Acute kidney injury and electrolyte disorders in COVID-19

Reviewed by:

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Introduction

The 2019 coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been declared a pandemic and has infected around 21.2 million people, causing over 761,000 deaths in countries and territories worldwide. COVID-19 presents as an acute infection of the upper and lower airways, leading to pneumonia and also affecting several other tissues and organs.[1]

Recently, it has been shown that one out of every four patients admitted to the hospital with COVID-19 had abnormal kidney function. Acute kidney injury (AKI) has been found to be the most common consequence in COVID-19 patients. It is also noted that among the various systemic complications caused by SARS-CoV-2, changes in electrolyte concentrations are not only present but are also independently associated with poor outcome. The incidence of electrolyte imbalances and AKI in COVID-19 patients was 12.5% and 11.0%, respectively.[1,2]

Acute Kidney Injury

As previously mentioned, acute kidney injury is the most common kidney syndrome in hospitalized COVID-19 patients. According to KDIGO, AKI is defined as follows: [1,3]

- Increase in serum creatinine (SCr) by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 h
- Increase in SCr ≥ 1.5 times of baseline within the prior 7 days
- Urine volume < 0.5 mL/kg/hour for 6 h.

> Acute kidney injury is the most common consequence in patients with COVID-19 and electrolyte abnormalities are not only present in these patients but are also independently associated with poor outcome

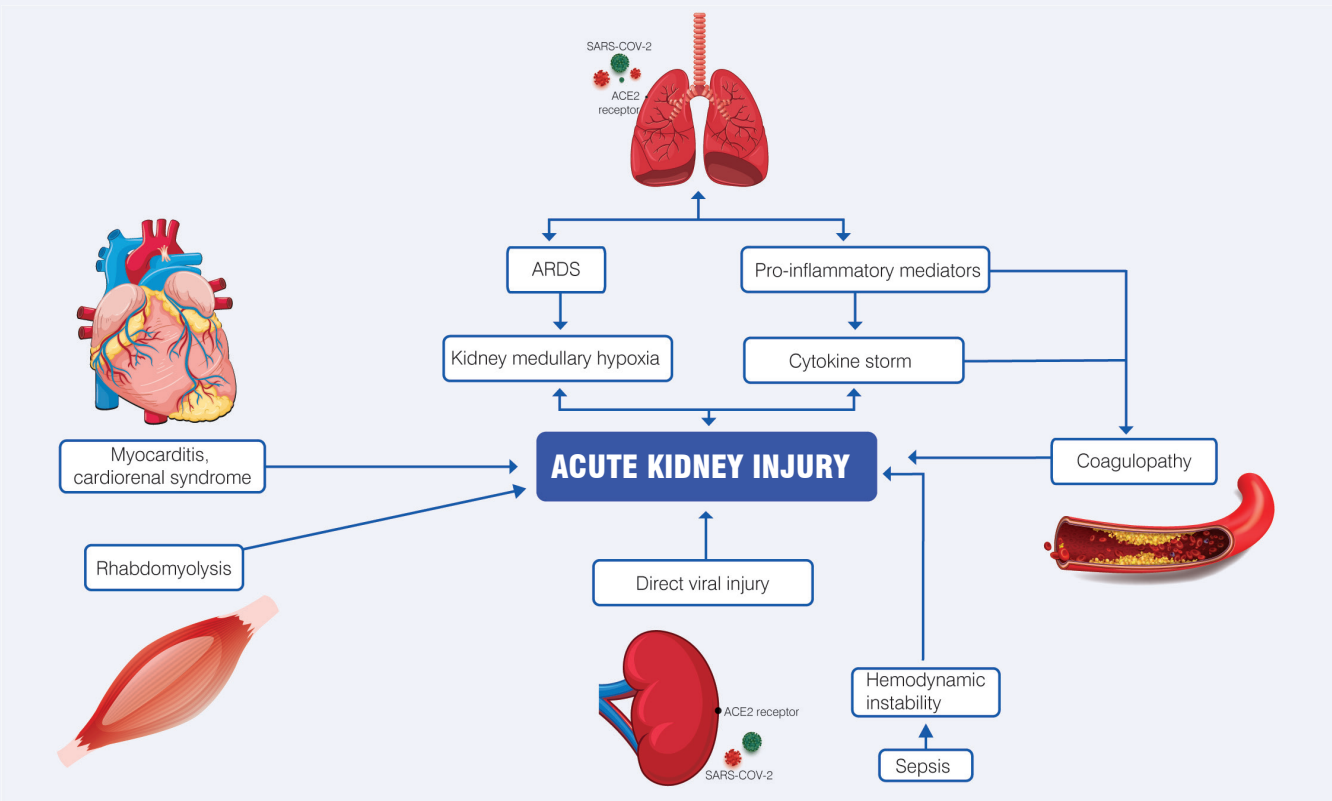
In addition, AKI develops far more frequently in severe and critically ill patients and is associated with a poor prognosis and higher mortality. Therefore, understanding the underlying pathophysiology of kidney damage during the course of COVID-19 is crucial for early detection of damage and implementation of optimal treatment.

Pathophysiology of AKI in COVID-19

The mechanism of AKI in COVID-19 is most likely multifactorial (Figure 1). In direct pathogenic mechanism, SARS-CoV-2 enters via the angiotensin converting enzyme 2 (ACE2) receptors. ACE2 is much more expressed in the kidney than in the lung, particularly on the apical brush border membrane of the proximal tubule and also at lower levels in podocytes. Under normal physiological conditions, ACE2 is a counter-regulatory enzyme that breaks down angiotensin-2 to form angiotensin 1-7, which further mediates vasodilation and attenuates angiotensin-2-mediated inflammation. However, due to the binding of SARS-CoV-2 to ACE2, the expression of this molecule is downregulated, resulting in an increased activity of angiotensin 2. As a consequence, angiotensin-2 causes systemic vasoconstriction and also increases inflammation, endothelial cell dysfunction, oxidative stress, collagen synthesis in fibroblasts and fibrosis in target organs and further contributes to the onset of AKI.[1,2,3]

Besides the direct virulence of SARS-CoV-2 and the cytokine storm, there are potentially other factors contributing to AKI, such as systemic hypoxia, abnormal coagulation, and possibly drug-induced or hyperventilation-related rhabdomyolysis. All of these factors further lead to impairment of kidney function.[1,3]

Figure 1: Different mechanism of COVID-19 associated AKI



Adapted from: Legrand M, Bell S, Forni L, et al. Pathophysiology of COVID-19-associated acute kidney injury. Nat Rev Nephrol. 2021;17(11):751-764.

Clinical manifestation

Studies have shown that most common renal findings in Covid 19 infected patients were increased SCr and blood urea nitrogen, and reduction in eGFR; it may be associated with proteinuria and hematuria as well.[1,3]

Risk factors

Older age, diabetes, hypertension, cardiovascular disease, obesity and respiratory failure are the possible risk factors associated with AKI. Non- specific factors that are common in critically ill patients, such as mechanical ventilation, hypoxia, hypotension, low cardiac output and nephrotoxic agents, might also contribute to kidney injury and/or functional decline in the most severely affected patients (Table 1).[1,4,5]

Management of COVID 19 associated AKI

There is no specific treatment for AKI caused by COVID-19. The 25th Acute Disease Quality Initiative Workgroup defined a few strategies for dealing with COVID-19 associated AKI. The standard measures that have an evidence level of 1B or above include:[2,3,5]

- Measurement of kidney function through serum creatinine and urine output
- Use of dynamic assessment of cardiovascular status

Table 1. Factors that may contribute to COVID 19 associated AKI

Acute tubular injury	▸ Regional inflammation ▸ Direct viral infection ▸ Tissue hypoxia ▸ Nephrotoxic-induced injury ▸ Rhabdomyolysis
Vascular injury	▸ Endothelitis ▸ Microthrombi ▸ Thrombotic microangiopathy
Glomerular injury	▸ Interferon-associated podocyte injury ▸ Glomerulonephritis
Interstitial injury	▸ Acute interstitial nephritis ▸ Interstitial edema

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to mitigate the risk of AKI and ARDS, avoiding hemodynamic imbalance

- Volume expansion with balanced crystalloids to decrease the chances of developing AKI, unless there are indications for the use of other kinds of fluids
- Limit the patients' exposure to nephrotoxins whenever possible and monitor their kidney functionality when the use of nephrotoxins is necessary
- When contrast media are required, optimize intravascular volume as a means to prevent AKI

In addition, AKI can lead to many complications. Therefore, complications should be treated. Along with this systemic therapy can be given based on the underlying cause of AKI, which includes antiviral drugs, antibiotics, corticosteroids, renin angiotensin inhibitors, statins, and anticoagulants (Table 2). Drug therapy can reduce the risk of developing AKI.[3]

Table 2. Systemic treatment for the management of acute kidney injury

Pathogenic mechanism	Treatment
Direct mechanism of action of SARS-CoV2 to kidney injury	Anti-viral agents
Cytokine storm and kidney injury	Immunomodulators
Systemic hypoxia	Oxygen inhalation or artificial assisted breathing
Renal hypoperfusion	Manage fluid imbalance and hypertension
Drug related or hyperventilation relevant rhabdomyosis	Blood perfusion therapy

Adapted from: Cheng, Y., Wang, W., Wu, L. et al. SARS-CoV-2-Related Kidney Injury: Current Concern and Challenges. SN Compr. Clin. Med. 2, 2015–2024 (2020).

Electrolyte disorders

Clinically significant electrolyte disorders can occur in patients with COVID-19. The main disorders are hyponatremia, hypokalemia, and hypocalcemia. The pathophysiological mechanisms are complex and imply changes in the renin angiotensin aldosterone pathway as well as immuno-inflammatory events, which are generally associated with kidney and/or gastrointestinal damage.[1,7,8] A general overview of the pathophysiology of the most frequent electrolyte disorders associated with COVID-19 is shown in Table 3.

Hyponatremia

- Hyponatremia is the most frequent electrolyte disorder in clinical practice, with a prevalence of 20% to 30% in hospitalized patients, and is defined by serum sodium levels below 135 mEq/L
- Studies have shown that hyponatremia is one of the possible complication of COVID 19
- In patients with COVID-19, SIAD is associated with elevated levels of IL-6, which induces non-osmotic release of antidiuretic hormone
- Evidence showed an inverse relationship between serum sodium levels and IL-6 levels.[2,7,9]

Hypokalemia

- Hypokalemia corresponds to the most frequent potassium disorder and is characterized by a serum concentration of potassium below 3.5 mEq/L
- The literature indicates an incidence between 10% and 41% of patients hospitalized for COVID-19
- In addition, it is also reported that hypokalemia is associated with longer hospital stays

Table 3 : Pathophysiology of electrolyte imbalances most common in COVID-19

Electrolyte disorder	Pathophysiological mechanisms
Hyponatremia	Syndrome of inappropriate antidiuresis (SIAD)
Hypokalemia	Viral interaction with ACE2, volume loss, and use of medications (diuretics, glucocorticoids etc)
Hypocalcemia	Vitamin D deficiency and parathyroid imbalance

Adapted from: Nogueira GM, Silva NLOR, Moura AF, Duarte Silveira MA, Moura-Neto JA. Acute kidney injury and electrolyte disorders in COVID-19. World J Virol. 2022 Sep 25;11(5):283-292.

> Earlier prediction of electrolyte imbalances can reduce longer hospital stay and mortality through appropriate therapeutic and preventive measures

- In severe cases, hypokalemia can increase respiratory stress and the risk of cardiac injury.[2,7,8]

Hypocalcemia

- Studies have shown that hypocalcemia is prevalent in patients with COVID-19 and is potentially associated with poor prognosis
- The hypocalcemia rate was higher in patients with COVID-19 than in non-COVID-19 respiratory disease patients, despite similar characteristics at baseline.[2,10]

Hypochloremia and hypernatremia have also been reported though these are seen less frequently.

Conclusion

Acute kidney injury is common in patients with SARS-CoV-2 infection, particularly the critically ill, and is undoubtedly associated with higher mortality. There are numerous possible pathomechanisms that are still under investigation, however, the most likely are direct cell invasion, ARDS, cytokine storm, and hypovolemia. Clinical management includes systemic management, and standard AKI management. In addition, electrolyte imbalances are associated with poorer outcomes, longer hospital stays, and mortality in patients with COVID-19. Therefore, earlier prediction of these disorders can reduce mortality through appropriate therapeutic and preventive measures.

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