Multidisciplinary basic and clinical research of acute kidney injury with COVID-19: pathophysiology and mechanisms, incidence, management, and issue of kidney transplantation during COVID-19

Acute kidney injury associated with COVID-19

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Abstract

Acute kidney injury (AKI) linked to COVID-19 had been identified in the course of the disease, AKI could be mild or severe that is dependent on the presence of comorbidities and severity of COVID-19. Patients who had been hospitalized with COVID-19, it was reported in patient admitted to intensive care unit. The etiology of AKI associated with COVID-19 is multifactorial. Prevention of severe AKI is the prime task in patients with COVID-19 that necessitate a battery of measurements and precautions in management. Patients with AKI whom have needed dialysis are in an increased risk to develop chronic kidney disease (CKD) or progression of their existing CKD. Kidney transplantation patients with COVID-19 are in need for special management to adjust the doses of immunosuppression drugs and corticosteroid to guard against graft rejection and not to suppress the immune system to stand the COVID-19 infection. Immunosuppression drugs and corticosteroid for patients who had kidney transplant has to be adjusted on laboratory results and is individualized aiming at protection of the transplanted from rejection.

Key Words: Acute kidney injury; COVID-19; SARS-COV-2; Kidney transplantation; Dialysis; Immunosuppressant; Intensive care unit; Mortality; Cytokine storm.


Core Tip: Acute kidney injury (AKI) in patients with COVID-19 is initiated by multifactorial events including direct viral effect, cardiac causes, thromboembolic phenomenon, and cytokine storm. AKI attributed to collapsing glomerulopathy, acute tubular necrosis, and mitochondrial dysfunction. Management of AKI is multidisciplinary dependent on severity of COVID-19, associated comorbidities, ICU admission, and artificial ventilation. Management is initial control fluid balance, in severe cases an early initiation of renal replacement and extracorporeal organ support would support the organs and prevent disease progression. Kidney transplantation patients are at risk of developing AKI due to the state of immunocompromised status caused by regular medication of immunosuppressants; this situation indicates adjustment of immunosuppressors in condition of treatment of cytokine storm with corticosteroids.
INTRODUCTION

Coronavirus disease-2019 (COVID-19) is caused by one of the coronaviridae family that has single-stranded RNA, and it causes severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On March 11, 2022, following its rapidly worldwide spread, the World Health Organization (WHO) recognized the disease as a pandemic. \(^1\)

COVID-19 initially affects the lungs, it also affects other organs including the heart, intestine, and the kidneys, and causes acute kidney injury (AKI). Up to 25% of patients who had severe COVID-19 developed AKI\(^{2,3}\). Since 2019 new variant of SARS-CoV-2 had been identified, these new variant has the similar effects and would cause AKI.

Acute kidney injury due to COVID-19 is multifactorial, that include cardiovascular comorbidity, direct effects of the virus on the kidney, dysregulation of immune system, hypercoagulopathy and endotheliosi, collapsing glomerulopathy, and thrombotic microangiopathy\(^{4,5,6}\).

Risk factors for AKI in patients with COVID-19 are older age, obesity, diabetes, hypertension, heart failure, chronic kidney disease, immunosuppression status, cancer chemotherapy. Adding factors are anemia, lymphopenia, leukocytosis, increase in inflammatory markers (D-dimer and IL-6) and need for mechanical ventilation and vasoactive drugs, all this would aggravate the condition.

AKI is a complication of SARS-CoV-2 Infection, AKI presents as mild or severe and is ranged from grade 1 to grade 3. AKI and could be managed conservatively or will be in need for hemodialysis dependent on severity. 10–15% of all hospitalized patients had some degrees of AKI, while patients in the intensive care unit (ICU) the incidence would exceed 50%\(^{10}\).

The hemodialysis initiation timing depends on the severity of AKI, continuous venous–venous hemodiafiltration is preferable for patients requiring vasoactive drug infusion and/or having hypervolemia.

Kidney transplant recipients are at considerable risk for development of AKI, due to chronic immunosuppression. Patients who had kidney transplantation and are COVID-19 patients and are on maintenance immunosuppressant drugs including corticosteroids, the doses of steroids would be adjusted for every case independently.
Pathophysiology and mechanisms of COVID-19-induced AKI

Acute kidney injury due to COVID-19 is multifactorial, that include cardiovascular comorbidity, direct effects of the virus on the kidney, dysregulation of immune system, hypercoagulopathy and endotheliosis. Angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) which are present in the kidney and they are targeted by SARS-CoV-2 causing AKI. In the glomerulus, podocytes and endothelial cells have been found to be the sites for viral infection resulting in podocyte dysfunction that lead to affection of glomerular filtration leading to proteinuria and haematuria. Viral infection of endothelial cells leads to changes in glomerular capillary hemostasis that cause fibrin thrombi. SARS-CoV-2 was detected in the proximal tubular cells and was attributed to vacuolar degeneration and loss of brush border of tubular epithelial cells, the tubular lumen contains necrotic epithelium, interstitium shows massive macrophage infiltration. Other non-viral mechanism that contribute to AKI includes focal segmental glomerulosclerosis, hemodynamic factors, cardiac dysfunction, high levels of mechanical ventilation, hypovolaemia secondary to decreased fluid intake, fever, sepsis, and the use of nephrotoxic antibiotics.

Cardiac factors. COVID-19 pneumonia would lead to right ventricular failure that led to kidney congestion and AKI. Left ventricular dysfunction would lead to hypotension, decreased cardiac output, and hypo perfusion of the kidneys and ultimately AKI [4].

Direct effects of COVID-19 virus on the kidney. The virus particles were reported to be present in renal endothelial cells, indicating viraemia as a cause of endothelial damage and a probable contributor to SARS-CoV-2 infects the renal tubular epithelium and podocytes through ACE2, and cause acute tubular necrosis, collapsing glomerulopathy, mitochondrial dysfunction, protein leakage in Bowman’s capsule, and protein reabsorption vacuoles [5, 6, 7].

Cytokine stroke. Would alter the immune response and development of lymphopenia, Hypercoagulability that will cause microthrombi and microemboli.

Rhabdomyosis. Severe COVID-19 would lead to skeletal muscle damage leading to myoglobin release that induces renal damage through formation of pigment casts that cause tubular obstruction, iron release has direct tubular toxicity, myoglobin casts had been demonstrated in renal tubules [8, 9].
**Sepsis.** Systemic inflammation due to sepsis is leading to release of multiple molecular patterns that are damage and pathogen-associated that enters the bloodstream and is filtered at the glomerulus.

**Hypoxemia and dehydration.** They are caused from high fevers, fluid restriction, and diuretics that are used for management acute respiratory distress syndrome, combined with mechanical ventilation would reduce renal perfusion.

**Hypercoagulable state.** Would injure renal microvasculature.

**Macrophage-activation syndrome.** With cytokine storm and high plasma ferritin would lead to AKI \[^{19}\].

**Direct effect of SARS-CoV-2 virus on tubular epithelium.**

The SARS-CoV-2 virus binds with ACE2 which is highly expressed in the kidney, there is particularly also high expression in podocytes \[^{11}\]. Direct viral infection is highly possible to contribute to injury mechanisms. Autopsies from 6 patients who died due to COVID-19 associates AKI showed that kidney tissues, on light microscopy exhibit-severe acute tubular necrosis, infiltration of tubular interstitium with CD68\(^+\) macrophage, and deposition of C5b-9. Immunohistochemistry study demonstrated the presence of SARS-CoV-2 nucleocapsid protein in the kidneys \[^{12}\]. High viral RNA titers were demonstrated in in the kidney \[^{23}\]. Electron microscopic examination elicited clusters of SARS-CoV-2 particles with its distinctive spikes in the tubular epithelium and podocytes. The pathological changes of the kidney in AKI associated with COVID-19 include vascular, glomerular, and tubulointerstitial damage. High viral RNA titers were demonstrated in in the kidney \[^{23}\]. Electron microscopic examination elicited clusters of SARS-CoV-2 particles with its distinctive spikes in the tubular epithelium and podocytes. The pathological changes of the kidney in AKI associated with COVID-19 include vascular, glomerular, and tubulointerstitial damage.

**Vascular events.** Vasoconstriction of intrarenal vessels, increased vascular permeability, formation of microthrombi, and vascular endothelium damage, these events contributes to development of AKI \[^{13}\].

**Glomeruli.** Autopsy studies of kidney of patients who died of COVID-19 showed focal and diffuse fibrin thrombi in glomerular capillaries, collapsing glomerulopathy, glomerular epithelial damage, loss of podocytes integrity, with hyperplasia and hypertrophy of the glomerular
epithelium, endothelial injury, erythrocyte stagnation in the glomerular capillary with glomerular loop occlusion by erythrocytes \(^{[14]}\).

**Proximal tubules.** Autopsies from kidneys of COVID-19 patients shows on light microscopy diffuse kidney injury, the renal tubules showed loss of the brush border and necrosis associated with tubulointerstitial fibrosis and vacuolar degeneration. Electron microscopy studies shows SARS-CoV-2 viruses was demonstrated in the tubular epithelium of proximal tubule and podocytes \(^{[13, 14]}\).

**The interstitium.** Shows inflammatory cell infiltration and edema that is attributed to the increased permeability of the endothelium and leakage of the glomerular filtrate in the tubules to the interstitium \(^{[14]}\).

**Inflammation and thrombotic microangiopathy.** COVID-19 initiate the release of a vast number of pro-inflammatory cytokines known as cytokine storm syndrome (CSS) and would lead to multiple organ dysfunctions, It would also lead to endothelial dysfunction and a pro-thrombotic event that led to small vessel vasculitis and extensive microthrombosis, a condition known as thrombotic microangiopathy, it is one of the main causes of mortalities in COVID-19. Its development might be mediated by inflammation, endothelial dysfunction and microthrombosis. Interleukin-6 (IL-6) has a critical leading role in CRS. An increase plasma levels of IL-6 in patients with COVID-19, denotes worse prognosis. CSS may cause renal medullary hypoxia and tubular cell damage that demonstrate the close relationship between the lungs and kidneys \(^{[15, 16, 17, 18, 19, 20]}\).

**Incidence of AKI linked to SARS-CoV-2 Infection**

Acute kidney injury is a complication of SARS-CoV-2 Infection it could happen in either moderate or severe cases of COVID-19. AKI would manifest as mild or severe forms, it could be managed conservatively or will be in need for hemodialysis. Incidence of AKI of all hospitalized patients is 10–15% with varying degrees of severity, while patients in the ICU the incidence would be higher and exceed 50% \(^{[10]}\).

Development of AKI in patients with COVID-19 depends on the level of severity and whither they are outpatient, hospitalized, or in the ICU. *The incidence of AKI during a hospital stay is reported with range of [11% (8–17%)], in critically ill patient the ranges is [23% (14–35%)]* \(^{[20]}\).
Several studies had reported the prevalence of AKI in COVID-19 patients, these studies are case series, observational study, retrospective single-center study, prospective cohort study, and retrospective observational cohort study. The studies implemented the definition of acute kidney injury adopted by “Kidney Disease: Improving Global Outcome (KDIGO)” which is defined as an increase in the serum creatinine level up to 1.5 times the baseline level, or increase at least 0.3 mg/dL within the past 48 h. Another used definition of AKI was that established by the “Acute Kidney Injury Network” (AKIN) where the criteria of AKI is defined as an increase in the serum creatinine level up to 1.5 times the baseline level, or increase at least 0.3 mg/dL within the past 48 h (Table 1).

Established diagnosis of COVID-19 infection is by the findings of positive PCR test for SARS-CoV-2, elevated laboratory values of D-dimer > 0.5 μg/ml, fibrinogen, Ferritin, LDH, CK, CRP, serum creatinine, cystatin C, and hematuria with urine deposits, decreased eGFR, mL/min per 1.73 m², and computerized tomography (CT) of the chest that shows round glass appearance. The incidence of AKI in published data ranges from 4.5% to 36.6%, the real incidence of AKI in COVID-19 remains uncertain due to a lack of reported studies.

In a Retrospective Brazilian study on 102 patient who had COVID-19 and were admitted to the ICU, AKI was diagnosed in 54 (56.8%) of the cases that was grade 1 in 22.2%, being KDIGO 1, grade 2 in (7.4%), and grade 3 in (70.3%). Patients with grade 3 AKI were old adults (64.9 ± 15.1 years of age) and had comorbidity of diabetes and hypertension. Patients who had immunosuppression condition secondary to chemotherapy treatment for cancer were (11.6%). Patients who had chronic kidney disease stage 2-4 were (16.8%). Patients who had comorbidities and developed AKI had received mechanical ventilation and vasoactive drugs that reflected the severity of the disease. Patients requiring hemodialysis were hypertensive, diabetic, and immunosuppressed.

**Patient under dialysis and/or on vasoactive drugs have higher indication rate of mechanical ventilation (93.8% vs. non dialysis 38, 1%).** Continuous renal replacement therapy was initiated in 26 patients (81.3%) out of 32 patients who were submitted to dialysis therapy. Eleven patients (34.4%) who received dialysis died, while 21 (65.6%) experienced recovery of renal function with maintained glomerular filtration rate. When comparing patients who died to those who are still alive and both had AKI due COVID-19, it was found that those who died were older, diabetic, immunosuppressed, received mechanical ventilation, and were on vasoactive drugs with range of: (78.6 vs. 61.9 years of age), (47.1 vs. 23.1%), (29.4 vs. 7.7%), (88.8 vs. 72.2), (94.1 vs. 48.7%) respectively.\(^{[28]}\)
Management of AKI related to Covid-19

Basic patient’s data for planning of management of AKI linked to COVID-19 are: gender, age, the presence of comorbidities as diabetes mellitus, hypertension, CKD, presence of chronic obstructive pulmonary disease, associated malignancies, and maintenance medications with immunosuppression drugs. Laboratory tests for COVID-19 are: D-dimer, C-reactive protein (CRP), lactate dehydrogenase (LDH), blood count, reverse transcription polymerase chain reaction (RT-PCR) for COVID-19 virus, blood urea, serum creatinine, liver function tests, ECG, echo cardiogram, and chest CT. AKI is defined according to the KDIGO criteria which is based on the creatinine values and urine output. The classification of AKI by KDIGO is 1, 2, or 3 according to clinical and laboratory data.

AKI KDIGO 1: is an increase of creatinine ≥0.3 mg/dL or 1.5–1.9 times baseline and/or urine output <0.5 mL/kg/h for 6–12 h.

AKI KDIGO 2: is an increase of creatinine of 2.0–2.9 times baseline and/or urine output <0.5 mL/kg/h for 12 h.

AKI KDIGO: 3 is increase of creatinine of 3.0 times baseline or increase in serum creatinine to ≥4.0 mg/dL and/or urine output <0.3 mL/kg/h for ≥24 h or anuria for ≥12 h, or initiation of renal replacement therapy (RRT).

Consideration includes medications for COVID-19: anti-IL6, ivermectin, and nitazoxanide. Ultimate evaluation of patients with AKI due to COVID-19 is: days of ICU stay, period of mechanical ventilation time, and total hospitalization period.

The hemodialysis initiation timing depends on the severity of AKI. A hemodialysis catheter of 15.5 Fr is placed in the patients, continuous venous–venous hemofiltration is preferable for patients requiring vasoactive drug infusion and/or having hypervolemia. The recommended dialysis dose is 25–30 mL/kg/h with regional citrate anticoagulation. Patients who do not need vasoactive would be on classic hemodialysis.[29]

Measures to be considered in the management of Covid-19 and patient in the ICU to stabilize kidney function and to avoid AKI:

1. Nephrotoxic drugs would be avoided; serum creatinine and urine output are regularly monitored.
Initiation of lung-protective ventilation to avoid hemodynamic changes and to diminish the sequences of cytokine burden on the kidney. 

To avoid volume overload that reduces the risk of pulmonary oedema, fluid balance should be adjusted according to volume responsiveness, restoration of normal volume status would avoid right ventricular overload, congestion, and subsequent AKI.

Hypovolemia should be corrected to prevent AKI.

Renal replacements therapy and extracorporeal support. Are indicated in case the conservative management fails, patients with volume overload should be considered for RRT, patients with nonresponding hypoxemia are candidates for extracorporeal support. Early initiation of RRT and extracorporeal organ support (ECOS) would support the organs and prevent progression of COVID-19 and AKI.

Hypercoagulable state. Severely ill patients with COVID-19 are often has hypercoagulable state, anticoagulation protocols for the extracorporeal circuit should be implemented.

Cytokine storm. Application of hemoperfusion with sorbent cartridges might prevent cytokine-induced kidney damage.

Lung-protective ventilation. Is applied with appropriate tidal volume to avoid hypercapnia, respiratory acidosis, increased need for vasopressors, and in severe cases of AKI. In these patients, extracorporeal carbon dioxide removal (ECCO₂R) might help in these patients to prevent progression of severity.

Extracorporeal membrane oxygenation (ECMO). Is indicated in cases where respiratory exchanges further deteriorate.

Patients with SARS-CoV-2 infection. Bacterial infection co-occurs syndrome and a sepsis-like would develop, the use of sequential extracorporeal therapies for immunomodulation and endotoxin and cytokine removal, extra corporeal organ support (ECOS) for various organs should be considered, as clinical progression can be rapid.

Kidney transplantation during COVID-19
Kidney transplant recipients (KTRs) are at considerable risk for development of AKI, due to maintenance use of immunosuppression, in addition to co-morbidities.
Since the Covid-19 pandemic there is a significant reduction of kidney transplantation procedures \cite{37}.

Presentation of COVID-19 in this specific group of patients is fever and cough; atypical presentation is gastrointestinal symptoms \cite{38}. In a series of KTRs showed that the median age (51–62 years), duration between transplantation to diagnosis of COVID-19 was ranged from 2 to 3 years. It is reported in two series that two patients had positive data of COVID-19 after 3 months of kidney transplantation \cite{39,40}.

Indication for mechanical ventilation in KTRs who had COVID-19 was (22-91%), while mortality rate was (7-30%). These KTRs who had COVID-19 were on maintenance immunosuppression. Patients who had AKI were (30–57%), the need of with variable rates of RRT were (5–43%), mortality was high as 32\% \cite{41,42,43,44,44,45,46} (Table 2).

Patients who had kidney transplantation and are COVID-19 positive, and while steroids are a part of their maintenance immunosuppression, cessation would not be recommended, and the dose would be adjusted for every case independently.

Patient who had transplantation and are on Tacrolimus (FK506) and corticosteroids, the dosed would be manipulated according to the level of FK506 (Prograf level in blood) which had been found to be decreased in patient who had COVID-19 infection, consequently the doses of prograf and corticosteroid will be increased. Myfortic (mycophenolic acid) is an immunosuppressant that is given with cyclosporine and corticosteroid to prevent organ rejection after a kidney transplant, it weakens immune system that helps to prevent kidney rejection. Myfortic would be stopped while paragraph and corticosteroid to be increased in dose, in case a patient who had kidney transplant and had COVID-19 infection, doses of myfortic and corticosteroids will be manipulated according to the regular laboratory data to guard against severity of COVID-19 and avoidance of kidney rejection.

**ACUTE KIDNEY INJURY ASSOCIATED WITH COVID-19**

Revised manuscript
CONCLUSION

Acute kidney injury in patients with COVID-19 is initiated by multifactorial etiopathology events including direct viral effect, cardiac causes secondary to right sided heart failure and cardiomyopathy, thromboembolic phenomenon, vascular factors, cytokine storm, toxic drugs to the kidney that are given during treatment of pneumonia of COVID-19. Pathophysiology of AKI is attributed to collapsing glomerulopathy, acute tubular necrosis, mitochondrial dysfunction, and arterial occlusion.

Management of AKI is a multidisciplinary approach and personalized depending on several factors: severity of COVID-19 disease, ICU admission, induction of artificial ventilation, and associated comorbidities, patients who had all these elements would have severe AKI, management is to preserve kidney function and prevent aggravation of the disease.

Main treatment steps are initial control fluid balance, in severe cases an early initiation of renal replacement and extracorporeal organ support would support the organs and prevent progression of COVID-19 and AKI.

Kidney transplantation patients are at risk of developing AKI due to the immunocompromised status caused by regular medication of immunosuppressants, this situation indicates modification of immunosuppressors in setting of treatment of cytokine storm with corticosteroids. In specific cases it would indicate to stop myfortic immunosuppressant and to increase corticosteroid with modification of the dose of paragraf

Patients who are in regular hemodialysis they need to adjust the anticoagulant dose when the patient receives anticoagulant to treat or prevent hyper coagulopathy state resulted from COVID-19.
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