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

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Abstract

Acute kidney injury (AKI) linked to coronavirus disease 2019 (COVID-19) has been identified in the course of the disease. AKI can be mild or severe and that is dependent on the presence of comorbidities and the severity of COVID-19. Among patients who had been hospitalized with COVID-19, some were 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 necessitates a battery of measurements and precautions in management. Patients with AKI who have needed dialysis are in an increased risk to develop chronic kidney disease (CKD) or a progression of their existing CKD. Kidney transplantation patients with COVID-19 are in need of special management to adjust the doses of immunosuppression drugs and corticosteroids to guard against graft rejection but not to suppress the immune system to place the patient at risk of developing a COVID-19 infection. Immunosuppression drugs and corticosteroids for patients who have had a kidney transplant has to be adjusted based on laboratory results and is individualized aiming at the 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

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Core Tip: Acute kidney injury (AKI) in patients with coronavirus disease 2019 (COVID-19) is initiated by multifactorial events including direct viral effect, cardiac causes, thromboembolic phenomenon and cytokine storm. AKI is attributed to collapsing glomerulopathy, acute tubular necrosis and mitochondrial dysfunction. Management of AKI is multidisciplinary dependent on severity of COVID-19, associated comorbidities, intensive care unit admission and artificial ventilation. Management is initial control of fluid balance and in severe cases an early initiation of renal replacement and extracorporeal organ support which would support the organs and prevent disease progression. Kidney transplantation patients are at risk of developing AKI due to the state of their immunocompromised status caused by regular use of immunosuppressants; this situation indicates the adjustment of immunosuppressors in the condition of treatment of cytokine storm with corticosteroids.

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INTRODUCTION

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

COVID-19 initially affects the lungs, but 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, the new variants of SARS-CoV-2 have been identified and these new variants have similar effects and can cause AKI.

Acute kidney injury due to COVID-19 is multifactorial and this includes cardiovascular comorbidity, direct effects of the virus on the kidney, dysregulation of the immune system, hypercoagulopathy and endotheliosis, collapsing glomerulopathy and thrombotic microangiopathy[4-6].

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

AKI is a complication of SARS-CoV-2 Infection and presents as mild or severe and is ranged from grade 1 to grade 3. AKI could be managed conservatively or the patient will be in need of hemodialysis which is dependent on severity. 10%-15% of all hospitalized patients had some degrees of AKI but patients in the intensive care unit (ICU) experienced an incidence that would exceed 50%[10].

The hemodialysis initiation timing depends on the severity of AKI and 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 develop COVID-19 are on maintenance immunosuppressant drugs including corticosteroids and the doses of steroids should be adjusted for every case independently.

PATHOPHYSIOLOGY AND MECHANISM OF COVID-19-INDUCED AKI

Acute kidney injury due to COVID-19 is multifactorial including 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 which are present in the kidney 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 effects glomerular filtration leading to proteinuria and hematuria. 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 the brush border of tubular epithelial cells. The tubular lumen contains necrotic epithelium and the interstitium shows massive macrophage infiltration. Other non-viral mechanisms that contribute to AKI includes focal segmental glomerulosclerosis, hemodynamic factors, cardiac dysfunction, high levels of mechanical

ventilation, hypovolemia secondary to decreased fluid intake, fever, sepsis and the use of nephrotoxic antibiotics.

Cardiac factors

COVID-19 pneumonia can cause right ventricular failure and lead to kidney congestion and finally AKI. Left ventricular dysfunction can 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 infecting the renal tubular epithelium and podocytes through ACE2 and causing acute tubular necrosis, collapsing glomerulopathy, mitochondrial dysfunction, protein leakage in Bowman's capsule and protein reabsorption vacuoles[5-7].

Cytokine stroke

Cytokines can alter the immune response and the development of lymphopenia. Hypercoagulability occurs that will cause microthrombi and microemboli ultimately leading to stroke.

Rhabdomyolysis

Severe COVID-19 can lead to skeletal muscle damage leading to myoglobin release which induces renal damage through formation of pigment casts that cause tubular obstruction and iron release that has a direct effect on tubular toxicity. Myoglobin casts have been demonstrated in renal tubules[8,9].

Sepsis

Systemic inflammation due to sepsis leads to release of multiple molecular patterns that are damaging and pathogen-associated that enters the bloodstream and is filtered at the glomerulus.

Hypoxemia and dehydration

Hypoxemia and dehydration are caused by high fevers, fluid restriction and diuretics that are used for the management of acute respiratory distress syndrome. This is combined with mechanical ventilation which reduces renal perfusion.

Hypercoagulable state

It attributes to injury of renal microvasculature.

Macrophage-activation syndrome

Macrophage-activation syndrome involves cytokine storm and high plasma ferritin, which lead to AKI [10].

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 and there is also high expression in podocytes[11]. Direct viral infection is highly probable to contribute to injury mechanisms. Autopsies from 6 patients who died due to COVID-19 associates AKI and showed that kidney tissues, on light microscopy, exhibit severe acute tubular necrosis, infiltration of tubular interstitium with CD68⁺ macrophage and deposition of C5b-9. An immunohistochemistry study demonstrated the presence of SARS-CoV-2 nucleocapsid protein in the kidneys[12]. High viral RNA titers were demonstrated in the kidneys[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 tubulointerstitium damage.

Vascular events

Vasoconstriction of intrarenal vessels increased vascular permeability, formation of microthrombi and vascular endothelium damage. These events contribute to development of AKI[13].

Glomeruli

Autopsy studies of the kidneys of patients who died from 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 were demonstrated in the tubular epithelium of the proximal tubule and podocytes[13,14].

Interstitialium

It 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 initiates the release of a vast number of pro-inflammatory cytokines known as the cytokine storm syndrome (CSS) and can lead to multiple organ dysfunctions. It would also lead to endothelial dysfunction and a pro-thrombotic event that leads to small vessel vasculitis and extensive microthrombosis. A condition known as thrombotic microangiopathy 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 in plasma levels of IL-6 in patients with COVID-19 denotes a worse prognosis. CSS may cause renal medullary hypoxia and tubular cell damage that demonstrate the close relationship between the lungs and the kidneys[15-20].

INCIDENCE OF AKI LINKED TO SARS-CoV-2 INFECTION

Acute kidney injury is a complication of SARS-CoV-2 Infection and it can happen in either moderate or severe cases of COVID-19. AKI can manifest as a mild or more severe form. It could be managed conservatively or the patient may be in need of hemodialysis. Incidence of AKI of all hospitalized patients is 10-15% with varying degrees of severity while for patients in the ICU, the incidence can be higher and exceed 50%[10].

The development of AKI in patients with COVID-19 depends on the level of severity and whether they are outpatient, hospitalized or in the ICU. The incidence of AKI during a hospital stay is reported with a range of [11% (8%-17%)]. In the critically ill patient, the range is [23% (14%-50%)] [20,21].

Several studies have 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 an increase of at least 0.3 mg/dL within the past 48 h. Another useful definition of AKI was one 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 an increase of at least 0.3 mg/dL within the past 48 h (Table 1)[21-29].

An established diagnosis of COVID-19 infection is by a 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 a 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 patients 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 older adults (64.9 ± 15.1 years of age) and had comorbidities of diabetes and hypertension. Patients who had an immunosuppression condition secondary to chemotherapy treatment for cancer were (11.6%). Patients who had chronic kidney disease stages 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.

Patients under dialysis and/or on vasoactive drugs have a 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 to COVID-19, it was found that those who died were older, diabetic, immunosuppressed, received mechanical ventilation and were on vasoactive drugs with a 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[29].

MANAGEMENT OF AKI RELATED TO COVID-19

Basic patient data for the planning of management in AKI linked to COVID-19 are gender, age, the

Table 1 Incidence of acute kidney injury linked to severe acute respiratory syndrome coronavirus 2 infection

| Ref. | Country | Type of study | Coronavirus disease patients , n | Patients admitted to intensive care unit, n (%) | Patients developed acute kidney injury, n (%) |
|---------------------------------|---------------|---|----------------------------------|---|---|
| Arentz <i>et al</i> [22], 2020 | United States | Case series | 21 | 4 (19.1) | 4 (19.1) |
| Hirsch <i>et al</i> [23], 2020 | United States | Retrospective observational cohort study | 5449 | 1395 (25.6) | 1993 (36.6) |
| Thakkar <i>et al</i> [24], 2020 | United States | Retrospective observational study | 300 | 300 | 224 (75) |
| Yidirim <i>et al</i> [25], 2021 | Turkey | Retrospective study | 331 | 17 | 17 (5.1) |
| Yan <i>et al</i> [26], 2020 | China | Retrospective, observational cohort study | 882 | 105 (11.9) | 115 (13) |
| Zhang <i>et al</i> [27], 2020 | China | Case series | 221 | 55 (24.8) | 10 (4.5) |
| Chen <i>et al</i> [28], 2020 | China | Case series | 274 | 50 (18.5) | 29 (11) |
| Cheng <i>et al</i> [29], 2021 | China | Prospective cohort study | 701 | 73 (10.4) | 36 (5.1) |
| Neves <i>et al</i> [30], 2021 | Brazil | Retrospective study | 102 | 95 | 54 |

presence of comorbidities such 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), ferritin, 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 an increase of creatinine of 3.0 times baseline or an 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 with continuous venous-venous hemodiafiltration and 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. For patients who do not need a vasoactive drug infusion, they 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

Nephrotoxic drugs should 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 kidneys [30].

Avoid volume overload that reduces the risk of pulmonary edema. Fluid balance should be adjusted according to volume responsiveness, restoration of normal volume status should avoid right ventricular overload, congestion and subsequent AKI.

Hypovolemia should be corrected to prevent AKI.

Renal replacements therapy and extracorporeal support

Renal replacements and extracorporeal support are indicated in case 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) will support the organs and prevent progression of COVID-19 and AKI [31].

Hypercoagulable state

Severely ill patients with COVID-19 often have a hypercoagulable state and anticoagulation protocols for the extracorporeal circuit should be implemented[32].

Cytokine storm

The application of hemoperfusion with sorbent cartridges might prevent cytokine-induced kidney damage[33].

Lung-protective ventilation

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 to prevent progression of severity[34].

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation is indicated in cases where respiratory exchanges further deteriorate.

Bacterial infection

Patients with SARS-CoV-2 can develop a sepsis-like syndrome. 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[33].

KIDNEY TRANSPLANTATION DURING COVID-19

Kidney transplant recipients (KTRs) are at considerable risk for development of AKI due to the maintenance use of immunosuppression and in addition to co-morbidities[35,36].

Since the Covid-19 pandemic, there is a significant reduction of kidney transplantation procedures[37, 38].

Presentation of COVID-19 in this specific group of patients is fever and cough; atypical presentation is gastrointestinal symptoms. 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 years to 3 years. It is reported in two series that 2 patients had positive data of COVID-19 after 3 mo of kidney transplantation[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 was (30%-57%) and the need of with variable rates of RRT were (5%-43%). Mortality rate was as high as 32% (Table 2)[35,40-46,48].

Patients who had kidney transplantation and are COVID-19 positive while on steroids as a part of their maintenance immunosuppression because cessation would not be recommended, should have their dose adjusted depending on their personal case.

Patients who had transplantation and are on immunosuppressant corticosteroids and tacrolimus (TAC or FK506), the oral fast release of TAC is (Prograf) which is a calcineurin inhibitor employed to reduce the risk of acute rejection and allograft loss. For Tacrolimus and corticosteroids, the dose would be manipulated according to the level of FK506 in the blood which has been found to be decreased in patients who had a COVID-19 infection, consequently, the doses of tacrolimus 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 the immune system that helps to prevent kidney rejection. Myfortic should be stopped while tacrolimus and corticosteroids should be increased in cases where a patient who had kidney transplant and also have 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.

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 from 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 should be personalized depending on several factors: severity of COVID-19 disease, ICU admission, induction of artificial ventilation and associated comorbidities. Patients who have all of these elements will have severe AKI and management is to preserve kidney function and prevent aggravation of the disease.

Table 2 Demographic data of kidney transplant recipients who had severe acute respiratory syndrome coronavirus 2 and developed acute kidney injury and the incidence of survival vs mortality

| Study | n | Median age, yr | Median Transplant, yr | Acute kidney injury incidence, % | Renal replacement therapy, % | Mechanical ventilation, % | Mortality, % |
|----------------------------------|-----|----------------|-----------------------|----------------------------------|------------------------------|---------------------------|--------------|
| Banerjee <i>et al</i> [40], 2020 | 7 | 54 | 2 | 57 | 43 | 14 | 14 |
| Nair <i>et al</i> [42], 2020 | 10 | 57 | 7.7 | 50 | 10 | 40 | 30 |
| Columbia <i>et al</i> [43], 2020 | 15 | 51 | 4 | 40 | 14 | 27 | 7 |
| Alberici <i>et al</i> [35], 2020 | 20 | 59 | 13 | 30 | 5 | 0 | 25 |
| Akalin <i>et al</i> [48], 2020 | 36 | 60 | NR | NR | 21 | 39 | 28 |
| Lubetsky <i>et al</i> [44], 2020 | 54 | 57 | 4.7 | 51 | 10 | 28 | 13 |
| Cravedi <i>et al</i> [41], 2020 | 144 | 62 | 5 | 52 | NR | 30 | 32 |
| Caillard <i>et al</i> [45], 2020 | 279 | 62 | 5 | 44 | 11 | 30 | 23 |
| Elias <i>et al</i> [46], 2020 | 6 | 54 | NR | 42 | 11 | 22 | 24 |

NR: Not reported.

Main treatment steps are to control fluid balance in severe cases and an early initiation of renal replacement and extracorporeal organ support which 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 doses of immunosuppressants. This situation indicates modification of immunosuppressors and the setting of treatment of cytokine storm with corticosteroids. In specific cases, there is an indication to stop myfortic immunosuppressant and to increase corticosteroid and modify the dose of tacrolimus.

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

FOOTNOTES

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