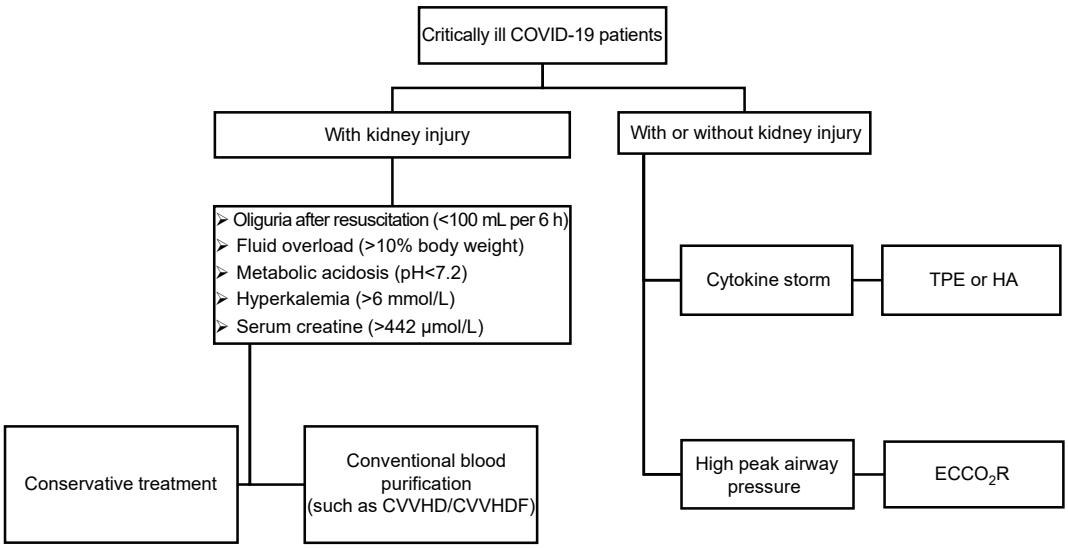

Fig. 1 Modality options of extracorporeal purification therapies for critically ill COVID-19 patients. COVID-19: coronavirus disease 2019; CVVHD: continuous veno-venous hemodialysis; CVVHDF: continuous veno-venous hemodiafiltration; TPE: therapeutic plasma exchange; HA: hemoadsorption; $ECCO_2R$: extracorporeal carbon dioxide removal.

Table 1 Outcomes of the application of extracorporeal therapies in critically ill COVID-19 patients

Reference	Study design	Patient number	Baseline characteristics of the patients	Blood purification therapy	Inflammatory markers before therapy	Respiratory parameters and other laboratory findings before therapy	Inflammatory markers after therapy	Respiratory parameters and other outcomes after therapy	Survival rate
Xiang et al., 2021	Retrospective multicenter, descriptive study	38	Age, (66.9±11.8) years; male (31), female (7); hypertension (19), diabetes (7)	CRRT (without detail)	CRP, 120.10 mg/L (64.66–160.00 mg/L); D-dimer, 7.08 μg/mL (2.29–12.14 μg/mL); lymphocyte count, 0.54×10^9 L^{-1} (0.36×10^9–0.96×10^9 L^{-1}); procalcitonin, 1.67 ng/mL (0.70–4.69 ng/mL)	Blood oxygen saturation, 90.0% (84.5%–95.0%); albumin, (28.68±4.79) g/L	CRP, 63.60 mg/L (42.11–128.00 mg/L); D-dimer, 3.94 μg/mL (1.88–7.18 μg/mL); lymphocyte count, 0.54×10^9 L^{-1} (0.24×10^9–1.02×10^9 L^{-1}); procalcitonin, 2.58 ng/mL (0.69–6.50 ng/mL)	Blood oxygen saturation, 93% (88.0%–95.5%)	
Alharthy et al., 2021	Retrospective case series	50	Age, (49.64±8.90) years; male (39), female (11); BMI, (26.70±2.76) kg/m^2; hypertension (25), diabetes (14), cardiovascular disease (4)	CVVHD with CytoSorb cartridge (a blood flow rate of 100–250 mL/min, citrate anticoagulant)	CRP, (145.4±98.3) mg/L; IL-6, (612.85±185.63) pg/mL; ferritin, (602.34±142.18) ng/mL; D-dimer, (2.86±0.78) μg/mL; lymphocyte count, $(0.73\pm0.23)\times10^9$ L^{-1}	PaO_2/FiO_2 ratio, 113.00±34.68; SOFA score, 9.86±1.94	CRP, (43.6±26.2) mg/L; IL-6, (170.11±77.78) pg/mL; ferritin, (296.46±62.93) ng/mL; D-dimer, (1.15±0.90) μg/mL; lymphocyte count, $(0.92\pm0.21)\times10^9$ L^{-1}	PaO_2/FiO_2 ratio, 303.43±37.41; SOFA score, 2.23±1.03; duration of mechanical ventilation, (17.38±7.39) d	35/50 (70.0%)
Burke et al., 2021	Single-center prospective observational study	43	Age, (63±14) years; male (25), female (18); BMI, 26–34 kg/m^2; hypertension (30), diabetes (18), kidney disease (12)	CVVH and IHD	CRP, 144 mg/L (81–190 mg/L); D-dimer, 2.0 mg/L (1.0–4.4 mg/L); IL-6, 12 pg/mL (5–34 pg/mL)	SOFA score, 5 (4–8); fluid balance, 900 mL/d (300–3100 mL/d)	CRP, 119 mg/L (58–190 mg/L); D-dimer, 1.7 mg/L (1.0–3.1 mg/L); IL-6, 8 pg/mL (4–14 pg/mL)	SOFA score, 5 (3–8); fluid balance, 800 mL/d (100–2800 mL/d)	19/43 (44.2%)

To be continued

Table 1

Reference	Study design	Patient number	Baseline characteristics of the patients	Blood purification therapy	Inflammatory markers before therapy	Respiratory parameters and other laboratory findings before therapy	Inflammatory markers after therapy	Respiratory parameters and other outcomes after therapy	Survival rate
Doher et al., 2021	Retrospective cohort study	34	Age, 57.2–82.0 years; male (27), female (7); BMI, 26.1–32.4 kg/m^2; hypertension (21), diabetes (19), heart failure (9), pneumopathy (2)	CVVHDF at a prescribed dose of 30–35 mL/(kg·h) of effluent and with RCA	CRP, 107.0–230.5 mg/dL; IL-6, 335.9–981.3 pg/mL; D-dimer, 838–2236 pg/mL; ferritin, 1016–3577 ng/mL; lymphocyte count, 0.50×10^9–1.04×10^9 L^{-1}	SOFA score, 4 (2–8); PaO_2, 80.9 mmHg (42.6–124.5 mmHg); $PaCO_2$, 40.0 mmHg (37.3–44.7 mmHg); pH, 7.37 (7.32–7.42)	Creatinine at discharge, 3.50 mg/dL (2.00–4.34 mg/dL)	Duration of ventilation in survivors, 11.8–36.8 d; ICU length of stay, 19.5–37.0 d; hospital length of stay, 30–40 d	22/34 (64.7%)
Kamran et al., 2021	Retrospective propensity matched control study	45	Age, 32–73 years; male (45); hypertension (9), diabetes (11), obstructive air way disease (2)	TPE (COBE Spectra Apheresis machine Version 7 with continuous flow centrifugation)	CRP, 147 μg/mL (56–260 μg/mL); IL-6, 104 pg/mL (7–178 pg/mL); D-dimer, 647 pg/mL (300–1100 pg/mL); ferritin, 1410 ng/mL (395–4500) ng/mL	Discharge days, 15 d (7–45 d); time for CRS resolution, 12 d (5–42 d); positive Day 7 PCR, 33.3%	CRP, 145 μg/mL (21–278 μg/mL); IL-6, 78 pg/mL (6–400 pg/mL); D-dimer, 350 pg/mL (150–1700 pg/mL); ferritin, 1500 ng/mL (336–7877 ng/mL)	Discharge days, 10 d (4–37 d); time for CRS resolution, 6 d (2–23 d); positive Day 7 PCR, 31%	41/45 (91.1%)
Jaiswal et al., 2021	Prospective case-cohort study	14	Age, (49.14±12.50) years; male (11), female (3); BMI, (29.66±4.99) kg/m^2; comorbidities (10)	TPE (a total of 30−40 mL/kg bodyweight of plasma exchange, FFP as a replacement solution) followed by convalescent plasma transfusion	CRP, (86.74±79.86) μg/mL; D-dimer, (4.20±5.46) μg/mL; ferritin, (1416.25±1150.62) ng/mL; lymphocyte count, (0.70±0.54)×10^9 L^{-1}	PaO_2/FiO_2 ratio, 138.89±41.90; body temperature, (37.24±0.92) °C	CRP, (30.56±30.73) μg/mL; D-dimer, (4.21±5.93) μg/mL; ferritin, (1051.42±740.96) ng/mL; lymphocyte count, (1.04±0.49)×10^9 L^{-1}	PaO_2/FiO_2 ratio, 224.78±136.35; body temperature, (37.16±0.77) °C	14/14 (100.0%)
Gucyetmez et al., 2020	Retrospective study	12	Age, (61±14) years; male (8), female (4); BMI, (28.5±6.1) kg/m^2	TPE plus therapeutic anticoagulation	CRP, 0.4–29.7 mg/dL; IL-6, 36.2–2958.0 pg/mL; D-dimer, 2.1–35.2 mg/L; ferritin, 399–6110 ng/mL; LDH, 322–550 IU/L; lymphocyte count, 0.5×10^3–1.3×10^3 μL^{-1}	PaO_2/FiO_2 ratio, 98±30; SpO_2, 91%; PEEP, 12 cmH_2O; SOFA score, 6; APACHE II,17±4	CRP, 0.3–7.2 mg/dL; IL-6, 1.5–130.0 pg/mL; D-dimer, 0.6–3.9 mg/L; ferritin, 157–1650 ng/mL; LDH, 181–297 IU/L; lymphocyte count, 0.77×10^3–1.27×10^3 μL^{-1}	PaO_2/FiO_2 ratio, 104.0±32.4; SpO_2, 92%; PEEP, (12.0±2.3) cmH_2O; SOFA score, 6; APACHE II, 17.0±3.3	11/12 (91.7%)

To be continued

Table 1

Reference	Study design	Patient number	Baseline characteristics of the patients	Blood purification therapy	Inflammatory markers before therapy	Respiratory parameters and other laboratory findings before therapy	Inflammatory markers after therapy	Respiratory parameters and other outcomes after therapy	Survival rate
Katagiri et al., 2021b	Case series	12	Age, 36–83 years; male (9), female (3); BMI, 19.2–31.9 kg/m^2; hypertension (5), diabetes (3), AKI Stages 1/2/3 (2/1/1)	Hemoperfusion using a polymyxin B-immobilized polystyrene column (PMX-DHP)	IL-6, 2–40 pg/mL; IL-1β, 0.7–3.8 pg/mL; platelet-derived growth factor-BB, 250–1700 ng/mL; vascular endothelial growth factor, 65–100 pg/mL	PaO_2/FiO_2 ratio, 69.0–327.1; urinary β2MG, (62–70 725) μg/L; urinary L-FABP, (0.1–167.0) μg/g creatinine	IL-6, 0.5–7.0 pg/mL; IL-1β, 0.5–3.3 pg/mL; platelet-derived growth factor-BB, 490–1510 ng/mL; vascular endothelial growth factor, 20–95 pg/mL	PaO_2/FiO_2 ratio, 172.8–464.8; urinary β2MG, 30–9435 μg/L; urinary L-FABP, 1.1–803.4 μg/g creatinine	9/12 (75.0%)
Asgharpour et al., 2020	RCT	10	Age, (57.30±18.07) years; male (5), female (5); hypertension (2), diabetes (3), cardiovascular disease (2), kidney disease (2)	Hemoperfusion with HA-280 or HA-230 cartridge	CRP, (136.25±84.39) mg/L; IL-6, (139.70±105.62) ng/mL; BUN, 12–98 mg/dL; creatinine, 0.6–4.3 mg/dL; lymphocyte, 1.6%–12.2%	Mean SpO_2, (89.60±3.94)%	CRP, (72.06±65.87) mg/L; IL-6, (78.25±38.67) ng/mL; BUN, 9–79 mg/dL, creatinine, 0.5–3.7 mg/dL, lymphocyte, 2.0%–17.0%	Mean SpO_2, (92.13±3.28)%	6/10 (60.0%)
Akkanti et al., 2021	Retrospective multicenter cohort study	29	Age, (54.7±11.5) years; male (18), female (11); BMI (33.5±10.5) kg/m^2; hypertension (8), diabetes (9), history of transplant (2)	$ECCO_2R$ using the Hemolung Respiratory Assist System (at blood flows of 350–550 mL/min)		PCO_2, (79±23) mmHg; respiratory rate, (26.6±5.4) times/min; tidal volume, (407±100) mL; minute ventilation, (10.2±3.2) L/min; pH, 7.24±0.12		PCO_2, (58±14) mmHg; respiratory rate, (23.4±4.9) times/min; tidal volume, (386±75) mL; minute ventilation, (8.7±2.2) L/min; pH 7.35±0.07	11/29 (38.0%)

COVID-19: coronavirus disease 2019; CRRT: continuous renal replacement therapy; CRS: cytokine release syndrome; CRP: C-reactive protein; CVVHD: continuous veno-venous hemodialysis; IL-6: interleukin-6; LDH: lactate dehydrogenase; PMX-DHP: polymyxin B-direct hemoperfusion; SOFA: sequential organ failure assessment; CVVH: continuous veno-venous hemofiltration; IHD: intermittent haemodialysis; CVVHDF: continuous veno-venous hemodiafiltration; RCA: regional citrate anticoagulation; ICU: intensive care unit; PCR: protein to creatinine ratio; TPE: therapeutic plasma exchange; FFP: fresh frozen plasma; PEEP: positive end-expiratory pressure; BMI: body mass index; AKI: acute kidney injury; β2MG: β2-microglobulin; APACHE II: acute physiology and chronic health evaluation II; L-FABP: liver-type fatty acid-binding protein; BUN: blood urea nitrogen; HA: hemoadsorption; RCT: randomized clinical trial; $ECCO_2R$: extracorporeal carbon dioxide removal; PaO_2: arterial oxygen partial pressure; FiO_2: fractional inspired oxygen; SpO_2: peripheral capillary oxygen saturation; PCO_2: partial pressure of carbon dioxide. 1 mmHg=0.133 kPa; 1 cmH_2O=0.098 kPa.

Table 2 Advantages and limitations of some extracorporeal therapies in treating critically ill COVID-19 patients

Blood purification therapy	Advantage	Limitation
CRRT	Eliminates toxic substances, inflammatory mediators, and inflammatory cytokines. CRRT-induced low temperature can reduce the production of CO_2. Reduces lung–kidney interaction. Does not easily cause hemodynamic changes, and can achieve the goal of fluid balance with higher hemodynamic stability. CVVHD or CVVHDF modality can reduce the filtration fraction and protect the life of cardiopulmonary bypass.	Short supply of CRRT resources in many hospitals. The need for intense nursing care requires a large number of nursing staff. Increased frequency of circuit clotting. Loss of trace elements; catheter-related infection. Patients need anticoagulation therapy. The timing and treatment dose of CRRT when treating critically ill COVID-19 patients are controversial.
PIRRT	Can increase patients' coverage of CRRT machines by allowing several patients treated with the same machine per day. Has a low rate of circuit clotting.	Transitory intradialytic hypotension may occur. A lack of standardized PIRRT prescription guidelines. Frequent exchanges of solutions compared to CRRT to process the same volume of blood. Variability of drug pharmacokinetics because of heterogeneity in prescription.
TPE	Can remove inflammatory cytokines, stabilize the endothelial membrane, and reset the hypercoagulable state. Can replace the protective factors like protein C, ADAMTS-13, and angiopoietin-1.	Can remove the neutralizing antibodies against SARS-CoV-2. Can block the release of cytokines only temporarily. Can cause hypocalcemia and anaphylactic shock.
HP	Can remove inflammatory cytokines, endotoxins, DAMPs, and PAMPs. Can eliminate the toxins associated with acute liver failure.	Has not yet been formally studied. Still needs more RCTs.
ECMO	Can gain valuable time for the recovery of cardiopulmonary system. Some evidence shows an additional survival benefit with the use of ECMO.	A lack of relevant clinical evidence. The timing, indications, management, and risks of ECMO are still controversial. Needs a lot of medical resources in short supply during the COVID-19 epidemic. Complicated treatment process and potential complications such as fatal bleeding and infection.
$ECCO_2R$	Uses lower blood flow rates through smaller cannula and provides substantial CO_2 elimination. Simple operation method; single subject can operate independently. Lower cost than some extracorporeal life supports like ECOM.	Weaker oxygenation effect than ECOM; needs to extend the ventilation time to make up for its oxygenation effect.

COVID-19: coronavirus disease 2019; CRRT: continuous renal replacement therapy; PIRRT: prolonged intermittent renal replacement therapy; TPE: therapeutic plasma exchange; HP: hemoperfusion; ECMO: extracorporeal membrane oxygenation; $ECCO_2R$: extracorporeal carbon dioxide removal; CVVHD: continuous veno-venous hemodialysis; CVVHDF: continuous veno-venous hemodiafiltration; ADAMTS-13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; DAMP: danger-associated molecular pattern; PAMP: pathogen-associated molecular pattern; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; RCT: randomized clinical trial.

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Author contributions

Zhifeng ZHOU, Huang KUANG, and Yuexian MA searched the literature; Zhifeng ZHOU and Huang KUANG drafted the manuscript; Ling ZHANG contributed to the design

and revision of this manuscript. All authors approved the final manuscript.

Compliance with ethics guidelines

Zhifeng ZHOU, Huang KUANG, Yuexian MA, and Ling ZHANG declare that they have no conflict of interest.

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