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# Perspectives on the relationship of renal disease and coronavirus disease 2019

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## ABSTRACT

Coronavirus disease 2019 (COVID-19) is now a pandemic and its death toll is rocketing up. Patients with acute kidney injury (AKI) and chronic kidney disease (CKD) are at high risk of developing COVID-19 complications and COVID-19 infection can also lead to renal dysfunction. Considering the importance of kidney function in COVID-19 patients, the present review is aimed to dig into the available evidence about kidney and COVID-19. We summarize the mechanisms underlying the renal injury in COVID-19 patients, and treatment strategies in dialysis and kidney transplant patients. We conclude, it is imperative to highlight the early monitoring of patients with AKI and carefully control kidney function during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

### Implication for health policy/practice/research/medical education:

It is imperative to highlight the early monitoring of patients with AKI and carefully control kidney function during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

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## Introduction

Coronaviridae family of viruses can cause diseases in mammals and birds, and possess enveloped particles containing single-stranded and positive-sense RNA. Coronavirus infection can lead to the diseases ranging from a mild condition such as common cold to severe diseases including severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus emerged in Wuhan city, China (1, 2). Coronavirus disease 2019 (COVID-19) pandemic continues to expand quickly all over the world. The virus is transmitted through the same mechanisms as of influenza virus, from person to person through sneezing and coughing or contact with the secretion of infected persons. COVID-19 disease is more severe in the elderly, and persons with other chronic diseases such

as chronic respiratory disease, diabetes, cardiovascular disease, hypertension, and renal injury (3). The most common symptom and signs of COVID-19 illness include fatigue, fever, and dry cough, as well as sputum production, headache, hemoptysis, diarrhea, dyspnea, and lymphopenia (4). Numerous trials are underway to identify effective drug regimens for COVID-19. The development of preventative vaccine or the discovery of novel drug candidates are in early phases. However, some broad-spectrum drugs are in use to mitigate the infection in patients with COVID-19 (5). A minority of patients develop multi-organ failure which aggravates COVID 19 mortality rate. It is estimated that organ dysfunction in patients with COVID-19 occurs in about 33%, of which 3-7% are related to acute kidney injury (AKI) (6,7). Old data from SARS and MERS-CoV infections have reported AKI development in 5%-15% cases (8). COVID-19 progression leads to renal dysfunction or renal injury as

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well as respiratory system injury (9). Given the importance of kidney function in COVID-19 patients, the present review is allocated to focus on the available evidence of renal disease and COVID-19.

### COVID-19 and renal impairment

Patients with renal injury are at high risk of developing COVID-19 and AKI is an important risk factor for COVID-19 patients (8). Furthermore, renal impairment is one of the complications of SARS-CoV-2 infection. A large prospective study demonstrated that kidney impairment is more prevalent among hospitalized COVID-19 patients and is also associated with increased in-hospital death. Frequently COVID-19 patients, at the time of admission have proteinuria (44%), hematuria (26.9%), increased blood urea nitrogen (14.1%), and increased plasma creatinine (15.5%) (10). During this study, 3.2% of patients developed AKI in the early days. This study emphasized the need for early interventions such as proper hemodynamic support and abstinence of nephrotoxic drugs as well as performing urine analysis in patients with COVID-19 to prevent kidney injury (10). In contrast to this survey, a study found that AKI is rare in COVID-19 and SARS-CoV-2 infection does not lead to renal disturbance or exacerbation of chronic kidney disease (CKD) in COVID-19 patients (11). Hong et al, which evaluated the incidence of early renal injury in COVID-19 patients demonstrated the presence of abnormalities in levels of estimated glomerular filtration rate (66.7%), creatinine clearance (41.7%), and increased microalbuminuria (41.7%), without significant abnormalities in blood urea nitrogen and plasma creatinine. They found that the measurement of urine microalbumin,  $\alpha$ 1-microglobulin, urine immunoglobulin-G, and urine transferrin are more helpful in the diagnosis of early renal injury in COVID-19 patients (12).

Available data suggest that SARS-CoV-2 infection can have a direct cytotoxic effect on renal tubules and cause acute renal failure. Retrospective analysis of 85 patients with COVID-19 demonstrated that 27.06% of patients developed acute renal failure, especially in elder patients. Furthermore, kidney tissue examinations of postmortem specimens confirmed lymphocyte infiltration, severe acute tubular necrosis, and accumulation of viral nucleocapsid protein antigen in kidney tubules (13). The presence of SARS-CoV-2 virus particles in urine of COVID-19 patients might be due to penetration of viral particles through glomerular barrier (14). It is also reported that 51.67 % of patients affected by novel coronavirus pneumonia had proteinuria since the severity of pneumonia was directly associated with levels of urine protein (15).

### COVID-19 and kidney transplant recipients

Infections are a leading cause of morbidity and mortality in renal allograft recipients throughout the post-transplant course. Viruses are the most common causes

of opportunistic infection after transplantation. Different factors that promote active invasive viral infection after organ transplantation include inflammation, graft rejection, tissue injury, and immune suppression (16). Previous studies have reported the SARS-CoV and MERS-CoV infections in transplant recipients (17,18). In the current pandemic, SARS-CoV-2 infection has been reported in kidney transplant patients from China and Spain (19,20). Reduction of immunosuppressive agents, along with low dose methylprednisolone-based regimes could improve COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppressive therapy (21). Although there is not much data available on the incidence of COVID-19 in transplant recipients, it is recommended to follow preventive modalities and guidelines to prevent the spread of the disease (22, 23).

### COVID-19 and dialysis patients

COVID-19 is a serious threat for dialysis patients in hemodialysis (HD) centers. Dialysis patients are more vulnerable to SARS-CoV-2 infection than the general people, due to thrice-weekly outside exposure for HD, older age and underlying chronic conditions (24). The study by Ma et al on 230 HD patients and 33 staff members of 61 HD centers in Wuhan confirmed the presence of COVID-19 infection in 37 of HD patients and 4 staff members. Among 37 COVID-19 infected HD patients, death occurred in 6 cases that was presumably due to cardiovascular, cerebrovascular diseases, and hyperkalemia but not exclusively due to COVID-19 pneumonia (25). Despite higher level of inflammatory cytokines in HD patients, compared to controls, lower serum level of inflammatory cytokines in COVID-19 patients on HD compared to other COVID-19 was detected. Additionally, HD patients with COVID-19 showed lower frequency of lymphocytes in peripheral blood mononuclear cells than other COVID-19 patients (25). Currently, the risk of SARS-CoV-2 infection transmission to HD patients and their families, medical staff, workers, and others is significantly high in HD centers (8). Therefore, the Taiwan society of nephrology (26), the Chinese society of nephrology (27), and the Centers for Disease Control and Prevention (28) have published guidelines for HD centers for the COVID-19 pandemic. As the prevention, protection, screening, isolation, and distribution are basic principles in the reduction and containment of the COVID-19 in HD centers, the management of dialysis patients with COVID-19 must be conducted based on standard protocols (29).

### Mechanisms of renal injury in COVID-19

Recent studies revealed that renal dysfunction during SARS-CoV-2 infection is closely related to death in severe cases of COVID-19 patients. Although the exact mechanism is not fully clarified, it is possible that the expression pattern of angiotensin-converting enzyme 2

(ACE2) can be associated with cellular susceptibility of SARS-CoV infection (30). SARS-CoV-2 enters into cells using the ACE2 receptor and cellular transmembrane serine proteases (TMPRSSs) as a co-receptor. ACE2, as a membrane-bound aminopeptidase, is highly expressed in the lungs, heart, intestine, kidneys and plays a fundamental role in the immune and cardiovascular systems and renal function (31,32). The penetration of SARS-CoV-2 virus into the renal tubular cells, by binding to ACE2, induces cytotoxicity and renal function impairment (33). Single-cell RNA sequencing analysis of kidney cells has revealed that ACE2 is expressed along with TMPRSSs in proximal straight tubule cells and podocytes, indicating that the kidney cells are exposed to SARS-CoV-2 infection. TMPRSSs activate the spike protein of the virus surface for membrane fusion into host cells (34).

The cytokine storm syndrome involved in pathogenesis of the acute respiratory distress syndrome (ARDS) and various organs failure during SARS-CoV infection, seems to be related to enormous inflammatory reaction. The viral replication in targeted organs, including kidneys, induces systematic viral sepsis and systematic inflammatory responses, and subsequently cell damage in multiple organs (35). Additionally, SARS-CoV-2 infection activates cytokine cascade through releasing pro-inflammatory cytokines (IL-4, IL-10, IL-1b, IFN-c, IP-10 and MCP-1) and chemokines (CCL2, CCL3, CCL5, CXCL1, CXCL8 and CXCL9), thereby resulting in the death of patients, as observed in SARS-CoV and MERS-CoV infections (36, 37). In addition, renal failure in COVID-19 patients may occur due to rhabdomyolysis, hypoxemia, dehydration, presence of underlying diseases, and improper consumption of non-steroidal anti-inflammatory drugs (Figure 1) (38,39).

### ACE2-based therapeutic strategies

Renal disorders, which initially appeared as mild abnormalities, may later be diagnosed as severe AKI in a significant proportion of patients. Since the progression

of AKI in COVID-19 patients is an important prognostic factor, patients may be treated with some more directive interventions (9). Findings have suggested that the kidney cells are one of the target organs of COVID-19 virus, due to the expression of ACE2 and TMPRSS2. Agents targeting virus spike protein, protease TMPRSS2, and ACE2 receptor are to emerging as potential clinical strategies for prevention and therapy (40). In vitro studies using Vero-E6 monkey kidney cell line, demonstrated that SARS-CoV replication is blocked by a soluble form of ACE2 (41). Hence, it has been assumed that the soluble recombinant human ACE2 protein may be a therapeutic option to combat or limit SARS-CoV-2 infection progression (42). In support of this hypothesis, a previous study on an animal model has illustrated the beneficial effect of small ACE2 variants in the improvement of AKI by regulating kidney renin-angiotensin system activity (43). Further studies in engineered human organoids, including kidney organoids, revealed that the human recombinant soluble ACE2 (hrsACE2) can block the growth of SARS-CoV-2 in the early stages of infection (44). In addition, a clinically proven TMPRSS2 inhibitor, named camostat mesylate, prevents the cell entry of SARS-CoV-2 and might constitute a treatment option for COVID-19 (45).

### Conclusion

COVID-19 virus attacks the cells expressing ACE2 and induces multiple organ injury. Kidney injury caused by COVID-19 increases mortality and morbidity substantially. Close monitoring of patients renal function, avoidance of nephrotoxins, and minimizing studies and interventions that can potentially harm kidneys, are especially important. In the absence of proven established drug regimens, aggressive supportive measures are needed in caring for patients with COVID 19 multiorgan failure. Still much further studies are warranted to reveal more and newer information on our uncharted understanding of this disease.

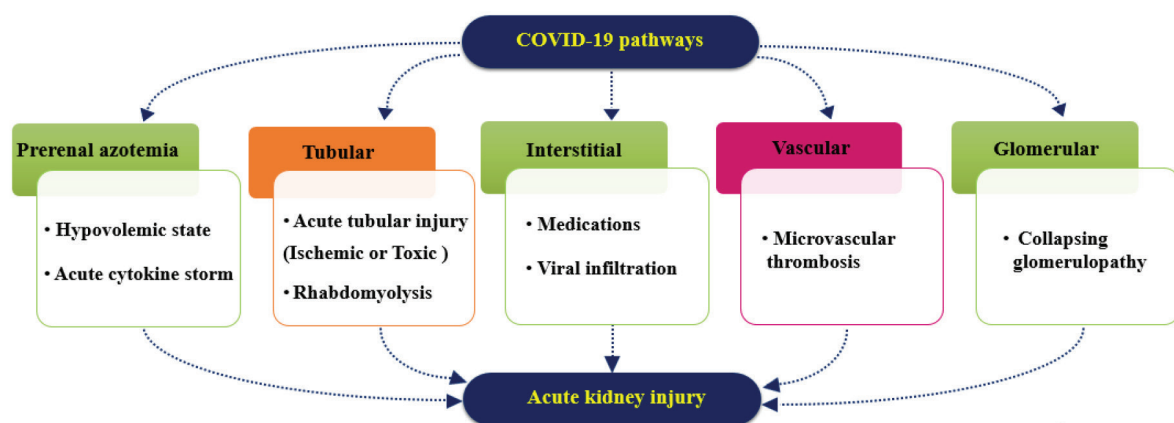


Figure 1. COVID-19 -induced acute kidney injury.

### Authors' contribution

BY and LM prepared the primary draft. LVKSB and BR edited the paper. All authors read and signed the final paper.

### Conflicts of interest

Authors who have no conflicts of interest to declare.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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