

COVID 19: How does it Impact the Kidneys?

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Introduction

A novel Coronavirus 2019 infection now known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first identified in Wuhan, China, in December 2019 and spread rapidly all over the world, and was declared a global pandemic in March 2020 by the world health organization (WHO). This was a third novel virus belonging to the large family “coronavirus” similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [1]. However, COVID-19 though has a low fatality rate, but it is associated with a high rate of infection than previous epidemics from SARS-CoV and MERS-CoV. Various epidemiological studies have reported that patients with comorbidities such as diabetes, hypertension, cardiovascular disease are more susceptible to getting an infection with COVID-19 and cause an increased risk of severe illness. The mortality rate is high when the disease is accompanied by multi-organ dysfunction such as lung, heart, gastrointestinal tract, and kidney. Apart from lungs novel coronavirus, the next target has shown to be kidneys due to high levels of ACE2 protein [1,2]. Involvement of the kidney in coronavirus infection has huge prognostic implications and independent predictor of morbidity and mortality [3,4]. There is limited information about how COVID-19 affects the kidney. Thus, this review focusses on how the novel coronavirus affects the kidneys of normal individuals and individuals with kidney disease.

Epidemiology of kidney disease in COVID-19

COVID-19 infection is associated with adverse outcomes, worsening of comorbidities among patients with kidney disease, and need for healthcare facilities in a resource-constrained country like India [5,6]. Recent reports have demonstrated that AKI is more prevalent among the COVID-

19 population, particularly in ICU settings. The incidence of COVID-19 AKI was higher (15.4%) in hospitalized patients, particularly among patients with severe COVID-19 (53%; range 42.7%-63.3%). Thus, growing evidence demonstrates that it affects more than 20% of hospitalized patients and more than 50% of ICU patients [7-12]. The majority of AKI cases are likely mild to moderate. Patients with COVID-19 AKI are likely to require more renal replacement therapy and are less likely to recover kidney function. Dialysis rates may be as high as 30% and survival may be dramatically reduced when AKI occurs.[13]

The incidence of COVID-19 in patients with chronic kidney disease (CKD) differed from 0.7 to 47.6% [14]. In addition, mortality due to COVID-19 in the dialysis population is reported to be higher than the normal population (14.2%-30.4% vs 2.8%) [15]. Moreover, most importantly, kidney transplant patients are likely at higher risk for severe COVID-19 disease. Notably, there is an unusually high mortality rate of 20-28% in patients with a kidney transplant than the general population (1-5%) [16-20].

Potential demographic risk factors for kidney dysfunction in COVID-19 include male sex, older age, black race, diabetes mellitus, hypertension, cardiovascular disease or congestive heart failure, high BMI, CKD, genetic risk factors (e.g. APOL1 genotype; ACE2 polymorphisms), immunosuppressed state, and Smoking history[21].

Pathogenesis of kidney injury in COVID-19

The mechanism of kidney involvement in COVID-19 is multifactorial. It has been hypothesized that the development of kidney dysfunction in COVID-19 involves a direct pathogenic mechanism that includes coronavirus-induced cytopathic effect, hypoperfusion, sepsis leading to cytokine storm-induced systemic inflammatory response, Endothelial dysfunction, coagulopathy, complement activation, and microvascular thrombosis [22]. The molecular study showed that SARS-CoV-2 spike binding protein directly enter into the host cells and bind to membrane-bound ACE-2 receptor protein which is highly expressed on kidney tubular epithelial cells as well as podocytes [23]. Compared to lungs, kidneys have a 100-fold higher expression of ACE2. The indirect mechanism involved systemic effects of COVID-19 infection or effect

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of the virus on distant organs like lungs and critical care intervention may contribute to kidney injury. Moreover, COVID-19 facilitates imbalance in renin-angiotensin-aldosterone system (RAAS) and induces downregulation of ACE2 receptor that causes accumulation of angiotensin-II [24]. It leads to inflammation, vasoconstriction, and fibrosis. In addition, patients with severe COVID-19 demonstrate acute respiratory distress syndrome (ARDS) which can be linked to AKI. Studies on COVID-19 patients do not support the hypothesis of immune complex-mediated glomerular injury although T cell-mediated injury could be another mechanism. There is substantial evidence of involvement of the hypercoagulable state, and direct virus invasion through ACE-2 expression on PT tubules. Laboratory changes include high lactate, coagulopathy, hyperbilirubinemia, thrombocytopenia, acidosis, and a high level of cytokines (interleukins, TNF- α).

Small autopsy studies demonstrated severe PT injury, glomerular fibrin thrombi, peritubular erythrocyte aggregation, and collapsing glomerulopathy among COVID-19 patients [25,26]. Small pigment casts indicate some extent of inflammation and acute tubular necrosis (ATN) [27]. Thrombotic microangiopathy (TMA) leading to ATN is also possible. Some studies also showed evidence of viral RNA in the urine samples of the infected patients, suggesting the kidney as the target of this novel COVID-19 [28].

Impact of COVID-19 on kidney function

COVID-19 in healthy individuals with Normal Kidney Function

Individual with healthy kidneys if encounter COVID-19 have shown to develop in 5 to 15 % of cases hematuria, proteinuria (most common) leading to AKI which may

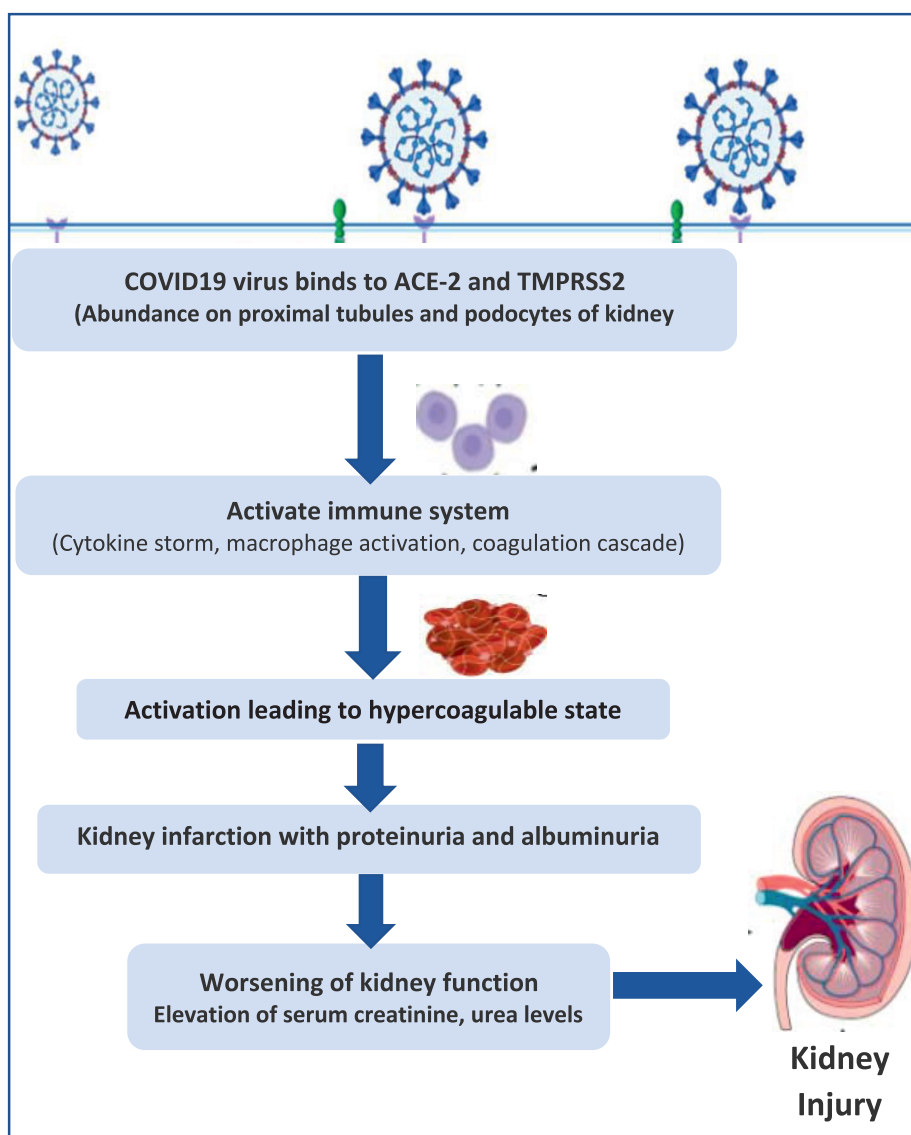


Figure 1: The mechanisms of kidney involvement in COVID-19.

progress to CKD if not treated. The effect of COVID-19 on kidneys is multifactorial. Kidney injuries occur as a result of cytokine storm, hypoxia, disseminated intravascular coagulation which ultimately leads to thrombus formation and kidney infarction. There is evidence of viral inclusion bodies on electron microscopy in podocytes and endothelial cells indicating a direct entry and replication of novel coronavirus within the renal tubular epithelium [29]. Thus COVID-19 infection has various effects on the kidneys of normal individuals out of which acute kidney injury is most common.

COVID-19 in patients with AKI

COVID-19-AKI is likely to be of variable etiology. Majority of the patients presented with severe hypoxemia and AKI can be a consequence of critical hypoxia. Late cardiac involvement has also been reported and causes the cardio-renal syndrome. Furthermore, critically ill patients with COVID-19 exhibit significant systemic hyper-inflammation, and a small number may even develop a macrophage-activation, cytokine storm, high plasma ferritin. COVID-19 patients can also AKI develop due to infection of renal tubular epithelial cells.

The clinical course of patients infected with COVID-19 is widely unpredictable and variable, showing asymptomatic to multi-organ dysfunction and progress to death. Patients with COVID-19 AKI were generally admitted to ICU and required mechanical ventilation and vasopressors. Few studies reported a temporal relationship between the development of AKI and the onset or severity of infection. However, one-third of patients presented with AKI or developed AKI within 24 hours, and another study reported a delay in the development of AKI in COVID-19 (around 15 days after presentation) [30,31].

Information on the duration of renal recovery from COVID-19 AKI is poorly understood. However, evidence suggests that patients with AKI who survive with COVID-19 may be vulnerable to re-hospitalization, cardiac complications, recurrent AKI, and increased mortality within the first year of hospitalization [32]. AKI monitoring should also be incorporated in the after-care programs for COVID-19 survivors. Patients should be monitored for AKI throughout their hospital course and followed over a period of at least 2-3 months depending on the severity of illness.

COVID 19 in CKD Patients

As CKD is an immunocompromised state COVID-19 virus in CKD patients causes profound immunocompression leading to multi-organ failure and death. It was found that CKD patients with COVID-19 are more vulnerable to death as compared to individuals with chronic heart disease, chronic lung disease, hypertension, diabetes and other

comorbidities [33]. COVID 19 infection is indirect correlation with the level of kidney dysfunction. Thus, CKD patients with COVID-19 are an alarming situation for the Nephrologist community. The impact of discontinuation/switch of RAAS inhibitors is questionable in patients with CKD who tested positive for COVID-19. Recommendations on the continuation of RAAS inhibitors in CKD patients are generally concerned with hemodynamic status, renal capacity, and clinical stability of the individual [34]. There is no evidence of impact of RAAS inhibitors on prevention of kidney dysfunction in COVID-19.

COVID-19 in dialysis patients

Dialysis patients are most vulnerable to COVID-19 infection due to profound immunosuppression. Patients missing dialysis sessions require emergency dialysis sessions. Patients must keep on getting their dialysis sessions and follow treatment guidelines. Dialysis centers should keep basic protective measures to minimize the spread of COVID-19 in dialysis units such as expanding preventive efforts, implement universal screening, and isolating patients who tested positive for COVID-19. However, patients on hemodialysis tend to produce long lasting antibodies [35]. The mechanism of fluid overload in COVID19 is illustrated in figure 2.

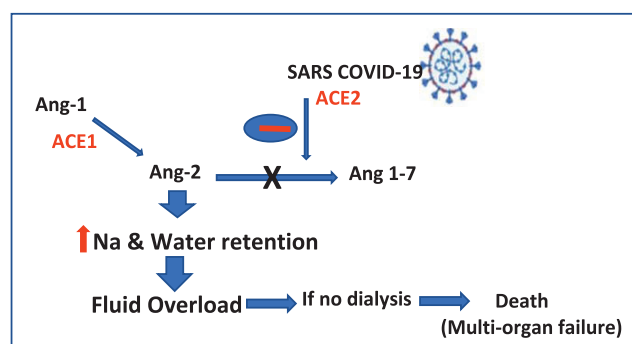


Figure 2 : Mechanism of fluid overload in COVID-19

COVID-19 in Kidney Transplant Patients

Transplant patients are most vulnerable to COVID-19 infection due to the intake of immunosuppressive drugs. A donor with a COVID-19 infection is not eligible for the donation of a kidney. COVID-19 patients with transplant kidneys can develop flu-like symptoms or in some cases remain asymptomatic. Therefore, screening of transplant patients is essential on account of immunosuppression and must include a screening of COVID-19 infection. A study done by Gandolfini and colleague, result revealed that COVID-19 positive patients with long duration of transplant and on immunosuppressive drugs have higher chances of death than patients with short duration of transplant and immunosuppressive drugs [36].

Effect of COVID-19 on cognition of CKD patients

Elderly CKD population (>75years) with COVID-19 infection has higher chances of developing dementia and delirium as compared to patients less than 75 years old. Thus COVID-19 infection is like a crab that builds its web not only in the lungs but infects multi-organs out of which the brain is its new victim.

Psychosocial impact of COVID-19 in patients with CKD

COVID-19 has a devastating impact on the social and mental health of patients with CKD specifically those receiving in-center dialysis treatment. Majority of patients with hemodialysis worried about obtaining dialysis due to risk of infection from close contact in dialysis unit or during transportation to the dialysis center. Some patients missed in-center hemodialysis treatment due to COVID-19 related concerns and cause worsen their illness and increase risk of hospitalization and mortality. Psychosocial impacts include stress, depression, anxiety, insomnia and worry about pandemic's effects on their emotional/mental health and interpersonal relationships [37]. Thus, despite health concerns, health care professionals may have a significant role in observing psychological needs and providing psychological assistance to the patients with chronic kidney disease [38].

Prevention and management of COVID-19 associated kidney dysfunction

Prevention and management strategy should be based on risk and stage for COVID-19 AKI patients. Patients with COVID-19 AKI/CKD should be treated as per the KDIGO guideline-based standard of care [39,40]. Management strategy for kidney disease in COVID-19 patients is not different than kidney disease (AKI/CKD) from other causes and few management recommendations for AKI/CKD should be etiology specific. In addition, there is a paucity of evidence of the effectiveness of antiviral on COVID-19 AKI. There is no evidence of the impact of RAAS inhibitors on the prevention of COVID-19 AKI. Consider acute RRT in COVID-19 AKI when metabolic and fluid demands exceed the total capacity of the kidney. Prolong modalities of RRT such as continuous RRT, prolong intermittent RRT, or slow-low efficiency dialysis (SLED) may be better tolerated for hemodynamically unstable patients with COVID-19 AKI those with massive fluid overload with a poorly tolerated shift in fluid balance [39]. The dose of the RRT should be as per the KDIGO guideline for AKI and CKD and the dose may be adjusted as per variation in clinical, physiological, and/or metabolic status [39,41].

Conclusion and future research recommendation

COVID-19 is not only a potential threat for normal patients with normal kidney function but also for patients with already kidney dysfunction. Therefore, serum creatinine as a baseline test should be performed in all COVID-19 positive patients to detect underlying renal injuries. The pathophysiological mechanism of COVID-19 AKI is multifactorial which is in line with the other form of AKI. More research is needed to understand the mechanism of COVID 19 related kidney injury and its behavioral aspects. Various treatment modalities of COVID 19 related kidney injury remain unanswered. Future studies should also incorporate information on potential risk factors for developing COVID-19 AKI before and during hospitalization including the proportion of possible comorbidities in patients with and without AKI. Different phenotypic characteristics of COVID-19 AKI should be determined based on a clinical presentation at diagnosis, the severity of AKI, the pattern of injury, duration of AKI, and progression to CKD. Clinical implications of various traditional and novel kidney injury markers for the diagnosis and prognosis of kidney dysfunction need to be evaluated for the population of kidney disease tested positive for COVID-19.

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