
Acute Kidney Injury in COVID -19

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Coronavirus disease 2019 (COVID-19) continues to affect millions of people worldwide. As data from all over the world emerge, it is becoming more and more evident that extra pulmonary organ involvement, particularly the kidneys, has a significant bearing on mortality. The incidence of Acute Kidney Injury (AKI) has been estimated to be 30% in COVID-19 non-survivors. Current evidence suggests four broad mechanisms of renal injury: Hypovolaemia, acute respiratory distress syndrome related, cytokine storm, and direct viral invasion, as seen on renal autopsy findings. I shall briefly discuss the mechanisms and management of Covid 19 associated AKI.

Introduction

The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infection leading to the corona virus disease 2019 (COVID-19) is affecting millions of people worldwide, carrying a case fatality rate between 0.9% to 7.2% depending on the demographics, implementation of preventative measures, testing strategies and availability of health care resources. Severe disease is seen in approximately 20% of cases, of which around 6% represent critically ill COVID-19 patients. Amongst the critically ill, 65% to 95% have acute respiratory distress syndrome (ARDS), followed by AKI and acute cardiac injury/cardiomyopathy. AKI is common among critically ill patients with COVID-19 and is an independent marker of mortality. Prompt recognition and management of AKI in COVID-19 can limit its progression and contribute to reducing morbidity and mortality. Multiple mechanisms of kidney injury have emerged as we learn more about SARS-CoV-2.

Epidemiology

AKI, in general, has an incidence of around 3%-18% in hospitalized patients and is associated with 10%-20% mortality in the non-intensive care hospital setting, with up to 50% mortality in the intensive care setting. There is a paucity of evidence identifying the role AKI plays in COVID-19. The majority of studies use Kidney Disease: Improving Global Outcomes (KDIGO) criteria to define AKI in COVID-19.

Assessment of data from major published cohorts on COVID-19, combining results from intensive care unit (ICU) admissions with non-ICU admission, reveals an overall AKI incidence of around 4 %.

What is the mechanism of AKI in COVID-19?

Four possible key mechanisms are becoming evident in the COVID-19 pandemic: Hypovolaemia, ARDS related AKI, cytokine storm syndrome (CSS) associated AKI, and direct viral tropism for proximal tubular cells and podocytes *via* the angiotensin-converting enzyme 2 (ACE2) carboxypeptidase.

Hypovolaemia

A majority of patients have significant insensible water losses due to high-grade pyrexia and tachypnoea on presentation. A subgroup of patients has substantial gastrointestinal symptoms leading to extrarenal volume loss. These patients are particularly prone to developing pre-renal AKI.

ARDS related AKI

AKI is seen in around 35%-50% of patients who develop ARDS and substantially increases mortality by nearly two-fold in the ICU. ARDS and its associated mechanical

ventilation strategies can cause or aggravate renal injury *via* multiple pathways. There are broadly five categories; hemodynamic effects, gas exchange impairment (hypoxemia/hypercapnia), acid-base dysregulation, hyperinflammation, and neurohormonal effects. In COVID-19, significant AKI generally develops after the onset of ARDS, suggesting lung-kidney crosstalk as the dominant mechanism of kidney injury.

The hemodynamic effects of the acute pulmonary disease resulting in increased pulmonary artery pressures, right ventricular failure, venous congestion, and increased intra-abdominal/intrathoracic pressures.

Impaired gaseous exchange with hypercapnia leads to a reduction of renal vasodilatory response and renal blood flow with altered diuresis and increased oxygen utilization in the proximal tubule. Severe hypoxemia also causes a reduction in renal blood flow with possible activation of the hypoxia-inducible factor system, influencing lung and kidney outcomes. The activation of the renin-angiotensin-aldosterone system, with increased aldosterone secretion with resultant activation of the sympathetic nervous system and release of non-osmotic vasopressin. An immune-mediated/inflammatory response is noted in ARDS with the release of interleukin (IL)-6, tumor necrosis factor (TNF alpha), IL-1, transforming growth factor, and substance P.

Mechanical ventilation can worsen the hemodynamic effects and cause ventilator-induced lung injury leading to further cytokine release and multi-organ dysfunction syndrome. The effects of excessive positive end-expiratory pressure (and high tidal volumes) on kidney function include a further increase in intrathoracic pressures, which causes increased right ventricular dysfunction, reduced venous return, and reduced cardiac output AKI independently worsens ARDS. AKI leads to increased production, decreased clearance of inflammatory cytokines, and down-regulation

of lung aquaporin and ion channels. The rise in circulatory cytokines, particularly IL-6, leads to increased infiltration of lungs with neutrophils and macrophages, and increased pulmonary vasculature permeability worsens ARDS. In the later phase of inflammation, IL-6 promotes IL-10 production, which has anti-inflammatory and organ protective effects. Limited data suggest AKI promotes neutrophil dysfunction, causing reduced clearance of infection and increasing lung permeability. Haemodynamically, the inflammatory state and increased alveolar-capillary permeability combined with decreased urine output in AKI worsen pulmonary oedema.

The incidence of shock is variable in COVID-19 based on the reported cohort studies; it may be as high as 35% in the ICU setting. This vasopressor-dependent state causes renal blood flow dysregulation, including ischemia-reperfusion injury, metabolic reprogramming, and inflammation resulting in AKI.

The cardio-renal syndrome can play a significant role in critically ill COVID-19 patients. In cardio-renal syndrome, excessive inflammation and rise in cytokines seem central to the pathophysiological process. The high levels of IL-6, TNF, and IL-1 have a direct cardio-depressant effect and may promote myocardial cell injury. Acidaemia promotes pulmonary vasoconstriction, increases right ventricular afterload, and exacerbates the negative inotropic effect. Myocarditis may also occur in COVID-19.

The overall combined effect of this entire process is an inflammatory, cardiodepressant, acidotic, volume retaining state with high intrathoracic and intraabdominal pressures resulting in high renal back pressures, decreased and dysregulated renal blood flow, and severe renal tubular injury.

Cytokine storm syndrome associated AKI

Observational data from a subgroup of patients with COVID-19 suggest the development of features consistent with CSS triggered by SARS-CoV-2 virus characterized by high serum ferritin, D-dimer, lactate dehydrogenase, cytopenia, ARDS, acute cardiac injury, abnormal liver function test, raised IL-6, and coagulation abnormalities. The use of dexamethasone, a potent anti-inflammatory steroid, has demonstrated a significant reduction in mortality amongst critically ill COVID-19 patients, highlighting the major role of hyper inflammation. Can this hyper-inflammatory state cause AKI? Various case series have indicated significant renal involvement, particularly in CSS associated with secondary haemophagocytic lymphohistiocytosis (sHLH). The majority present with AKI with or without nephrotic range proteinuria. Histological and observational findings indicate polymorphic renal lesions with acute tubular necrosis (ATN) being the most common, followed by tubulointerstitial nephritis (TIN), collapsing glomerulopathy, and thrombotic microangiopathy (TMA). ATN and TIN are most likely due to sepsis-related hemodynamic changes, coagulopathy (DIC), and perhaps the direct toxic effect of raised cytokines (IL-6 and TNF) on renal epithelial cells. Nephrotic syndrome with collapsing glomerulopathy and podocytopathies are generally seen in severe cases of sHLH with African ethnic predisposition. It is hypothesized a circulating cytokine during the CSS phase of sHLH may cause podocytopathy. Hyperinflammation, as seen in COVID-19, also leads to a hypercoagulable state that can cause fibrin thrombi occlusions in renal capillaries.

Renal biopsy histology of patients of black ethnicity who had AKI and were subsequently SARS-CoV-2 positive showed collapsing glomerulopathy, severe podocyte effacement with acute tubular injury (ATI).

The hyperinflammatory state can cause renal injury *via* multiple mechanisms, as highlighted; however, the discussion is incomplete without further assessing the role of direct viral tropism for renal parenchyma and renal autopsy findings.

Direct viral invasion

Viruses must gain entry into a cell and use the host cell machinery to replicate. The ACE2 is the coreceptor used by SARS-CoV-2 to gain entry to the cells. ACE2 forms part of the renin-angiotensin-aldosterone system, a cascading peptide-pathway in regulating vascular tone and salt and water balance. The ACE2 degrades angiotensin II to angiotensin, resulting in vasodilation and countering the effects of ACE. The ACE2 is expressed in the kidney, staining abundantly in the brush border of tubular epithelial cells, moderately in parietal epithelial cells, and absent in glomerular or mesangial endothelial cells. Although hypertension may be a risk factor for poor prognosis with SARS-CoV-2 infection, inferences that this is due to effects on ACE2 expression as a consequence of ACE inhibitor or angiotensin receptor blocker (ARB) use are not supported by data.

The data on whether SARS-CoV-2 caused direct kidney injury through viral entry are conflicting. Using a murine monoclonal antibody specific for SARS-CoV-2 nucleoprotein in four patients who died of SARS, SARS-CoV-2 antigen and RNA were found in the epithelial cells of distal convoluted renal tubules. Observational and histopathological studies on COVID-19 have suggested renal parenchymal involvement.

Early histopathological analysis from autopsies conducted on COVID-19 patients demonstrated on light microscopy primarily proximal ATI and ATN with vacuolar degeneration, TIN, endothelial injury, diffuse red blood cell aggregation in peritubular capillaries and glomerular capillary loops,

rarely with focal fibrin thrombi. Electron microscopy showed SARS-CoV-2 viral particles in the cytoplasm of the proximal tubule, distal tubule, and podocytes. The ACE2 expression was prominent in proximal tubular cells, particularly in areas with severe ATI. Furthermore, focal strong parietal epithelial cells staining were present, as well as occasional weaker podocyte staining of ACE2. Six autopsy cases showed the presence of CD68+ macrophages and membrane attack complex, C5b-C9, in the tubulointerstitium.

Based on limited evidence, it is plausible that during severe infection and high viral loads, SARS-CoV-2 infection and replication in renal tubular cells and podocytes causes ATI and ATN with subsequent TIN, which is further exacerbated by CSS.

Fibrin thrombi and a TMA pattern of renal injury may be present due to a hypercoagulable state. This entire process of kidney injury with the presence of SARS-CoV-2 in the renal parenchyma can be described as COVID-19 nephropathy. Patients with dysregulation or a genetic variant of ACE2, allowing rapid SARS-CoV-2 infiltration, may show early signs of intrinsic renal injury by new-onset proteinuria and haematuria.

Causes of Acute Kidney Injury in Covid-19 Patients

Cause	Supporting Evidence
Prerenal (volume depletion)	Increased BUN: creatinine ratio (> 20), urine sodium < 20 mmol/L, FeNa $< 1\%$ Urine sediment may show hyaline casts
Acute tubular injury	Urine sodium > 20 mmol/L, FeNa $> 1\%$ Urine sediment- granular /muddy brown casts
Acute interstitial nephritis	Rash, eosinophilia, WBCs on urine microscopy Urine sediment with WBC casts urine eosinophils are not sensitive or specific
Rhabdomyolysis	Increased serum creatine kinase and myoglobin in the urine Positive urine dipstick for blood, no RBCs on microscopy
Abdominal compartment syndrome	Increased intra-abdominal pressure (> 20 mm Hg)
Coagulopathy	Elevated prothrombin time, partial thromboplastin time, D-dimer, fibrinogen
Cardiorenal syndrome	Jugular venous distention, low ejection fraction on echocardiography, urine sodium < 20 mmol/L

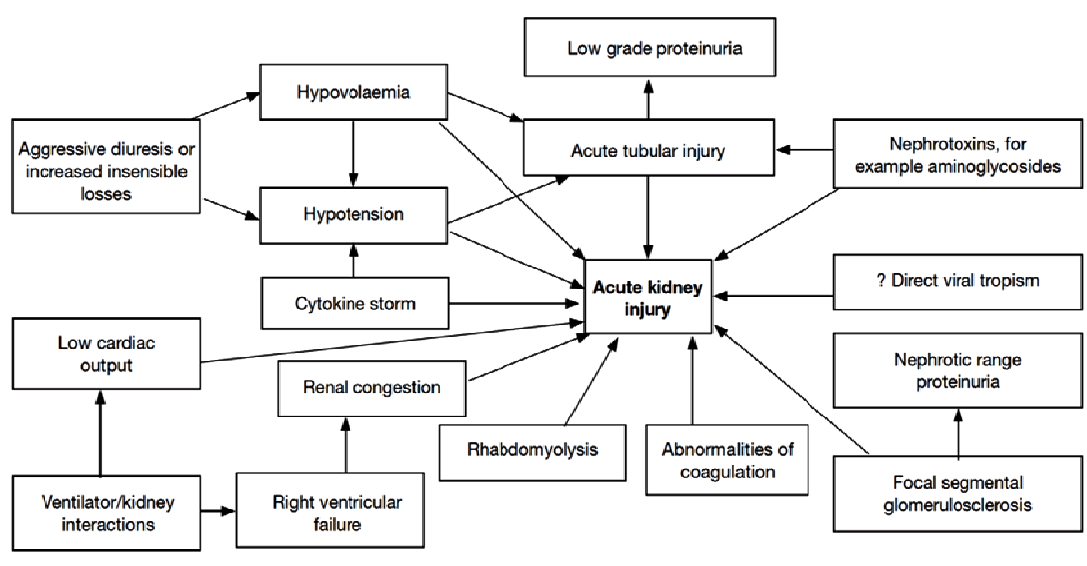


Figure 1: Potential pathophysiological mechanisms behind the development of COVID-19-associated AKI

Renal management of COVID-19

The COVID-19 can be divided into three phases. The first phase is mild symptoms, characterized by fever and cough, continuing for approximately five days, progressing to the second phase with new-onset or worsening dyspnoea or hypoxia (silent hypoxia), which lasts 2 to 5 d. The final phase is demonstrating severe viral pneumonitis and ARDS requiring ICU management. The majority of the patients (81%) remain in the first phase and do not require significant hospitalization. As mentioned previously, AKI significantly increases in-hospital mortality, particularly in the ICU setting, which also holds in the case of COVID-19.

Risk factors

A majority of the patients that present to the hospital with COVID-19 are 60 years or older, with a high proportion having diabetes, hypertension, and ischaemic heart disease. These co-morbidities are associated with micro and macrovascular complications, all affecting renal blood flow. Any minor hemodynamic or nephrotoxic insult can lead to a substantial AKI in these patients.

All patients presenting with symptoms of COVID-19 should have urinalysis (urine dipstick, midstream urine, and spot urine protein to creatinine ratio) and should be possibly repeated at each phase of the disease. Identification of haematuria and proteinuria may allow early recognition of patients with a high risk of disease progression to ARDS, AKI, and increased mortality. Active urinary sediments are seen in a much larger proportion of COVID-19 patients than those with only diabetes and hypertension. Urinalysis should be considered in conjunction with other baseline investigations such as FBC, renal profile, liver function tests, D-dimer, fibrinogen, ferritin, procalcitonin, lactate dehydrogenase, IL-6, C reactive protein, troponins, creatine kinase, and Sequential Organ Failure Assessment (SOFA) score.

Data extrapolated from research looking at risk factors for AKI in ARDS highlights age, presence of diabetes and heart failure, worsening acidosis on day 1 of ARDS, higher severity of illness score (SOFA and APACHE III), and obesity as strongly associated with the development of AKI. Drug dosing needs to be adjusted as per creatinine clearance, and potential nephrotoxic treatment options need to be assessed for risk-benefit. All drugs can cause acute interstitial nephritis, and a high diagnostic suspicion is of paramount importance. Remdesivir, an antiviral drug, has shown some quicker recovery and trend towards lower mortality amongst patients with severe COVID-19. However, the drug is primarily renally excreted and is currently not recommended in patients with an e GFR rate below 30 mL/min/1.73 m².

Volume management

The primary management of severe COVID-19 revolves around oxygenation and achieving an appropriate volume status. From a volume perspective, patients who present early during the disease can be hypovolaemic with gastrointestinal symptoms, fever, and/or have an exacerbation of heart failure; therefore, volume management should aim to achieve euvoemia and stabilization blood pressure, which may be achieved through diuretics or intravenous fluids. The minimum required volume should be used to achieve effective arterial volume.

Choice of fluids remains a matter of literature debate; however, current data suggest large volume resuscitation should be through balanced crystalloids rather than isotonic saline due to lower incidence of AKI. Isotonic saline can lead to the development of hyperchloremic acidosis, which harms organ perfusion. Acidosis is also an independent risk factor for developing AKI in ARDS. Isotonic bicarbonate can be considered in hypovolemic patients with significant metabolic acidosis (particularly in pH < 7.20) and AKI. Once

initial volume resuscitation is accomplished, the next aim should be to achieve and maintain a cumulative net even balance.

Despite its inaccuracies, targeting a central venous pressure of around 8 mmHg and pulmonary artery occlusion pressure of around 12 mmHg with monitoring of urine output provided the best outcomes. Volumes assessment is based on many other factors, including passive leg raise response, inferior vena cava diameter, lung ultrasound, ejection fraction, capillary refill time, and blood pressure and vasopressor requirements. It is important to note volume management strategies need to be individualized, and various other factors such as ethnicity may impact decision making. Until more robust evidence is available in volume management of COVID-19 induced ARDS, continue to support a relatively conservative fluid management strategy.

Role of Continuous Renal Replacement Therapy in COVID-19

Around 20% of non-survivors in COVID-19 required RRT, which was primarily continuous renal replacement therapy (CRRT). Many of these patients required it due to AKI with severe electrolyte derangements and/or volume overload intending to achieve net even or negative fluid balance. The timing of initiating CRRT varies amongst centers. However, two major randomized control trials over the last decade showed a delayed strategy of either absolute indications developing or AKI KDIGO stage 3 for more than 48 h compared to an early strategy of RRT within 6-12 h of AKI KDIGO stage 3 that had no difference in mortality, ICU-free days, ventilator-free days and vasopressor-free days. Many patients did not require CRRT in the delayed group due to recovery of native renal function. However, a large proportion of COVID-19 patients are in ARDS at the time of AKI, and some small randomized control trials have suggested early

initiation of CRRT in ARDS improved oxygenation and mechanical ventilation-free days. Some observational data are suggesting a higher incidence of circuit clotting in COVID-19. Thus regional citrate anticoagulation should be first-line based on the availability of trained staff and centre experience.

CRRT timing should be based on an individual patient's physiological reserve. This depends on age, cardiovascular risk factors, pulmonary comorbidities, baseline renal function and the trend of inflammatory and renal injury markers. A delayed strategy of waiting for 48–72 h after progressing to AKI KDIGO 3 or until an absolute indication arises may apply to most COVID-19 patients with septic shock.

CRRT can be applied earlier in ARDS patients, who, despite optimum volume management with diuretics, are not able to attain an early cumulative net even or negative fluid balance. Some authors have suggested using extracorporeal blood purification technologies, particularly in the context of CSS seen in COVID-19 patients. These technologies are primarily direct haemoperfusion, plasma adsorption on a resin, CRRT with hollow fiber filters with adsorptive properties, and high-dose CRRT with medium cut-off or high cut-off membranes. Extracorporeal cytokine adsorption and removal can be potentially beneficial in patients with CSS. Currently no recommendation on the use of extracorporeal blood purification outside the standard use of CRRT in COVID-19 due to inconclusive evidence.

Conclusion

AKI leads to worse outcomes in COVID-19. Multiple mechanisms of renal injury are involved but can broadly be categorized into hypovolaemic, ARDS related, CSS associated, and direct viral invasion of the renal parenchyma. Haematuria and proteinuria are associated with higher mortality and may

signify aggressive disease early. Thus all patients should have a baseline urinalysis. SARS-CoV-2 has an affinity towards the renal parenchyma and is seen in renal autopsies with associated intrinsic renal damage, collectively termed as COVID-19 nephropathy.

Volume assessment is key in managing COVID-19; patients can present hypovolaemic during the early phase, particularly transplant recipients, due to a high incidence of gastrointestinal symptoms. The aim should be to achieve euvolemia. Current evidence supports a conservative fluid management strategy during ARDS. Standard indications for CRRT apply. However, early initiation can be considered in ARDS if diuretics fail to support a conservative fluid management strategy. The science on COVID-19 is rapidly evolving, and new evidence is being published on a daily basis.

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