Coronavirus diseases 2019 and kidney injury: a brief review based on current evidence

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To the Editor: The global pandemic of coronavirus disease 2019 (COVID-19) is not under control, and COVID-19 has affected tens of millions of people worldwide. Although the main features of COVID-19 are diffuse alveolar damage and acute respiratory failure, damage to other organs is also of concern because these patients tend to have more severe symptoms and worse prognosis. In this article, we briefly review the characteristics of kidney involvement in COVID-19 and the impact of kidney injury on prognosis of the disease, in order to better understand the COVID-19 epidemic from the perspective of a nephrologist.

The respiratory system is not the only target organ of COVID-19, as the most important organs of the metabolic and excretory system, kidneys have been shown to be involved in COVID-19. According to the current literature, some patients manifested with kidney injury, such as hematuria, proteinuria, serum creatinine (Scr) fluctuations or even acute kidney injury (AKI). The incidence of kidney involvement in the patients with COVID-19 varies from different studies, depending on the proportion of severe patients. In addition, the patients with COVID-19 who already have kidney disease are more likely to develop kidney injury, and the renal functions are more likely to be damaged if the COVID-19 patients are in critical condition. Meanwhile, kidney damage will deteriorate the progress of COVID-19, leading to poor prognosis and higher mortality. In the early stages of the COVID-19 outbreak, the high incidence of kidney damage in critically ill patients may be due to lack of clinical experience and shortage of medical resources. Retrospective data from the Wuhan Tongji Hospital reported an association between abnormal kidney function and mortality in the hospitalized COVID-19 patients. In this cohort, 701 patients were admitted, including 297 (42.4%) severe patients, and 113 (16.1%) of these patients died in the hospital. The incidences of proteinuria, hematuria, and elevated Scr were 43.9%, 26.7%, and 14.4%, respectively. In addition, 13.1% of patients had estimated glomerular filtration rate levels under 60 mL·min⁻¹·1.73 m⁻², and 5.1% of patients suffered from AKI during hospitalization. Patients with elevated baseline level of Scr were more likely to develop AKI (11.9% vs. normal baseline Scr 4.0%) and had more severe diseases, and further analysis indicated that patients with impaired renal function had higher risk for in-hospital mortality rate.1 Yang et al.2 observed the clinical course and outcomes of 52 critically ill adult patients with COVID-19 who were admitted to the intensive care unit (ICU) with a mean age of 59.7 years. In total, 15 (28.8%) patients suffered from AKI, and 32 (61.5%) patients died. Compared to survivors, non-survivors were older and more likely to develop acute respiratory distress syndrome (ARDS) (26 [81%] vs 9 [45%]) and AKI (12 [37.5%] vs. 3 [15%]). Another study showed that 36.6% of patients suffered from AKI in the 5449 patients with COVID-19, and the proportion of using ventilators was as high as 89.7% in the patients with AKI.3 The above clinical evidence showed that the incidence of renal impairment is high in hospitalized critically ill COVID-19 patients and is also closely related to in-hospital death. However, the mild to moderate COVID-19 does not commonly result in AKI. According to first-line data, there is no kidney involvement in most patients with mild COVID-19 symptoms. Wang et al.4 analyzed the clinical characteristics of 138 hospitalized COVID-19 patients, only five (3.6%) patients...
suffered from AKI and three of them were in critical condition, indicating that kidney impairment was not common in these patients.

The renal pathological changes in the COVID-19 patients usually presented with swollen glomerular endothelial cells, a small amount of protein exudate in the glomerular Bowman capsule, and transient thrombosis in intracapillaries. Moreover, edema, vacuolar degeneration, and shedding of renal tubular epithelial cells were observed. Protein casts and pigment casts were observed in the lumen, and renal interstitial hyperemia, microthrombosis and focal fibrosis were also observed. A few reports showed that novel coronavirus particles could be seen in the tubular epithelial cells and podocytes. It implied that the novel coronavirus may damage the kidney directly.[35]

However, from our experience, the causes of kidney injury in the COVID-19 patients may be mainly due to the clinical secondary factors, that is, renal damage caused by infection, hypoxemia, hemodynamic instability, and other comprehensive factors. Other risk factors of AKI in the COVID-19 also have been reported, such as high expression of angiotensin-converting enzyme 2 (ACE2) in the kidney, inflammation, and cytokines, but these mechanisms need to be further verified. In most patients with COVID-19, kidney injury only manifested with mild elevation of Scr or blood urea nitrogen. Nausea, vomiting, anorexia, malnutrition, insufficient intake of calories, and insufficient blood volume may attribute to the temporary abnormal renal function. The incidence of AKI increased in the critically ill patients with COVID-19 may be attributed to secondary injury, such as hypoxemia, severe infection, acid-base electrolyte balance disorder, and hemodynamic instabilities, including hypotension and infection-induced septic shock or high-dose vascular active drugs-induced renal hypoperfusion. Inflammation and cytokine storm-mediated kidney injury may be another potential mechanism of AKI. Current data showed that there were higher plasma levels of interleukin (IL)-2, IL-7, IL-10, granulocyte colony-stimulating factor, inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein-1 alpha, and tumor necrosis factor in the critical patients with COVID-19. Cytokine release syndrome (CRS) may also induce the kidney damage through increased vascular permeability under the conditions with inflammation, insufficient effective circulating blood volume, hypotension, and endothelial cell damage.[36]

It is believed that the novel coronavirus enters cells mainly by binding to ACE2 receptors on the cell surface through its envelope-anchored spike (S) protein. The transmembrane protease serine (TMPRSS) family acts as key cellular proteases in coronavirus S protein priming, which plays an important role after coronavirus enters cells. Therefore, cells with ACE2 expression may act as target cells of the novel coronavirus. It is reported that kidney proximal tubule cells exhibit significantly high ACE2 expression with an approximate proportion of ACE2-positive cells of 4%. Researchers also identified that ACE2 and TMPRSS genes are significantly co-expressed in glomerular podocytes and renal proximal convoluted tubules, and the expression level of ACE2 in the kidneys of Westerners is higher than that of Asians, suggesting that Western COVID-19 patients may be more likely to develop AKI. Proteinuria as a typical clinical symptom in the patients with COVID-19 may be due to podocyte damage.[37]

There is not any definite targeted treatment for COVID-19 until now. The prevention and control approaches to this disease include controlling the source of infection, strengthening personal protection to reduce the risk of transmission, early diagnosis/isolation, and symptomatic supportive care for the confirmed patients. In the treatment of COVID-19 patients with kidney involvement, early detection, and protection of kidney function are important to reduce mortality and improve the prognosis of the critically ill patients. Strategies include adequate hemodynamic support, avoidance of nephrotoxic drugs, and renal replacement therapy if it is necessary. The proportion of continuous renal replacement therapy (CRRT) in COVID-19 patients ranged from 1.5% to 9.0%, and the proportion of CRRT in severe and critically ill patients admitted to ICU ranged from 5.6% to 23%.[36] In a group of COVID-19 patients with invasive mechanical ventilation, up to 61.1% patients need to receive CRRT. Extracorporeal therapies may help to remove cytokines and prevent CRS-induced organ damage. Applicable blood purification modes include hemoperfusion, plasma adsorption or high-dose CRRT with high cut-off membranes.[6]

With regard to the prognosis of COVID-19, 3.4% to 41.8% of COVID-19 patients suffered from ARDS, whereas 7.4% to 32.8% of COVID-19 patients received mechanical ventilation treatment (including non-invasive and invasive). In addition, 5.0% to 31.7% of COVID-19 patients were admitted to the ICU, and the mortality rate of critically ill COVID-19 patients reached 63.9%.[13-16] Kidney involvement is associated with poor prognosis of COVID-19. Patients with AKI have a higher mortality rate compared to patients without AKI. In a population of 1099 laboratory-confirmed COVID-19 patients, AKI occurred only in six patients, but unfortunately an endpoint event (admission to ICU, use of mechanical ventilation, or death) was triggered in four of these patients. These data suggest that the prognosis of the patient is poor once AKI occurs.[6] In addition, the abnormalities of urine sediment tests, such as proteinuria and hematuria, also indicate a poor prognosis for the patient. Research data analysis indicated that increased baseline Scr/urea nitrogen, peak Scr >133 μmol/L, AKI, proteinuria, and hematuria were shown to be independent risk factors for the mortality of the patients with COVID-19.[11]

Overall, kidney involvement in patients with COVID-19 usually manifested with hematuria, proteinuria, or mild fluctuations in renal function, and changes in renal function are causal and harmful. Meanwhile, critically ill patients are much more prone to suffer from AKI followed by poor prognosis. For these patients, clinicians need to closely monitor changes in renal function, and early diagnosis and active treatment may reduce the incidence of AKI and the mortality rate.

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**Conflicts of interest**

None.

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