Coronavirus Disease 2019-Associated Acute Kidney Injury Garners More Attention

Since the first report of coronavirus disease 2019 (COVID-19) cases in early December 2019 in Wuhan, China, the COVID-19 epidemic with the driving force like a tsunami wave has rapidly spreadglobally.[1,2] COVID-19 is an infectious disease and almost all people lack specific immunity to this novel coronavirus (CoV).[3] As of February 28, 2021, there have been 113,467,303 confirmed cases of COVID-19, including 2,520,550 deaths across 237 countries, areas, or territories, as reported by the World Health Organization (https://covid19.who.int/). Currently, a challengeable task facing global medical staff is how to curb the transmission of COVID-19 across persons, and to prevent or delay the progression from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, or even death during hospitalization.

It is widely recognized that besides the lungs, COVID-19 in critical situations often causes damage to the other organs, including the stomach, intestine, liver, heart, and kidney.[4,5] For instance, as an extra-pulmonary complication, acute kidney injury (AKI) was commonly seen among critically ill patients with COVID-19 from Wuhan, China, with 28% of patients hospitalized in intensive care unit experiencing AKI, exceeding that of other complications such as cardiac injury (23%) and liver dysfunction (23%).[6] Consistent with the findings of a prospective cohort study in New York, 31% of COVID-19 patients who were critically ill with acute hypoxemic respiratory failure developed severe AKI requiring renal replacement therapy during hospitalization.[7] Further in patients with COVID-19 from Wuhan, China, the presence of AKI was identified as a significant independent risk factor for in-hospital deaths, with a higher AKI stage paralleling to higher mortality risk.[8] Hence, a better understanding of the molecular mechanisms implicated in the pathogenesis of AKI among critically ill patients with COVID-19 may help in developing effective programs and taking protective measures to combat the increasing occurrence of AKI.

Currently, why COVID-19 in critical situations may predispose patients to the development of AKI is still a matter of some speculation. Two major possible explanations might account for this predisposition.

The first explanation is that as a virus receptor, angiotensin-converting enzyme 2 (ACE2) opens the door for severe acute respiratory syndrome CoV 2 (SARS-CoV-2), which causes COVID-19, to attack the kidney.[9] ACE2, a Type I transmembrane protein, normally exhibits protective effects against severe pathological changes in the body,[10] and it is highly expressed in many human organs, including the kidney (especially in tubular epithelial cells).[11] There is evidence from autopsied kidney tissues revealing that SARS-CoV-2 viral particles were detected in renal tubular cells and podocytes.[12] Like SARS-CoV, SARS-CoV-2 enters and infects host cells by binding the N-terminal peptidase domain of ACE2 and hence downregulating its expression,[13] leading to a cascade of inflammation reactions and the disruption of renin-angiotensin-aldosterone system homeostasis[14] that subsequently attack and damage the kidneys.[15,16] Such information is important, as there is the potential to selectively targeting the binding sites between ACE2 and SARS-CoV-2 by developing small molecules as inhibitors to disrupt their attachment, which may represent a promising therapeutic strategy.

Another possible explanation is related to the impact of cytokine storm triggered by SARS-CoV-2 infection on the kidney via inducing sepsis, shock, hypoxia, and rhabdomyolysis. After infection with COVID-19, activated alveolar macrophages can amplify SARS-CoV-2 and release cytokines and chemokines, which lead to extensive activation of immune response and intensified cytokine storm in the lungs.[17-19] More cytokines enter into the circulation and cause injury in other organs, and if left untreated, the immune system would overreact or be out of control, leading to multi-organ failure, including the kidney, which in return, deteriorates the pathology of SARS-CoV-2.[20,21] Clinical observations revealed that the concentrations of some inflammatory cytokines, such as interleukin-6, interleukin-8, interleukin-10, and tumor necrosis factor α, were increased sharply in patients infected with SARS-CoV-2, yet they were decreased during recovery.[22] The fact that cytokine storms can exert an indirect impact on the failure of multiple organs might represent an early warning sign of catastrophic

consequences associated with the systematic spread of cytokines. As stated in the "COVID-19 Treatment Plan in China (tentative seventh edition)," in the case of decreased peripheral lymphocytes, progressively increased lactic acids, rapidly increased lesions in lungs in short-term, progressively increased circulating concentrations of interleukin-6 and C-reactive protein, a warning signal is sounded for the possible presence of severe or critical COVID-19. To weaken or extinguish the cytokine storm that originated in the lungs, it is hence of clinical importance to identify the proper time window for effective anti-inflammation treatment, as well as the key molecules for targeted interventions.

We hope that this Commentary can provide an anchoring point for a better understanding of the pathogenesis of AKI in critically ill patients with COVID-19. In particular, improved understanding of the molecular mechanisms of AKI may facilitate the development of new targeted forms of pharmacological agents that can minimize the mortality risk from COVID-19. Nonetheless, for practical reasons, intensive efforts to improve the awareness, treatment, and control, particularly for AKI among critically ill patients with COVID-19 during hospitalization should be remained at the top of the priority list of clinical health professionals in both emergency and intensive care sectors.

Conflict of Interest

Ping Li is the Co-Editor-in-Chief of the journal and Wenquan Niu is an Editorial Board Member. The article was subject to the journal's standard procedures, with peer review handled independently of the editors and their research groups.

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