INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is still prevalent worldwide and its rapid international spread poses a threat to global public health. According to the situation report from the World Health Organization, on February 28, 2021, this newly emerging respiratory infectious disease has affected 223 countries with more than 113.5 million confirmed cases and more than 2.52 million reported deaths. Although the main dysfunction of COVID-19 is characterized by diffuse alveolar damage and acute respiratory failure, damage to other organs such as heart, brain, and the kidney is also of concern because this multiorgan involvement patients tend to have more severe symptoms and worse prognosis. Nephrologists have concerned mainly with the relationship between COVID-19 and kidney injury. However, there are controversial findings about the observations of kidney involvement in COVID-19 patients. From the clinical experience of our medical team in Wuhan, abnormal urine tests (such as microscopic hematuria or mild proteinuria) may occur in the COVID-19 patients with mild to moderate clinical symptoms, but only a few of patients suffered with acute kidney injury (AKI). AKI mostly occurred in the elderly patients with multiple underlying disease and the critically ill patients with COVID-19. The prognosis of the patients with AKI was poor.
With the deepening understanding of COVID-19, many clinical data and high-quality research articles have been published recently.\textsuperscript{[5‑7]} Clinical data evidence regarding kidney involvement in COVID-19 patients is becoming more and more detailed.\textsuperscript{[7‑10]} This review summarizes the kidney involvement, clinical characteristics, pathological characteristics, pathogenesis, treatment strategies in the patients with COVID-19, and the impacts of kidney injury on the prognosis to further understand the disease. We hope that our work will help medical staff who are facing this pandemic on a daily basis.

THE PREVALENCE OF KIDNEY INJURY IN PATIENTS WITH CORONAVIRUS DISEASE 2019

The incidence of kidney injury in COVID-19 varies from different studies. According to the early data from China, the incidence of AKI reported was not very high.\textsuperscript{[7,11‑13]} Although findings of reports on the incidence of AKI are inconsistent, all the studies have shown that the incidence of AKI is higher in the elderly, the patients with multiple underlying disease, and the critically ill patients with COVID-19.\textsuperscript{[3,4,8‑10]} Therefore, the incidence of AKI reported in different studies should be interpreted dialectically, because of it largely depends on the critically ill ratio in the enrolled patients with COVID-19 in each study. Our clinical experience in Wuhan showed that there were few of AKI occurred in COVID-19 patients with the type of mild or moderate. AKI occurs mainly in the elderly and critically ill patients with COVID-19.\textsuperscript{[3,4]}

The incidence of kidney injury in critically ill patients with coronavirus disease 2019

In clinical, COVID-19 is classified into four types, such as mild, moderate, severe, and critical.\textsuperscript{[2]} According to the report published by the Chinese Center for Disease Control and Prevention (CDC), approximately 14% and 5% cases in the patients with COVID-19 were classified as severe or critical type, respectively [Figure 1].\textsuperscript{[5]} There was a higher incidence of AKI in critically ill patients, especially in the condition of a shortage of medical resources. The case rate of AKI in critically ill patients reported ranges from 14% to 81%.\textsuperscript{[8]} Cheng et al.\textsuperscript{[9]} first reported the association between abnormal kidney function and mortality in hospitalized patients with COVID-19. They investigated the occurrence of AKI in hospitalized patients with COVID-19 in Wuhan Tongji Hospital. In this cohort of patients (701 cases), the rate of severe type patients and inhospital deaths was 42.4% and 16.1%, respectively. The occurrence rate of proteinuria, hematuria, and elevated serum creatinine (Scr) was 43.9%, 26.7%, and 14.4%, respectively. About 5.1% of patients suffered from AKI during hospitalization. Further analysis indicated that patients with impaired renal function had higher risk for inhospital mortality rate. Abnormal the ratio of Scr/blood urea nitrogen (BUN) under the baseline, peak level of Scr more than 133 μmol/L, AKI, proteinuria, and hematuria were the independent risk factors for the mortality of the patients with COVID-19. Yang et al.\textsuperscript{[6]} observed the clinical course and outcome of 52 critically ill adult patients with COVID-19 patients, especially in critically ill patients. RR: Respiratory rate; SpO\textsubscript{2}: Pulse oxygen saturation; PaO\textsubscript{2}/FiO\textsubscript{2}: Partial pressure of arterial oxygen to fraction of inspired oxygen ratio

| Coronavirus Disease 2019 (COVID-19) (Percentage) | Mild/Moderate (14%) | Severe (14%) | Critical (5%) |
| --- | --- | --- | --- |
| No pneumonia/mild paranasal | | | |
| pneumonia, RR ≥ 10/min, BO_{2} ≤ 93%, PaO_{2}/FiO_{2} ≤ 300, and/or lung infiltrates > 50% within 24 to 48 hours | | | |
| | | respiratory failure, septic shock, and/or multiple organ dysfunction or failure | |

| Etiology and Pathogenesis | Secondary Factors | Direct Coronavirus Infection | Cytopathic Effects | Immune Mechanism | Others |
| --- | --- | --- | --- | --- | --- |
| Hypoxia | Inflammation | Cytokine Storm | Congestion disorder | Lung-kidney cross-talk | Rhabdomyolysis |

| Kidney Involvement | All COVID-19 patients (Percentage) | Acute Kidney Injury (AKI) (Percentage) |
| --- | --- | --- |
| Proteinuria 7.2%–63% | 0%–20% | 2.9%–8.1% |
| Hematuria 26.7% | Stage 1 18% | Stage 1 10.2%–44% |
| Elevated Scr 4.5%–19% | Stage 2 3% | Stage 2 5.3%–10% |
| | Stage 3 3% | Stage 3 3.9%–27% |

| Treatment Strategy | COVID-19 | COVID-19 with AKI |
| --- | --- | --- |
| controlling the source of infection | Adequate hemodynamic support | |
| Strengthening personal protection | Avoidance of nephrotoxic drugs | |
| Early diagnosis/isolation | Supportive treatment | |
| Symptomatic supportive care | Renal replacement therapy when necessary | |

| Outcomes (Mortality) (Percentage) | All COVID-19 Patients | Critically ill patients | COVID-19 with AKI |
| --- | --- | --- | --- |
| 2.22% | 8.1%–63.0% | 33.3%–96.6% |

| Conclusions | AKI frequently develops at later stages in critically ill patients, and it markedly influences the outcome of COVID-19. The importance of AKI in COVID-19 patients has been increasingly recognized, early diagnosis and active treatment may reduce the mortality of the patients with COVID-19. | |

Figure 1: Summary of the overall situation of COVID-19 with AKI. This figure generalized the epidemiology, clinical characteristics, etiology and pathogenesis, treatment strategy, and prognosis of kidney injury in patients with COVID-19 and gets the conclusion that we need to pay special attention to kidney injury in COVID-19 patients, especially in critically ill patients. RR: Respiratory rate; SpO\textsubscript{2}: Pulse oxygen saturation; PaO\textsubscript{2}/FiO\textsubscript{2}: Partial pressure of arterial oxygen to fraction of inspired oxygen ratio.
Several prospective observational studies investigated the clinical characteristics of 226 critically COVID-19 patients of 16 hospitals in Wuhan, China. 155 (68.6%) had one coexisting disease at least, 85 (37.6%) received invasive mechanical ventilation. 57 (25.2%) patients suffered from AKI, which including 23 (10.2%), 12 (5.3%), and 22 (9.7%) patients with AKI of Stage 1, Stage 2, and Stage 3, respectively. A retrospective study mainly focusing on renal function of the patients with COVID-19 investigated 59 patients, including 28 severe cases and three deaths. Of these patients, 63% had proteinuria, and 19% had increased Scr levels. All three deceased patients suffered from AKI. The renal imaging of 27 patients with COVID-19 undergoing computed tomography (CT) scans indicated that the CT value of bilateral renal parenchyma was significantly lower than that of normal. This result showed that there was renal parenchyma inflammation or edema in those patients with COVID-19. Studies from the other countries have reported higher occurrence of AKI in patients with COVID-19, especially the patients in critical condition. Richardson et al. assessed the outcomes for 2634 patients hospitalized with COVID-19 in the New York City area, who were discharged or died at the study end point. During hospitalization, 373 patients (14.2%) were treated in the ICU, 320 (12.2%) received invasive mechanical ventilation, and 553 (21%) died. The incidence of AKI was higher than that reported in China, with 523 (22.2%) patients suffered from AKI, and 81 (3.2%) were treated with kidney replacement therapy. In a multicenter observational cohort study enrolled with 22,122 patients, 2,600 had tested positive for SARS-CoV-2. In summary, few COVID-19 patients were compared. The results showed that the incidence of AKI in the patients with COVID-19 was higher than that of the patients without COVID-19 (30.6% vs. 18.2%). Compared with the AKI patients without COVID-19, the AKI patients with COVID-19 had higher proportion of severe AKI (Stage 2 or 3) (11.1% vs. 4.9%) and dialysis-requiring AKI (8.5% vs. 3.6%). Moreover, fewer patients recovered from AKI in the patients with COVID-19 (58.0% vs. 69.8%). In this study, 25.2% of COVID-19 patients admitted to ICU finally. Those patients had higher occurrence of AKI (58%). 11.1% of the patients were at AKI Stage 2 or 3, 15% of them were dialysis-requiring AKI, and 30% of the patients died. It indicated that AKI was common in COVID-19 patients, especially in the patients at ICU, with higher mortality and poor kidney prognoses. A meta-analysis including 30,657 hospitalized patients with COVID-19 from 54 studies, the result showed that the pooled incidence of AKI among patients admitted to ICU was 46.0%, which was higher than that of non-ICU patients (12%). 19% of COVID-19 patients in ICU required renal replacement therapy (RRT). Several reports on the high incidence of AKI in critically ill patients are mostly from Europe. Data from France showed higher incidence of AKI than previously reported. In this research, 100 patients with COVID-19 were admitted in ICU. AKI occurred in 81 patients (81%), including 44, 10, and 27 patients were in AKI Stages 1, 2, and 3, respectively. The clinical evidence above showed that the incidence of renal impairment is high in hospitalized critically ill patients with COVID-19, and it is related to inhospital death closely.

**Severe acute respiratory syndrome coronavirus 2 infection does not commonly result in acute kidney injury among the coronavirus disease 2019 patients with the type of mild to moderate**

According to the first-line clinical data, the occurrence of AKI is almost rare in the most COVID-19 patients with mild symptoms only. Wang et al. investigated the incidence of AKI in mild to moderate type COVID-19 patients. Of the 116 patients enrolled in their study (11 patients had ARDS), only 12 patients (10.8%) showed mild increases of Scr, eight patients (7.2%) showed albuminuria, and no patient was diagnosed with AKI. Wang et al. 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. In a population of 1099 laboratory-confirmed COVID-19 patients, only 1.6% patients had the level of Scr more than 133 µmol/L. In addition, AKI occurred in 6 (0.5%) patients only. It indicated that the kidney impairment was not common in these patients. Chen et al. analyzed the epidemiological and clinical characteristics of 99 cases with COVID-19, and they concluded that AKI only occurred in 3 (3%) patients. A retrospective study of 201 patients with confirmed COVID-19 showed that 4.5% of patients had elevated Scr level. However, no patient met the diagnostic criteria for AKI. Another retrospective cohort study enrolled a total of 191 COVID-19 patients, results also showed that, totally 28 COVID-19 patients suffered from AKI, 27 of them died. Among the nonsurviving patients (54), 27 case of AKI occurred (50%), however, among the surviving patients (137), only 1 case of AKI occurred (1%). In summary, few COVID-19 patients in the mild to moderate type had kidney damage, which manifested as proteinuria, hematuria, or a slight elevated the level of Scr. However, AKI is not prevalent in these patients with COVID-19.

**PATHOLOGICAL CHANGES OF KIDNEY**

The first report of kidney pathological changes of COVID-19 comes from China. The authors got the renal tissue sample...
using minimal invasive autopsies. They observed that renal tissue presented with swollen glomerular endothelial cells, a small amount of protein exudate in the glomerular Bowman’s capsule, and transparent thrombosis in intracapillary. Moreover, edema, vacuolar degeneration, and shedding of renal tubular epithelial cells were observed. Protein casts and pigment casts were observed in the lumen of renal tubules, and renal interstitial hyperemia, microthrombosis, and focal fibrosis were also observed. However, positive SARS-CoV-2 antigen or virus was not detected in the samples of kidney using immunohistochemistry and polymerase chain reaction (PCR) technique.\textsuperscript{[21]} Meanwhile, this study did not describe the patient’s case data and the changes of renal function during the course of the disease in detail.\textsuperscript{[21]} Su et al.\textsuperscript{[22]} elaborated on the renal clinical and histopathological data of 26 postmortem patients with COVID-19 in China. Nine of those patients manifested with increased Scr and/or new-onset proteinuria. Under the light microscope, obvious proximal renal tubular injury was mainly observed, including loss of brush border, nonisometric vacuolar degeneration, dilatation of the tubular lumen with cellular debris, pigment casts, and even frank necrosis, but there was no interstitial inflammation. The lumen of capillaries could see erythrocyte aggregates but did not see the accumulation of platelets and fibrin materials. Furthermore, the researchers found the clusters of coronavirus-like particles under the electron microscope, mainly located in tubular epithelium and podocytes. Immunostaining also indicated that SARS-CoV-2 nucleoprotein antibody was positive in the renal tubules. This study presented the pathological evidence for the direct infection of the kidney by the SARS-CoV-2 virus for the first time. Another postmortem study in UK patients with severe fatal COVID-19 also gets similar histopathological findings in kidneys. They observed notably acute tubular injury in all nine patients examined. In some patients, glomerular microaneurysms and thrombosis and interlobular arterial thrombosis were found in the kidneys. Intracellular SARS-CoV-2 RNA could also be detected in the kidney through real-time quantitative reverse transcription PCR (qRT-PCR).\textsuperscript{[23]} However, their results caused controversy subsequently. Sharma et al.\textsuperscript{[24]} evaluated biopsied kidney samples from ten patients with COVID-19 who had clinical features of AKI, proteinuria, or hematuria. Results showed that all biopsy samples manifested with varying degrees of acute tubular necrosis (ATN), but the immunohistochemical staining of SARS-CoV-2 in the kidney biopsy samples was negative in all the patients. On the other hand, a meta-analysis showed that no SARS-CoV-2 was detected in urine samples.\textsuperscript{[25]} Another study reported only a positive rate of 0.8% for viral RNA in the urine samples using qRT-PCR.\textsuperscript{[26]} A few of case reports observed the pathological manifestations of collapsing glomerulopathy in patients with COVID-19.\textsuperscript{[24,27,28]} In short, COVID-19 patients with AKI had different degrees of renal tubular necrosis in pathological manifestations. There are different opinions on whether SARS-CoV-2 can be detected in the kidney tissue, but no COVID-19-specific renal pathological changes have been found.

**ETIOLOGY AND PATHOGENESIS OF KIDNEY INJURY IN CORONAVIRUS DISEASE 2019 PATIENTS**

The pathogenesis of kidney injury in COVID-19 patients remains controversial. The etiology of the kidney injury is likely multifactorial. It may involve not only direct virus invasion but also injured in the form of inflammation, cytokine storm, immune dysregulated, and hypercoagulable state, etc. However, according to our clinical experience and the analysis of kidney damages in the COVID-19 patients, most of the kidney injuries occur in elderly patients with underlying diseases or with critical conditions. It indicated that kidney injury in COVID-19 patients was more likely due to secondary factors, such as hypoxemia, hemodynamic instability, inappropriate use of diuretics, nephrotoxic exposure, severe inflammatory response, and other comprehensive factors. It may be the causation that the renal pathological lesions of the patients with COVID-19 were inconsistent.\textsuperscript{[22,23,29]} In addition, a few of research showed that the high expression of angiotensin-converting enzyme 2 (ACE2) receptor in the kidney may play a significant role in the occurrence of renal injury.\textsuperscript{[30-33]} However, all the mechanisms listed above need to be further explored and verified.

**Kidney damage caused by secondary factors**

In some patients, kidney injury only presented with mild elevation of Scr or BUN. Nausea, vomiting, anorexia, malnutrition, insufficient intake of calories, and insufficient blood volume may attribute to the temporary abnormal renal function. In the critically ill patients with COVID-19, the incidence of AKI increased may be attributed to secondary injury by virtue of hypoxemia, severe infection, acid-base electrolyte balance disorder, and hemodynamic instabilities, including hypotension and infection-induced septic shock. The use of high-dose vascular active drugs (such as vasopressor) may cause renal hypoperfusion. Molendina et al.\textsuperscript{[10]} noted that compared with the COVID-19 patients without AKI, AKI patients developed more hypotension, used more vasopressors and diuretics, had more inflammatory reactions (higher level of C reactive protein and ferritin), and require more mechanical ventilation treatment.\textsuperscript{[10]} It suggested that AKI in COVID-19 patients may be caused by these typical secondary risk factors. However, after adjusted by all the traditional risk factors, COVID-19
remained an independent risk factor leading to AKI. It indicated that SARS-CoV-2 infection maybe has another pathway to induce AKI in the patients with COVID-19. A research report showed that fractional excretion of sodium (FENa) <1% was observed in 76% of patients with AKI, and urinary granular casts were found in 21% of patients. The authors summed up the etiology of AKI as following: ATN accounts for 28%, prerenal 13%, prerenal/ATN 11%, other causes 4%, but there was still 45% of patients with unknown etiology. All the above evidence shows that secondary factors are indeed a nonnegligible cause of AKI in patients with COVID-19. Nonetheless, COVID-19-specific pathogeneses also play a role in the process of coursing kidney damage.

**Direct coronavirus invasion, cytopathic effects, and immune mechanism**

The new coronavirus is thought to be of bat origin due to its 96% sequence identity at the whole-genome level to a bat coronavirus. It also shares 79.6% sequence identity to SARS-CoV-2 and uses the same receptors entry to cells as SARS-CoV-2. The novel coronavirus enters cells mainly by binding to ACE2 receptors on the cell surface through the viral spike (S) protein. The spike protein of coronaviruses is functionally divided into the S1 domain which is responsible for receptor binding and the S2 domain responsible for cell membrane fusion. The transmembrane serine protease (TMPRSS) family acts as key cellular proteases in coronavirus S protein priming, which plays an important role after coronavirus enter cells.

Therefore, cells with ACE2 expression may act as target cells for SARS-CoV-2. Using single-cell transcriptome analysis (scRNA-seq), researchers reported that in addition to lung tissue, ACE2 is also expressed in other organs, such as cardiovascular, digestive, and urinary systems. Moreover, kidney proximal tubule cells exhibit significantly high ACE2 expression with an approximate proportion of ACE2-positive cells of 4%, which is higher than that of respiratory epithelial cells (2%). Pan et al. reported that ACE2 and TMPRSS genes (by scRNA-seq analysis) are significantly co-expressed in podocytes and proximal convoluted tubules, suggesting that the cells of kidney may be a potential target host cell for COVID-19. They also observed that the expression level of ACE2 in the kidneys of Westerners is higher than that of in Asians, suggesting that Westerners with COVID-19 may be more likely to develop kidney injury. Some reports showed that proteinuria is a typical clinical symptom in the patients with COVID-19, which may be owing to the damage of podocyte in those patients.

A few of studies reported that the SARS-CoV-2 can be detected in the urine of COVID-19 patients. Researchers also found evidence of active replication of the virus in kidney tissue, based on the detection of subgenomic viral RNA transcripts in autopsy samples from the patients with COVID-19. Khan et al. summarized the four types of evidence of direct kidney infected by SARS-CoV-2, namely discovery of live viruses, detection of viral proteins by immunocytochemistry, observation of viral-like particles under electron microscopy, and detection of viral RNA using RT-PCR. Most of the aforementioned evidence was from the cases with severe multisystemic involvement. It suggested that direct SARS-CoV-2 infection of the kidney may be one of the mechanisms for developing critically ill conditions in patients with COVID-19.

It is speculated that SARS-CoV-2 may cause kidney damage by viral invasion through binding to the ACE2 receptors of kidney cells and then triggers cytotoxic damage of renal tubules and podocytes by the innate immune system, finally resulting in AKI, proteinuria or hematuria. However, high level of ACE2 receptor expression in the kidney does not result in as severe renal damage as the one in the lungs. Furthermore, whether SARS-CoV-2 can be detected in urine is also controversial. It suggested that the pathogenesis of COVID-19 may have another pathway of non-ACE2. It remains unknown whether COVID-19 can cause direct kidney damage through ACE2 receptors, and the mechanisms of renal damage require additional research.

**Inflammation and cytokine storm-mediated kidney damage**

Cytokine storm, also known as cytokine release syndrome (CRS), refers to the phenomenon of rapid release of multiple cytokines in the body, which generally occurs after infection or cellular immunotherapy. CRS is an important cause of ARDS and multiple organ dysfunction syndrome (MODS). Current data have shown that CRS is one of the pathophysiological mechanisms of COVID-19 in critically ill patients. Compared to non-ICU patients with COVID-19, ICU patients have higher plasma levels of interleukin (IL)-2, IL-7, IL-10, granulocyte colony-stimulating factors (G-CSF), interferon-gamma inducible protein-10, monocyte chemoattractant protein-1, macrophage inflammatory protein 1-alpha, and tumor necrosis factor-alpha (TNF-α). Researchers also found a higher IL-6 level in the COVID-19 patients with AKI than that in the patients without AKI. CRS can also cause kidney damage through mechanisms including increased vascular permeability under inflammatory conditions, insufficient effective circulating blood volume, hypotension, and endothelial cells damage.

**Other possible pathogenesis**

Coagulation disorder is also a prominent clinical manifestation of COVID-19. Hypercoagulable state especially marked
by elevation in D-dimer levels in patients with COVID-19. It also plays a very important role in the patient’s kidney injury.\[9,20\] Lee et al.\[29\] found that the level of blood D-dimer was significantly higher in the AKI patients without kidney function recovery than that of in the AKI patients with kidney function recovery. High-level D-dimer has also been recognized as a predictor of the need for dialysis in the critically ill patients with COVID-19.\[38\] Lung-kidney cross-talk, rhabdomyolysis, and so on are also thought the cause of kidney damage in patients with COVID-19.\[36\]

MANAGEMENT AND PROGNOSIS OF CORONAVIRUS DISEASE 2019 WITH ACUTE KIDNEY INJURY

No targeted treatment to SARS-CoV-2 has been recommended according to the guidelines for diagnosis and treatment of COVID-19 (eighth edition) provided by the Chinese National Health Commission.\[21\] 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 and/or isolation, and symptomatic supportive care for the affected patients. Antibacterial agents are ineffective, and no antiviral agents have been proven to be beneficial for treating COVID-19. In addition, although 45% of COVID-19 patients received methylprednisolone treatment, the benefit of hormone therapy is currently uncertain.\[12\] Findings of the following studies have shown that AKI usually occurs in the early period of hospitalization (within 2 days). Lee et al.\[29\] reported that the time interval from hospitalization to the occurrence of AKI was an average of 2.2 days in AKI Stage 1, 2.4 days in AKI Stage 2, and 1.6 days in AKI Stage 3, respectively. Therefore, early detection and protection of kidney function are important to reduce mortality and improve prognosis in the COVID-19 patients with AKI. Management recommendations focus on AKI in COVID-19 is based largely on the clinical experience. The treatment of AKI in the COVID-19 patients still relies on supportive treatment to a large extent.\[39\] Due to the absence of specific therapies, all therapeutic options should be considered according to each patient’s needs. The strategies of renal protection include adequate hemodynamic support, avoidance of nephrotoxic drugs, regular monitoring of Scr, urine output, and RRT when necessary. The maintenance of fluid balance according to volume responsiveness and tolerance assessment is one of the important options. Either volume overload or volume depletion should be avoided in the patients with COVID-19 because these two conditions can lead to the occurrence of AKI and the deterioration of renal function.\[39\]

Ventilation therapy especially lung-protective ventilation also could reduce the occurrence and severity of AKI in the COVID-19 patients by limiting ventilation-induced hemodynamic effects and the cytokine burden on the kidney.\[40\] However, it should be aware that relatively high positive end-expiratory pressure may further compromise cardiac output in the setting of relative hypovolemia, thereby affecting renal function. When the patient fails conservative treatment, timely initiation of RRT treatment is also an important treatment strategy. According to statistics, about 1.5%–9.0% patients with COVID-19 need the therapy of continuous RRT (CRRT), and 5.6%–23% severely and critically ill patients in ICU need CRRT treatment.\[6,9,12\] In a group of COVID-19 patients with invasive mechanical ventilation, up to 61.1% patients received CRRT.\[13\] CRRT 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 cutoff membranes.\[37\] In addition to CRRT, prolonged intermittent RRT (PIRRT) also could reduce all-cause mortality in COVID-19 patients undergoing invasive mechanical ventilation. In the study, researchers observed that increased IL-2 receptor, TNF-α, and procalcitonin levels were significantly associated with an increased risk of all-cause mortality. Furthermore, in the PIRRT group, IL-6 showed a significant difference before and after treatment. All the above evidence indicate that RRT may be beneficial due to the removal of pro-inflammatory cytokines.\[41\] The main indications of RRT include failure or insufficient of supportive therapies or significantly elevated levels of inflammatory parameters or cytokines.\[39\] Traditional Chinese Medicine (TCM) is also considered to have played a certain role in the treatment of COVID-19. For instance, respiratory detox shot, a TCM has been applied for severe or critically ill patients with COVID-19.\[42\] Based on the theory of syndrome differentiation, balance of Yin and Yang, and enhance body immunity, TCM has achieved certain curative effects by shortening the recovery time of the patients, delay disease progression and reduce mortality rate. Furthermore, TCM can also exhibit the protective effect for heart, kidney, and other organs.\[43\] The recommendations of the above treatment options are mostly based on the experience of doctors; the treatment of COVID-19 with AKI still needs to be tested in ideally randomized trials.

With regard to the prognosis of COVID-19, as reported by Chinese CDC, among a total of 44,672 confirmed cases of COVID-19, the overall case-fatality rate (CFR) in China was 2.3% (1023 deaths). The CFR increases with age and severity of illness. The CFR was 14.8% in those cases aged 80 years and older. Among the critically ill cases, the CFR was as high as 49.0%.\[5\] It indicated that the poor
Table 1: Summary of the clinical features of patients with coronavirus disease 2019

| Study          | n   | Age, average (range) | Severe/ ICU, n (%) | Comorbidities, n (%) | Complications, n (%) | Kidney injury, n (%) | Treatment, n (%) | Mortality, n (%) |
|----------------|-----|----------------------|--------------------|----------------------|----------------------|---------------------|------------------|------------------|
| Huang et al.[7] | 41  | 49 (41-58)           | All: N/A           | Age: 13 (32)         | Shock: 3 (7)         | AKI: 3 (7)          | Antibiotics: 41 (100) | 6 (15)          |
|                |     |                      | ICU: 13 (31.7)     |                      |                       | Elevated Scr: N/A   | Antiviral: 38 (93)  |                  |
| Cheng et al.[8] | 701 | 63 (50-71)           | All: 297 (42.6)    | HypT: 233 (33.4)     | AKI: 26 (5.1)        | Elevated Scr: 101 (14.4) | Antibiotics: 600 (85.6) | 113 (16.1)     |
|                |     |                      | ICU: 73 (10.4)     | CVD: 100 (14.3)      |                      | Proteinuria: 194 (43.9) | Antiviral: 658 (93.9) |                  |
| Wang et al.[11]| 116 | 54 (38-69)           | All: 46 (39.7)     | HypT: 43 (37.1)      | Shock: 12 (8.7)      | AKI: 5 (3.6)        | Antibiotics: N/A     | 7 (6.03)        |
|                |     |                      | ICU: 11 (9.5)      | CVD: 18 (15.5)       |                      | Elevated Scr: 12 (10.8) | Antiviral: 124 (89.9) |                  |
| Wang et al.[12]| 138 | 56 (42-68)           | All: 36 (26)       | HypT: 43 (37.1)      | Shock: 12 (8.7)      | AKI: 6 (0.5)        | Antibiotics: N/A     | 6 (4.3)         |
|                |     |                      | ICU: N/A           | CVD: 14 (10.1)       |                      | Elevated Scr: 12 (1.6) | Antiviral: 393 (35.8) |                  |
| Guan et al.[13]| 1099| 47 (35-58)           | All: 173 (15.7)    | HypT: 165 (15.0)     | Shock: 12 (1.1)      | AKI: 6 (0.5)        | Antibiotics: N/A     | 15 (1.4)        |
|                |     |                      | ICU: 33 (16.2)     | CVD: 27 (2.5)        |                      | Elevated Scr: 12 (1.6) | Antiviral: 353 (21.6) |                  |
| Li et al.[14]  | 59  | 52 (28-83)           | N/A                | N/A                  | AKI: N/A             | Elevated Scr: 11 (19) | Antibiotics: 637 (58)  | 3 (5.1)         |
| Richardson et al.[15] | 5700| 63 (52-75)           | All: N/A           | N/A                  | N/A                  | Elevated Scr: 32 (63) | Antiviral: N/A        | 553 (21)       |
|                |     |                      | ICU: 373 (14.2)    |                      |                      | Hematia: 29 (40)    | Glucocorticoid: N/A  |                  |
| Chen et al.[18] | 99  | 55.5 (SD 13.1)       | N/A                | N/A                  | AKI: 523 (22.2)      | Elevated Scr: N/A   | 70 (71)          |
|                |     |                      |                    |                      |                      | Proteinuria: N/A    | Antiviral: 75 (76)  | 11 (11)         |

Contd...
Clinical outcomes of COVID-19 associated with older age, multiunderlying disease, and critically ill conditions. Many studies have shown that AKI is also an independent risk factor for poor prognosis of COVID-19 patients. In the study from Joseph et al.,\textsuperscript{[17]} more than half of the patients with AKI Stages 2 and 3 died before day 28. The analysis of outcome showed that the severity of AKI was associated with mortality at day 28 ($P = 0.013$). Compared to the patients without COVID-19, the mortality in the patients with COVID-19 was higher (14.7% vs. 3.1%), and the rates were higher among those who suffered AKI in both groups (29.6% vs. 11.3%). The prognoses of kidneys were also poorer since fewer patients with COVID-19 had recovered from AKI at the time of discharge from hospital.\textsuperscript{[10]} Another COVID-19-related study reported that the COVID-19 patients with AKI have a higher mortality rate compared to the patients without AKI (40% vs. 8%). In addition, among the patients with AKI, only 48% of them recovered to their baseline kidney function.\textsuperscript{[29]} Abnormal urine sediment tests, such as proteinuria and hematuria, also indicate a poor prognosis for the patient.\textsuperscript{[9,15]} A systematic review and meta-analysis evaluated the survival rate in AKI superimposed COVID-19 patients. The result showed that severe AKI (Stage 3 and/or need for CRRT) was associated with higher risk of mortality (risk ratio = 3.08).\textsuperscript{[44]}

## Table 1: Contd...

| Study            | $n$   | Age, average (range) | Severe/ICU, $n$ (%) | Comorbidities, $n$ (%) | Complications, $n$ (%) | Kidney injury, $n$ (%) | Treatment, $n$ (%) | Mortality, $n$ (%) |
|------------------|-------|----------------------|---------------------|------------------------|------------------------|----------------------|-------------------|-------------------|
| Wu et al.\textsuperscript{[19]} | 201   | 51 (43-60)           | All: N/A            | Shock: N/A             | AKI: N/A               | Antibiotics: 196 (97.5) | 44 (21.9)        |
|                  |       |                      | ICU: 53 (26.4)      | HypT: 39 (19.4)        | ARDS: 84 (41.8)        | Glucocorticoid: 62 (30.8) |                  |
|                  |       |                      |                     | CVD: 8 (4)             | Stage 3: 83 (8)        | Oxygen: 165 (82.1)    |                  |
|                  |       |                      | DM: 22 (10.9)       | Shock: 38 (20)         | Stage 1: 182 (18)      | Glucocorticoid: 57 (30) |                  |
|                  |       |                      | CKD: 2 (1)          | ACI: 33 (17)           | Stage 2: 29 (3)        | Oxygen: 41 (21)       |                  |
|                  |       |                      |                      | ARDS: 59 (31)          | Stage 3: 83 (8)        | ECMO: 3 (2)          |                  |
| Zhou et al.\textsuperscript{[20]} | 191   | 56 (46-67)           | All: 53 (28)        | Shock: 28 (15)         | AKI: 294 (29)          | Antibiotics: N/A     | 172 (17)         |
|                  |       |                      | ICU: 50 (26)        | Proteinuria: N/A       | Stage 1: 182 (18)      | Glucocorticoid: N/A  |                  |
|                  |       |                      |                      | Hematuria: N/A         | Stage 2: 29 (3)        | Vasopressors: 261 (26)|                  |
|                  |       |                      |                      |                       | Stage 3: 83 (8)        | Oxygen: N/A          |                  |
| Lee et al.\textsuperscript{[29]} | 1002  | 66 (53-76)           | All: N/A            | Shock: N/A             | AKI: 294 (29)          | Antibiotics: N/A     | 172 (17)         |
|                  |       |                      | ICU: 274 (27)       | ACI: N/A               | Stage 1: 182 (18)      | Glucocorticoid: N/A  |                  |
|                  |       |                      |                      | ARDS: N/A              | Stage 2: 29 (3)        | Vasopressors: 261 (26)|                  |
|                  |       |                      | DM: 387 (38)        | MODS: N/A              | Stage 3: 83 (8)        | Oxygen: N/A          |                  |
|                  |       |                      | CKD: 138 (14)       |                       |                       | ECMO: N/A            |                  |
|                  |       |                      |                      |                       |                       | NIV: N/A             |                  |
|                  |       |                      |                      |                       |                       | MV: 261 (26)         |                  |
|                  |       |                      |                      |                       |                       | CKRT: 59 (6)         |                  |
|                  |       |                      |                      |                       |                       | ECMO: N/A            |                  |

All: N/A; AKI: Acute kidney injury, ACI: Acute cardiac injury, ARDS: Acute respiratory distress syndrome, CKD: Chronic kidney diseases, CVD: Cardiovascular diseases, CKRT: Continuous kidney replacement therapy, DM: Diabetes mellitus, MV: Mechanical ventilation, ECMO: Extracorporeal membrane oxygenation, HypT: Hypertension, ICU: Intensive care unit, IMV: Invasive MV, NIV: Noninvasive MV, MODS: Multiple organ dysfunction syndrome, N/A: Not available, SD: Standard deviation, Scr: Serum creatinine

## CORONAVIRUS DISEASE 2019 IN PATIENTS WITH UNDERLYING KIDNEY DISEASE

According to the current statistics, approximately 2%–9.2% of patients with COVID-19 have renal underlying disease.\textsuperscript{[6,12,18,45]} Due to the decline of the body’s immunity and the application of immunosuppressive agents, patients with kidney disease have high risk to COVID-19, especially in patients who need regular centralized treatment, such as hemodialysis (HD) patients. This group of patients generally has less lymphopenia, lower serum levels of inflammatory cytokines, and more comorbidities, which poses challenges to the medical staff in the dialysis center. During the initial outbreak of COVID-19 in Wuhan, China, 37 out of 230 HD patients suffered from COVID-19 infection in a single HD center, and six patients died. However, the presumed causes of death were not directly related to pneumonia but were also in connection with cardiovascular diseases, cerebrovascular diseases, and hyperkalemia.\textsuperscript{[46]} During the early outbreak of COVID-19 in the USA, the first two deaths of COVID-19 cases were reported in an HD unit.\textsuperscript{[85]} Wang et al.\textsuperscript{[47]} described the clinical and epidemiological features of five cases HD patients with COVID-19. The authors observed
| Study          | n   | Age            | Comorbidities, n (%) | Complications, n (%) | Kidney injury, n (%) | Treatment, n (%) | Mortality, n (%) |
|---------------|-----|----------------|----------------------|----------------------|----------------------|------------------|------------------|
| Yang et al.   | 52  | 59.7 (SD 13.3) | All: 21 (40)         | Shock: N/A           | AKI: 15 (29)         | Antibiotics: 49 (94) | 32 (61.5)        |
|               |     |                | HypT: N/A            | ACI: 12 (23)         | ARDS: 35 (67)        | Antiviral: 23 (44) |                 |
|               |     |                | CVD: 5 (10)          |                       |                      | Glucocorticoid: 30 (58) |                 |
|               |     |                | DM: 9 (17)           |                       |                      | Oxygen: 33 (63.5) |                 |
|               |     |                | CKD: N/A             |                       |                      | NIV: 29 (56)    |                 |
| Huang et al.  | 13  | 49 (41-61)     | All: 5 (38)          | Shock: 3 (23)        | AKI: 2 (23)          | Antibiotics: 13 (100) | 5 (38)           |
|               |     |                | HypT: 2 (15)         | ACI: 4 (31)          | ARDS: 11 (85)        | Antiviral: 12 (92) |                 |
|               |     |                | CVD: 3 (23)          |                       |                      | Glucocorticoid: 6 (46) |                 |
|               |     |                | DM: 1 (8)            |                       |                      | Oxygen: 1 (8)    |                 |
|               |     |                | CKD: N/A             |                       |                      | NIV: 8 (62)     |                 |
|               |     |                |                       |                       |                      | IMV: 2 (15)      |                 |
|               |     |                |                       |                       |                      | CRRT: 3 (23)    |                 |
|               |     |                |                       |                       |                      | ECMO: 2 (15)    |                 |
| Wang et al.   | 36  | 66 (57-78)     | All: 26 (72.2)       | Shock: 11 (30.6)     | AKI: 3 (8.3)         | Antiviral: 34 (94.4) | 6 (16.6)         |
|               |     |                | HypT: 21 (58.3)      | ACI: 8 (22.2)        | Elevated Scr: N/A    | Glucocorticoid: 26 (72.2) |                 |
|               |     |                | CVD: 9 (25)          | ARDS: 22 (61.1)      | Proteinuria: N/A     | CRRT: 2 (5.56)   |                 |
|               |     |                | DM: 8 (22.2)         |                       | Hematuria: N/A       | Oxygen: 4 (11.1) |                 |
|               |     |                | CKD: 2 (5.6)         |                       |                      | NIV: 15 (41.7)  |                 |
|               |     |                |                       |                       |                      | IMV: 17 (47.22)  |                 |
|               |     |                |                       |                       |                      | ECMO: 4 (11.1)  |                 |
| Guan et al.   | 173 | 52 (40-65)     | All: 67 (38.7)       | Shock: 11 (6.4)      | AKI: 5 (2.9)         | Antibiotics: 139 (80.3) | 14 (8.1)        |
|               |     |                | HypT: 43 (31.2)      | ACI: 27 (15.6)       | Elevated Scr: 6 (4.3) | Antiviral: 80 (46.2) |                 |
|               |     |                | CVD: 10 (5.8)        | ARDS: N/A            | Proteinuria: N/A     | Glucocorticoid: 77 (44.5) |                 |
|               |     |                | DM: 28 (16.2)        |                       | Hematuria: N/A       | Oxygen: 123 (71.1) |                 |
|               |     |                | CKD: 3 (1.7)         |                       |                      | NIV: 56 (32.4)   |                 |
|               |     |                |                       |                       |                      | IMV: 25 (14.5)   |                 |
|               |     |                |                       |                       |                      | CRRT: 9 (5.2)    |                 |
|               |     |                |                       |                       |                      | ECMO: 5 (2.9)    |                 |
| Yu et al.     | 226 | 64 (57-70)     | All: 155 (68.6)      | Shock: 36 (15.9)     | AKI 57 (25.2)        | Antibiotics: 168 (74.3) | 87 (38.5)       |
|               |     |                | HypT: 96 (42.5)      | ACI: 61 (27.0)       | Stage 1: 23 (30.2)   | Antiviral: 117 (51.8) |                 |
|               |     |                | CVD: 22 (9.7)        | ARDS: 161 (71.2)     | Stage 2: 12 (5.3)    | Glucocorticoid: 37 (16.4) |                 |
|               |     |                | DM: 47 (20.8)        | MODS: N/A            | Stage 3: 22 (9.7)    | Oxygen: 20 (8.8)  |                 |
|               |     |                | CKD: N/A             |                       |                      | IMV: 85 (37.6)   |                 |
|               |     |                |                       |                       |                      | CRRT: 22 (9.7)   |                 |
|               |     |                |                       |                       |                      | ECMO: 14 (6.2)   |                 |
| Joseph et al. | 100 | 59 (53-67)     | All: 85 (85)         | Shock: N/A           | AKI: 81 (81)         | Antibiotics: N/A | 29 (29)         |
|               |     |                | HypT: 56 (56)        | ACI: N/A             | Stage 1: 44 (44)     | Antiviral: N/A   |                 |
|               |     |                | CVD: 15 (15)         | ARS: N/A             | Stage 2: 10 (10)     | Glucocorticoid: N/A |                 |
|               |     |                | DM: 30 (30)          | MODS: N/A            | Stage 3: 27 (27)     | Vasopressors: 51 (51) |                 |
|               |     |                | CKD: 29 (29)         |                       |                      | Oxygen: N/A      |                 |
|               |     |                |                       |                       |                      | NIV: N/A         |                 |
|               |     |                |                       |                       |                      | IMV: 55 (55)     |                 |
|               |     |                |                       |                       |                      | CRRT: 13 (13)    |                 |
|               |     |                |                       |                       |                      | ECMO: N/A        |                 |
| Yang et al.   | 36  | 69.4 (SD 10.8) | All: N/A             | Shock: N/A           | AKI: 8 (22)          | Antibiotics: 34 (94.4) | 23 (63.9)       |
|               |     |                | HypT: 14 (38.9)      | ACI: 7 (19.4)        | Elevated Scr: N/A    | Antiviral: 14 (38.9) |                 |
|               |     |                | CVD: 12 (33)         | ARDS: 36 (100)       | Proteinuria: N/A     | Glucocorticoid: 29 (80.6) |                 |
|               |     |                | DM: 10 (27.8)        | MODS: 13 (36.1)      | Hematuria: N/A       | Oxygen: N/A      |                 |
|               |     |                | CKD: N/A             |                       |                      | NIV: 0           |                 |
|               |     |                |                       |                       |                      | IMV: 36 (100)    |                 |
|               |     |                |                       |                       |                      | CRRT: 22 (61.1)  |                 |
|               |     |                |                       |                       |                      | ECMO: N/A        |                 |

AKI: Acute kidney injury, ACI: Acute cardiac injury, ARDS: Acute respiratory distress syndrome, CKD: Chronic kidney diseases, CVD: Cardiovascular diseases, CKRT: Continuous kidney replacement therapy, DM: Diabetes mellitus, ECMO: Extracorporeal membrane oxygenation, HypT: Hypertension, ICU: Intensive care unit, MV: Mechanical ventilation, IMV: Invasive MV, NIV: Noninvasive MV, MODS: Multiple organ dysfunction syndrome, SD: Standard deviation, N/A: Not available, Scr: Serum creatinine; ACI: N/A
that the age range of patients was 47–67 years exhibiting such common symptoms as diarrhea (80%), fever (60%), and fatigue (60%). All the patients manifested with lymphopenia and ground-glass opacity in the imaging of the lung CT scans. However, no patients developed ARDS, shock, MODS, or death. Importantly, their clinical features were not much different from nondialysis patients with COVID-19.\(^{[47]}\)

The above events prompted the government to strengthen the control of the HD center. Several strategies (including patient screening, shunting of infected and uninfected patients, adjustment of dialysis mode, and medical stuff protective measures) have been suggested for the management of HD centers during the COVID-19 pandemic.\(^{[48,49]}\) There are no reports of large-scale outbreaks in dialysis rooms, and the impacts of COVID-19 on CKD patients have not been reported either, to date.

### CONCLUSIONS

Overall, the prevalence of kidney injury secondary to the infection of SARS-CoV-2 varies from the different studies [Table 1]. Patients with mild symptoms usually show hematuria, proteinuria, or mild fluctuations in the level of Scr or BUN. AKI frequently develops at later stages in critically ill patients, and it is recognized as a marker of multiple organ dysfunction and disease severity. Since AKI markedly influence on the outcome of COVID-19, the importance of AKI in COVID-19 patients has been increasingly recognized [Table 2]. The pathogenesis of AKI has not been fully understood yet. AKI should be identified promptly during SARS-CoV-2 infection. For the COVID-19 patients with AKI, clinicians need to closely monitor changes of their renal function, and early diagnosis and active treatment may reduce the mortality of the patient with COVID-19.

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### Conflicts of interest

Qingli Cheng is an Editorial Board Member of the journal. The article was subject to the journal’s standard procedures, with peer review handled independently of this editor and his research groups.

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