Post-COVID–19 complication and its effect on acute kidney injury

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Abstract
The novel coronavirus outbreak has become a global health emergency. The common symptoms of COVID-19 disease which have affected a large population are common cold, fatigue, headache and fever. However, complications such as multiple organ failure, acute respiratory syndrome and septic shock are seen in about 5% of patients with persisting severe symptoms and post-COVID syndrome. The COVID-19 acute kidney injury in patients displays damage in the kidney, proteinuria, hematuria and elevated serum creatinine. The symptoms of acute kidney injury vary from mild to severe, which necessitates proper clinical management and renal replacement therapy (RRT). Therefore, it is necessary to understand the pathophysiology of acute kidney injury involving infiltrated immune cells, thrombosis, and cytokine regulation. There is no definite treatment for acute kidney injury; the strategy for preventing the complications will only come through clinical experience. Therefore, more studies are needed for the proper understanding of the disease etiology in acute kidney injury patients with COVID-19. New strategies, International collaboration and multi-disciplinary research are needed to be implemented for the proper management.

Keywords: Post-COVID–19 complications, Acute kidney injury, Clinical management, Pathophysiology

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Introduction
Ever since the severe acute respiratory coronavirus-2 (SARS-CoV-2) and the resultant COVID-19 disease were first reported in the Wuhan province of China, it has emerged to be a global pandemic with more than 210 million cases and more than 4.49 million deaths as of August 24, 2021. As observed worldwide the disease resulted in a massive surge in hospitalizations and deaths from respiratory failure (1,2). In hospital settings, it was observed that the patients succumbed to death not only by the primary infection of the disease but also due to secondary infections. Early information on secondary infections as the consequence of COVID-19 showed an alarming figure of patients developing acute kidney injury (AKI) (3). Reports from Italy and China showed the incidence rate of AKI due to COVID-19 in a wide range of 0.5-29%, with most of the patients on the lower side of the range (4–6). While the initial reports from the U.S.A. showed an incidence of 28% to 46% (3,7).

These cases for the incidence of AKI in the COVID-19 infected patients have been possibly reported due to the fact that angiotensin-converting enzyme 2, vastly expressed in podocytes and proximal tubule cells, is also recognized as the binding site for coronavirus SARS-CoV-2 (4–6). This puts the kidney as a target organ for the infection and injury caused by COVID-19. The biopsy reports have shown clear renal injuries in the patients (8). In addition, collapsing focal segmental glomerulosclerosis has been also reported in Black patients (9,10).

In this review, we have discussed the current understanding of the post-COVID-19 complications and involvement of the kidney with special emphasis on the AKI, its clinical features, pathophysiology and clinical management with the potential use of various therapies.

Post-COVID-19 complications and AKI
SARS-CoV-2 is a novel coronavirus that has webbed the world with COVID-19 disease. The major symptoms of the disease include fever, cough, tiredness, difficulty in breathing and loss of taste with the smell. Although, the symptoms have variations in patients, ranging from mild symptomatic to asymptomatic; whereas few show acute respiratory distress syndrome (ARDS) which could be fatal (11). Symptoms, in the patients with COVID-19,
Implication for health policy/practice/research/medical education

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that subdue within four weeks are considered as acute COVID-19 symptoms, while patients who do not recover even after negative COVID-19 PCR reaction test and experience no symptoms of COVID-19 are considered as patients experiencing “post-COVID-19 syndrome” which may cause life-threatening severity. The National Institute for Health and Care Excellence (NICE) defines the post-COVID-19 syndrome as, “the symptoms or signs in patients that have developed due to COVID-19 and lasted for approximately three months, which could not be explained by an alternative diagnosis” (12).

The most common symptoms associated with the post-COVID-19 syndrome are headache, fatigue, body pain, anxiety and dyspnea. Evidence from studies has shown post-COVID-19 complications in patients associated with cardiac and pulmonary systems, including cardiac manifestations such as arrhythmia, ischemia and myocarditis; whereas pulmonary complications procuring pneumothorax, pleural effusion, and pneumonia are associated with bacteria (3). The most common reason for patients’ admission to intensive care unit (ICU) with COVID-19 is mainly respiratory failure necessitating the need for mechanical ventilation or vasopressor support. Though the data on complications related to AKI is limited, the recent report for AKI has shown a 15% of incidence rate (13). The clinical and autopsy reports of patients with COVID-19 confirm the pulmonary infarction, intravascular coagulation, thrombosis, procuring to increased D-dimer level, and decrease in platelet counts. Also, the organ system manifests the microangiopathy, splenic infarction, joint pain, and hematuria or proteinuria indicating the renal infarction (14,15). The analysis of kidney function in COVID-19 patients has found an increased level of blood urea and serum creatinine (16). A recent cohort study has defined COVID-19 AKI with the higher levels of proteinuria (ratio of protein to creatinine more than 0.5, 1+ or more than 30 mg/dL on urinalysis), hematuria (1+ or higher urinalysis) (17).

COVID-19 patients with comorbidities including old age, chronic renal insufficiency, cardiac-related problems, and hypertension are at higher risk of poor outcomes. Also, patients diagnosed with chronic kidney disease (CKD) are identified to be at an elevated risk of developing upper respiratory tract infection as a consequence of continuous pro-inflammatory cells from faults in innate and adaptive immunity.

Acute kidney injury

Being a health concern worldwide AKI has been associated with high mortality, healthcare expenses, and morbidity. AKI is estimated to impact around 13.3 million people per year with 1.7 million deaths (18). Though the direct relationship between AKI and death has been controversial the progression of AKI to CKD and end-stage renal disease (ESRD) further increases the human burden.

Being a multifactorial disease the etiology of AKI is complex (Figure 1). Some of the factors include renal injury due to the surgery, adverse response to the medications, sepsis, toxins, dehydration, acute illness, and inflammation (19). This etiological diversity and complexity together with the heterogeneous patient group present unique challenges in the treatment of the patients.

Figure 1. Acute kidney injury being a multifactorial disease is influenced by various factors such as age, ethnicity of the population, genetic and epigenetic modifications and several other conditions such as respiratory syndrome, viral infections, cardiovascular diseases and diabetes. These factors contribute towards the development of AKI. The development of AKI is further influenced by the duration and stage of the disease and may progress to chronic kidney disease and end-stage renal disease.
As of the current scenario, no other medical intervention other than dialysis has been shown to effectively improve the survival rate, fasten the recovery process and limit the injury. Even among the patients who may survive AKI, several long-term outcomes such as progression of CKD, ESRD have been frequently observed (20,21). Thus, the AKI, previously considered to have a gentle course in the recovered patients, can lead to the deterioration of the quality of life and finances (20,22).

**Pathophysiology of AKI**

Post COVID-19 complications and their manifestation as kidney disease can be attributed to various factors such as sepsis, nephrotoxicity, and hypovolemia along with cardiovascular comorbidity (Figure 2) (23). AKI can be a consequence of kidney congestion caused due to the failure of the right ventricle in cardiorenal syndrome, secondary to coronavirus infection.

The autopsy (24) data indicates the affected endothelium of the lungs and kidney, which is a probable cause of proteinuria. Moreover, the viral particles have also been reported to be present in the cells of the renal endothelium, suggesting the potential role of viremia in damaging the renal endothelial layer and subsequently leading to kidney injury. Furthermore, the SARS-CoV-2 can directly cause infection in podocytes and renal tubular epithelium by utilizing an angiotensin-converting enzyme 2-dependent pathway leading to protein leakage in Bowman’s capsule, acute tubular necrosis, protein reabsorption vacuoles’ formation, mitochondrial dysfunction, and collapsing glomerulopathy (8,9).

Another proposed mechanism for the pathogenesis of AKI as a consequence of post-COVID-19 infection involves the dysfunction of immune responses, as observed in cytokine storm and lymphopenia (6,23). The other factors which have the potential to contribute towards AKI are macrophage activation syndrome, rhabdomyolysis and development of microthrombi and microemboli with reference to endothelitis (endothelial injury) and hypercoagulability (24,25).

**Management of post-COVID-AKI**

Kidney injury in COVID-19 patients is closely linked to the disease’s severity. In the paucity of specific treatment alternatives, the care strategy for patients with COVID-19 in the ICU remains largely supportive. Considering the high frequency of kidney involvement in COVID-19, all known therapeutic strategies for supporting kidney function should be explored. For reducing the occurrence and severity of AKI in critically ill patients of COVID-19, the patient should implement the Kidney Disease; Improving Global Outcomes (KDIGO) supportive care guideline. This guideline includes avoiding nephrotoxins, avoiding non-steroidal anti-inflammatory drugs, regularly checking serum creatinine and urine output, and considering hemodynamic monitoring (26).

**Adjust fluid balance**

Adjusting the fluid balance is an essential option for managing the risk of acute renal failure, according to the volume responsiveness and tolerance assessment test. The major goal of this strategy is to return to the normal volume status to avoid volume overload and the danger of pulmonary edema, right ventricular overload, congestion, and AKI. Fluid deprivation at the time of admission may be common in COVID-19 patients since they frequently appear with fever and pre-hospital fluid resuscitation is rarely used. To avoid AKI, hypovolemia should be managed in these patients. Recruitment approaches and procedures with a relatively high positive end-
Extracorporeal treatment
AKI has been linked to an increased risk of death in people who have SARS. Approximately 1.5-9 percent of patients who got AKI as a result of COVID-19 infection required RRT in the form of continuous renal replacement therapy (CRRT). With severe infection, the number of cases who needed RRT jumped to 5.2-25 percent. If conventional care fails, early commencement of RRT and sequential extracorporeal organ support may provide sufficient organ support and limit the advancement of disease severity in patients with COVID-19 and AKI (29,30). However, future clinical trials should examine this technique.

In the treatment of coronavirus-associated pneumonia such as SARS and MERS, CRRT has been widely employed. Because SARS and COVID-19 are so similar, it's practically possible that CRRT will help COVID-19 sufferers (31,32). CRRT is a method that resembles the physiological glomerular filtration process by injecting arteriovenous blood through a semipermeable membrane filter that eliminates overexpressed pro-inflammatory and anti-inflammatory molecules from the blood circulation non-selectively through convection and diffusion. CRRT plays a pivotal role in inhibiting inflammatory signaling pathways, regulate water-electrolyte instability and acid-base balance. It also reduces the peak inflammatory factor concentration, reduces body inflammation and prevents unnecessary activation of inflammatory signaling molecules. Theses actions of CRRT lead to stable and balanced body internal environment (26,33). Early CRRT treatment for patients with severe COVID-19 can help prevent the condition from progressing to critical illness or mortality, as well as minimize the incidence of AKI.

In one trial, the combined CRRT/blood perfusion group surpassed the blood perfusion treatment alone in terms of disease efficacy, hospitalization time, platelet count, activated partial thromboplastin time, blood oxygen saturation, mean arterial pressure, urea nitrogen, and serum creatinine. The former had a lower mortality rate (34). Due to the high frequency of clotting in CRRT filters and catheters, patients undergoing CRRT must have systemic anticoagulation therapy.

Further investigation into the therapeutic impact and evaluation of CRRT in severe COVID-19 patients is still needed (35). Xiao et al (36), in their observational analysis of 287 individuals observed that maximum number of patients recovered from stage 1 AKI. On the contrary, the death rates were high for the patients who advanced to stage 2 or 3 of AKI (3). COVID-19’s effect on patients’ long-term kidney function should be studied further. Furthermore, larger, multi-center studies are required to acquire a better understanding of AKI in COVID-19 patients, as well as how to prevent and manage it.

Conclusion and future prospects
Regardless of very limited data present on the correlation between the incidence of AKI and COVID-19 infection, it is plausible that the AKI may be a consequence of complex process mediated by infection of the virus, dysregulation of immune pathways, cytokine storm and hypercoagulation and their interaction with other risk factors of AKI. The data on clinical characteristics of AKI is very scarce and hence more study on the underlying mechanism needs to be done. Also, the data that are available lack detailed analysis of parameters indicating the kidney functions such as, urine microscopy, urine electrolytes and kidney injury markers. The markers of the immune system such as macrophage activation markers, complement activation markers, coagulation markers and kidney imaging are some of the important data needed for the deep insight into underlying COVID-19 associated physiopathology of AKI. Also, the clearer picture painted by the elaborate data will help us in designing better prevention and intervention strategies against COVID-19 associated AKI.

Authors’ contribution
VSB, SS, VS, SKP and SD conducted the primary draft. NS, AKT and SSA completed the paper. NKV, DS and PB finalized the paper. All authors read and signed the final paper.

Conflicts of interest
The authors declare that they have no competing interests.

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