# COVID-19 infection: a magnified look at the kidneys

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The global health crisis of novel coronavirus 2019 (COVID-19) pandemic has overwhelmed all medical disciplines, including nephrology. This review focuses on how kidneys are affected by COVID-19 infection and discusses some etiologic, pathogenic, and clinical aspects of kidney involvement in COVID-19 infection, including clinical outcome. Special strategies are required to improve clinical outcome and should be regularly updated based on gained knowledge and evidence.

**Keywords:**
acute kidney injury, Coronavirus 2019 infection, dialysis, kidney, transplantation

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## Introduction

The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes coronavirus disease 2019 (COVID-19) infection, which so far has affected most countries around the globe, sparing no age group [1]. As of March 11, 2020, COVID-19 has been declared as a pandemic. In a matter of 6 months, more than 10 million people have been infected and more than half a million have died [2].

Coronaviruses (CoV) are animal and human pathogens that can cause lethal zoonotic infections. In 2003, CoV gained considerable attention as a significant cause of severe lower respiratory disease owing to severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 and most recently SARS-CoV-2 as the third emergence of CoV infection with severe lower respiratory tract disease [3–5].

Admittedly, COVID-19 pandemic has affected everyone; however, its exact effect on patients keeps evolving. Our understanding of its epidemiology, pathogenesis, and clinical presentation is still unfolding. A tsunami of published literature, coupled with rapidly growing and extensively increasing studies into the diseases, should provide further insights on this novel disease.

Even though COVID-19 infection chiefly affects the lungs, manifesting as acute respiratory disease, yet many other organs have been involved, mainly the kidney, but also the liver, heart, gastrointestinal tract, and central nervous system. Coronavirus infection cascading and potentially deleterious effects on kidneys can be mitigated if quickly and effectively dealt with [6–8].

## How does SARS-CoV-2 infection affect the kidney?

The interplay of many factors has been incriminated as possible pathogenic mechanism of kidney affection in COVID-19. Kidney injury in SARS-CoV-2-infected patients may be ascribed to different causes (Fig. 1).

(1) Direct cell invasion by binding to angiotensin converting enzyme 2 (ACE2) expressed in the apical brush borders of the proximal tubules and the podocytes, as well as transmembrane protease, serine 2 (TMPRSS2) expressed more specifically in the proximal tubules, which is able to cleave the viral spike. Interestingly, kidney expression of ACE2 is nearly 100-fold higher than in pulmonary tissue [9]. It was recently found that SARS-CoV-2 also invaded host cells via another route of CD147, a ubiquitously expressed transmembrane glycoprotein that is highly expressed on proximal tubular epithelial cells [10,11].
Virus entry leads to acute proximal tubular injury, resulting in tubular necrosis and podocyte dysfunction, leading to glomerular diseases such



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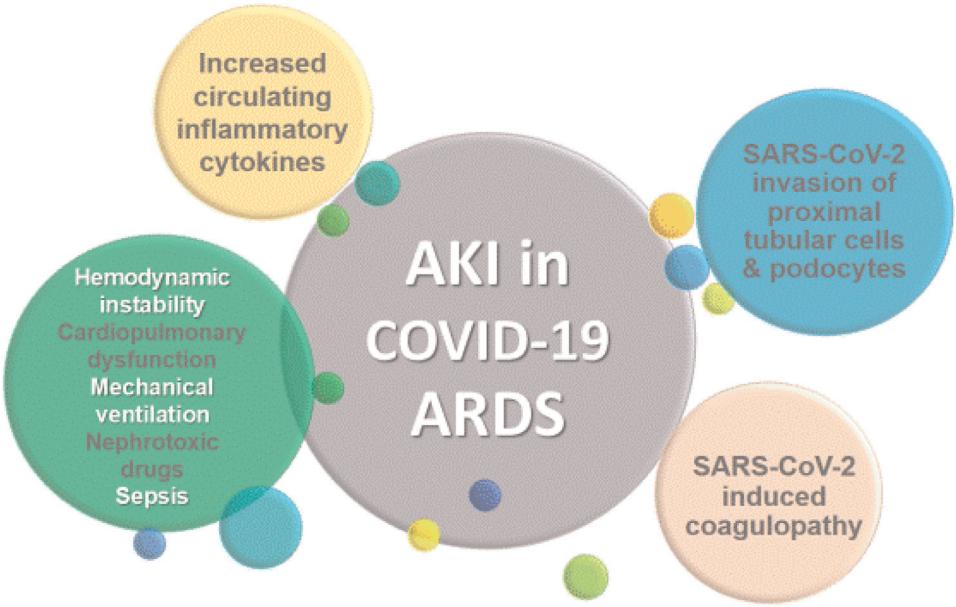
**Figure 1**




Mechanisms of acute kidney injury (AKI) in COVID-19 acute respiratory distress syndrome (ARDS).

as focal segmental glomerulosclerosis. This binding also leads to accumulation of angiotensin II by reducing its degradation into angiotensin 1–7, thus promoting an imbalanced renin angiotensin aldosterone system (RAAS) activation, leading to glomerular dysfunction, inflammation, fibrosis, and vasoconstriction [12]. Viral RNA has been identified in kidney tissue and urine in SARS-CoV, suggesting that the kidney is target of this novel coronavirus [13,14].

(2) Inflammatory and immune over-reaction is characterized by an enhanced release of inflammatory cytokines [8]. These circulating harmful cytokines may participate in kidney injury by interacting with kidney resident cells, thus inducing endothelial dysfunction, microcirculatory derangement, and tubular injury [15,16].

(3) Severe COVID-19 infection triggers coagulation activation, resulting in procoagulant state with evident vascular consequences of SARS-CoV-2-induced coagulopathy such as microvascular thrombosis, acute tubular and cortical necrosis with subsequent fibrinoid necrosis and glomerular ischemia, and irreversible kidney damage [17]. This is particularly aggravated in patients with preexisting endothelial dysfunction such as diabetes, hypertension, and obesity [18]. Whether therapies to stabilize the endothelium are potentially therapeutic in this respect remains to be fully elucidated [19].

(4) In severe COVID-19 patients with prolonged ICU stay, other factors may aggravate kidney injury and act synergistically with the aforementioned mechanisms of kidney damage, including hemodynamic instability, cardiopulmonary dysfunction, mechanical ventilation, nephrotoxic drugs, and sepsis [20].

#### Lung–kidney cross-talk

Interestingly, lung–kidney bidirectional damage mechanisms in COVID-19 infection aggravate disease progression. On one side, injury of renal tubular epithelium promotes the upregulation of interleukin-6, leading to higher alveolar-capillary permeability and pulmonary hemorrhage. On the other side, ARDS may result in renal medullary hypoxia, which aggravates renal tubular injury [20].

## What is the clinical effect of SARS-CoV-2 infection on kidney?

COVID-19 effect on kidneys of SARS-CoV-2-infected patients continues to unfold. Nevertheless, accumulating evidence to date categorizes kidney injury as major complication of COVID-19 infection and a significant risk factor of mortality.

#### Acute kidney injury

SARS-CoV2- higher affinity for ACE2, abundantly expressed in the kidneys, partially accounts for the increased vulnerability of the kidney in COVID-19 infection [21].

Initially, data on acute kidney injury (AKI) in COVID-19 were conflicting, with highly variable

incidence of this severe complication, particularly with the overwhelming effect of lower respiratory involvement and respiratory failure.

In a large cohort of 1099 patients with COVID-19, only 0.5% had AKI [22]. Yet in another single-center case series of 138 hospitalized patients with confirmed COVID-19 pneumonia, AKI was reported in 3.6% of all patients. Unsurprisingly, when calculated among the subset of study ICU admitted patients ICU, AKI increased to 8.3% [7].

In another cohort of 701 COVID-19-infected patients, 5.1% had AKI during their hospital stay; nevertheless, AKI was significantly higher in patients with chronic kidney disease (11.9%) compared with patients with no prior kidney disease (4.0%). Moreover, an association between kidney disease and mortality in hospitalized patients was reported. Four-fold increased risk of mortality had been reported among those with stage 3 AKI [23]. As such, close monitoring of kidney functions in hospitalized COVID-19-infected patients should be maintained at all times, particularly in critically ill patients. Timely diagnosis of early kidney injury, using sensitive AKI biomarkers when available, leads to timely intervention, thereby reducing mortality risk.

#### Disruption of dialysis services and transplantation programs

Numerous challenges face the medical care of dialysis patients during COVID-19 pandemic. Principally, they have compromised immune system in addition to preexisting conditions such as diabetes and cardiovascular disease among other comorbidities.

Many models had been developed to provide dialysis support for patients during this COVID-19 outbreak. Fundamental objectives were to provide the planned dialysis sessions to the patients with end-stage kidney disease, while implementing relevant infection control measures to minimize the risk of infection transmission in the dialysis facility between individual patients and healthcare workers, let alone its spread to the community [24]. Moreover, recommendations aiming at optimal management of COVID-19 patients in dialysis centers and ICU had been published. The multidisciplinary approach is highly emphasized to ensure safe and uninterrupted service [24,25]. Moreover, this pandemic had an adverse effect on kidney transplantation programs where transplantation had been limited to lifesaving conditions, and also in many centers, live kidney transplantation had been brought to a halt.

#### Treatment protocol modifications

Kidney transplant recipients require maintenance immunosuppression protocol for life delicately balancing efficacy and safety to prevent rejection while minimizing risk of infection. Higher risk of mortality had been reported among 1073 patients with COVID-19 and kidney failure from 26 countries registered in ERACODA, the ERA–EDTA COVID-19 database. Notably, 21% of kidney transplant patients and 25% of dialysis patients had died at 28-day follow-up [26].In the absence of specific therapy for SARS-CoV-2 infections, the main concern is therefore the issue of immunosuppression. Many nephrology societies had put together recommendations to reduce immunosuppression to safe levels; nevertheless, balancing their risks versus benefits can be quite complex [27]. The significant strain and resource constraints during the outbreak calls for contingency planning and optimal resource management to face the evolving challenges [28].

## Conclusion

The understanding of coronavirus disease 2019 epidemiology, pathogenesis, and clinical manifestations is rapidly evolving, perhaps even overwhelming to clinicians. Even though the lung is the main target organ, yet kidney involvement has been increasingly reported with significant higher mortality risk. Close monitoring of kidney functions and timely intervention are highly recommended to reduce morbidity/mortality risk. Developed strategies should be regularly updated to limit the untoward effect of the COVID-19 infection on dialysis patients and kidney transplant recipients while optimizing management to improve clinical outcome.

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#### Conflicts of interest

There are no conflicts of interest.

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