

COVID-19 Acute Kidney Injury: Current Knowledge and Barriers of Research

COVID-19 has accounted for over 2.4 million fatalities worldwide (Coronavirus Resource Center, Johns Hopkins University, February 2021). The disease is caused by the infection of a novel coronavirus, named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). While the upper respiratory airways serve as a port of entry for viral infection, SARS-CoV-2 has broad tropism owing to the presence of its cellular receptor angiotensin-converting enzyme-2 (ACE2) and the cellular transmembrane protease serine 2 (TMPRSS2) required for viral S activation on a large number of tissues including heart, brain, intestines, and kidneys. Because of the systemic tropism, infection with SARS-CoV-2 leads to a wide spectrum of clinical presentations. The severity of the disease ranges from asymptomatic to mild and from self-limited symptoms to severe acute respiratory distress syndrome and death. A hyperinflammatory state and cytokine release syndrome (“cytokine storm”) have been described as characteristics of the severe COVID-19 and this is associated with multiorgan failure.^[1,2]

Studies from both China, Europe, and USA suggest that renal complications are frequent in COVID-19 patients. A meta-analysis study on almost 5000 COVID-19 patients showed that renal dysfunction and significant increase of acute kidney injury (AKI) are associated with disease severity and prognosis.^[3] In fact, while about 10% of patients had elevated serum creatinine and blood urea nitrogen, more than 57% of the patients presented proteinuria at various degree, and the incidence of AKI in nonsurvivors was significantly higher than in survivors (52.9% vs. 0.7%, respectively).^[4] Data collected in over 3000 patients at Mount Sinai Hospital showed that AKI occurred in 46% of patients and within these 19% required renal replacement therapy (RRT).^[5] CKD is a major risk factor for AKI, and some patients with AKI develop CKD or ESRD while they recovered from COVID-19 pneumonia.^[5] However, about two-third of these patients recovered from AKI.^[5] While comorbidities heighten the mortality of COVID-19 patients, direct organ failure ultimately determines the disease outcome. In addition, kidney biopsies of COVID-19 patients with significant proteinuria revealed *de novo* glomerulopathies such as collapsing focal segmental glomerulosclerosis, minimal changes disease, and membranous nephropathy.^[6,7] However, the underlying mechanisms driving kidney injury remain poorly understood.

Given the systemic response to viral infection, the causes of AKI are likely multifactorial, such as cytokine storms, organ-organ crosstalk, and drug toxicity, which are quite similar to the causes of AKI in the regular septic patients from intensive care unit. However, a direct viral infection of kidney cells likely also contributes to AKI.^[8] The initial reports suggest local viral infection of kidney cells such as proximal tubular epithelial cells and podocytes by electronic microscopy finding of viral particles and immunofluorescence staining of viral proteins.^[9,10] However, these findings have been questioned by several renal pathologists and a series of renal biopsy reports did not reveal virus in the kidney cells by immunostaining and RNA *in situ* hybridization.^[6,7] These discrepancies could result from sampling issues, due to the focal nature of the infection, and the timing of sampling, due to the nature of transient viral infection. Indeed, a recent report established the presence of virus in kidney cells using multiple technologies such as immunofluorescence staining of viral particles, RNA *in situ* hybridization, and polymerase chain reaction analysis.^[2] They further confirmed that viral copy number in the kidney cells was associated with AKI and overall outcomes in COVID-19 patients.^[11] They found that albuminuria and hematuria could be an early marker for overall prognosis of COVID-19 patients with pneumonia.^[12] In addition, the finding of virus in urine indicates its presence in the kidneys.^[13] Nevertheless, the role of direct viral infection of kidney cells in AKI remains to be elucidated. In addition, it has been shown that viremia is rare in COVID-19 patients. Therefore, how SARS-CoV-2 infects kidney cells remains obscure.

In comparison to COVID-19-associated kidney injury, the pathogenesis of HIV-associated nephropathy (HIVAN) has been studied for more than 3 decades. Similarly, it has been argued for decades whether local infection of HIV in the kidney cells contributes to kidney injury. This has been confirmed by the transplant experiments showing that transplantation of HIV-infected kidneys into a normal mice developed kidney disease while transplantation of normal kidneys into HIV mice did not have kidney disease.^[14] In addition, several studies have shown that HIV infects kidney cells such as renal tubular cells and podocytes and that the kidney represents a separate compartment for HIV replication.^[15-17] HIV can be transferred to kidney cells through cell–cell contact with HIV-infected T-cells^[18,19] and nontraditional

receptors such as heparan sulfate proteoglycans.^[19] Whether SARS-CoV2 infects kidney cells through cell–cell contacts remains to be determined.

Despite many research works have been published in this field, two main obstacles remain to the progression of the studies on the alteration of renal function and SARS-CoV-2 infection-associated AKI: (a) the lack of animal models of viral pathogenesis that presents renal phenotype and that is easily amenable to genetic manipulation and (b) the safety containment required to handle the virus, which excludes most laboratories from the possibility of performing the necessary experimentation.

Significant progress has been made on the understanding of the pathogenesis of HIVAN due to the availability of the HIV-1 transgenic mouse models such as Tg26 mice. However, in comparison to HIV genes, SARS-CoV2 has a large genome and many of the viral proteins likely contribute to the pathogenesis of kidney cell injury. Therefore, it is challenging to make a transgenic mouse model expressing whole viral genome or individual transgenic mouse models for different viral genes. Hamsters and ferrets have proven representative models for the study of SARS-CoV-2 infection. However, they lack transgenic models and research reagents such as antibodies, thus making the investigators difficult to study the molecular mechanisms of kidney cell injury induced by SARS-CoV-2. Mice would be a great model to study kidney cell injury because of the large number of genetically engineered inbred genotypes and research tools that are already available. Unfortunately, the divergence of the murine ACE2 receptor from the human analog makes mice unsuitable host for SARS-CoV-2 infection. New transgenic models are generating to address these challenges.

Clinically, patients with COVID-19 AKI should be managed similarly to those with AKI of other etiologies such as keeping hemodynamic stable and avoiding nephrotoxic medications.^[8] It is also important to adjust dosages of medications according to actual renal function in these AKI patients. RRT should be initiated when there are indications. However, the evidence is still lacking on the use of RRT to remove cytokines in these patients. Future studies are required to determine the role of the antivirals, steroids, and systemic anticoagulants in the development and progression of AKI. It is also important to determine the pharmacokinetics of antivirals and immunomodulatory drugs during different phases of AKI and progression to acute kidney disease and with different types of RRT. The research is also required to investigate the nutritional status in patients with COVID-19 AKI and determine what is the optimal nutritional management for these patients.

In summary, patients with COVID-19 often develop kidney disease including AKI and glomerular disease. The pathogenesis of COVID-19 kidney disease remains unclear. It is likely that multiple factors contribute to the development of COVID-19 kidney disease, and direct viral infection of kidney cells may also play a role. Research in this area is limited due to lacking of reliable animal models. Therefore, it is critical for us to develop such models to help us better understand the pathogenesis of this disease. The management of patients with COVID-19 AKI should be similar to those with AKI of other etiologies.

Yifei Zhong, John Cijiang He¹

Department of Nephrology, Shanghai Traditional Chinese Medicine School, Longhua Hospital, Shanghai, China, ¹Department of Medicine, Division of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Address for correspondence: Prof. John Cijiang He, Department of Medicine, Division of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. E-mail: cijianghe@126.com

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