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Acute kidney injury and electrolyte disorders in Covid-19

AKI and electrolyte disorders in Covid-19

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Abstract

Acute kidney injury (AKI) and electrolyte disorders are important complications of hospitalized COVID-19 patients. AKI is thought to occur due to multiple pathophysiological mechanisms, such as multiple organ dysfunction (mainly cardiac and respiratory), direct viral entry in the renal tubules and cytokine release syndrome. AKI is present in approximately one in every ten hospitalized COVID-19 patients. The incidence rates of AKI increase in patients who are admitted to ICUs, with levels higher than 50%. Additionally, renal replacement therapy (RRT) is used in 7% of all AKI cases, but in nearly 20% of patients admitted to an ICU. AKI patients in COVID-19 are considered moderate-to-severe cases and are managed with multiple interdisciplinary conducts. AKI acts as a risk factor for mortality in SARS-CoV-2 infection, especially when RRT is needed.

Electrolyte disorders are also common manifestations in hospitalized COVID-19 patients, mainly hyponatremia, hypokalemia, and hypocalcemia. Hyponatremia occurs due to a combination of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and gastrointestinal fluid loss from vomiting and diarrhea. When it comes to hypokalemia, its mechanism isn't fully understood but may derive from hyperaldosteronism due to renin angiotensin aldosterone system (RAAS) overstimulation and gastrointestinal fluid loss as well. The clinical features of hypokalemia in COVID-19 are similar to those in other conditions. Hypocalcemia is the most common electrolyte disorder in COVID-19 and seems to occur because of vitamin D deficiency and parathyroid imbalance. It is also highly associated with longer hospital and ICU stay.

Key Words: COVID-19; SARS-CoV-2; acute kidney injury; electrolyte disorders; Renal dialysis

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Core Tip: Acute kidney injury and eletrolyte disorders are frequent clinical complication in hospitalized patients with COVID-19, being directly related to the severity of the disease and increasing the mortality.

INTRODUCTION

The Coronavirus disease 2019 (COVID-19) outbreak initiated in the first months of 2020. It corresponds to an illness caused by the SARS-CoV-2 virus. Although frequently asymptomatic, the malady is known for its wide variety of clinical signs and symptoms. These can range from pulmonary manifestations, such as dyspnea and cough, to extrapulmonary ones, which include fever, anosmia, ageusia, diarrhea and myalgia (1–3). This heterogeneity of clinical features is an indicative of the systemic character of COVID-19.

COVID-19 disease had an outstanding impact in the nephrology community. With over 4 million chronic kidney disease (CKD) patients on maintenance dialysis at risk (4), the pandemic caused profound changes to the sector (5). The kidney was also a commonly affected organ by COVID-19 disease; 1 in every 4 patients present abnormal renal function at hospital admission (6). According to the classification proposed by the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, acute kidney injury is defined as any of the following situations: increase in serum creatinine (SCr) by ≥ 0.3 mg/dL within 48 h; or increase in SCr ≥ 1.5 times baseline from seven days prior; or urinary volume < 0.5 mL/kg/h for a period of 6 h. The KDIGO guideline also proposes a stratification of AKI in three stages, numbered from 1 to 3 in crescent order of injury severity (7).

In primary analyses of patients with COVID-19, it was also noticed that, among the various systemic complications caused by the SARS-CoV-2 virus, changes in electrolyte concentrations are not only present, but also independently associated with a poor outcome (8,9).

In this review, we discuss the pathophysiology, epidemiology, clinical history, risk factors, management and prognosis of COVID-19 associated acute kidney injury (AKI) and the most reported electrolyte disorders in COVID-19, which are hyponatremia, hypokalemia, and hypocalcemia.

ACUTE KIDNEY INJURY

PATHOPHYSIOLOGY

The mechanism of AKI in COVID-19 is most likely multifactorial. Some of the proposed alterations induced by the viral disease that could damage the kidneys can be seen in Figure 1 (10).

The Coronaviruses have high affinity for the angiotensin-converting enzyme 2 (ACE2), a metallopeptidase often bound to cell membranes that is responsible for catalyzing the conversion of angiotensin 2 to angiotensin 1-7 (11–13). The transmembrane protease serine 2 (TMPRSS2) contributes with the entry of SARS-CoV-2 in the cell by cleaving and activating the spike (S) protein (14). After entry, followed by endocytosis, coronavirus infection causes PAK1 upregulation, a kinase that mediates inflammation and is associated with risk factors for mortality. Increased PAK1 Levels also suppress the adaptive immune response, facilitating viral replication (15). It was previously shown that SARS-CoV could bind to ACE2 *via* the virus' S protein (16). Being structurally similar to SARS-CoV, SARS-CoV-2 also uses ACE2 in order to enter the host cell and replicate in its cytoplasm (17). This enzyme is distributed across multiple tissues, such as vascular endothelium, alveolar epithelium, proximal tubular cells of the kidney, and glomerular epithelium (18).

The fact that kidney cells express ACE2 explains how they also act as host cells of the novel coronavirus, an information that was shown in autopsy studies. Histopathological examination found out varying degrees of tubular injury, such as diffuse proximal tubule injury with loss of the brush border, vacuolar degeneration, necrosis, hemosiderin granules and pigment casts. (19–21). RNA in situ hybridization

and electron microscopy also found evidence that SARS-CoV-2 directly infects the renal tubules (20,21). A small number of patients with AKI may present virus in urine samples, which also supports a direct viral cytopathic effect hypothesis. These patients may have a greater predilection for proteinuria (22).

Due to the binding of SARS-CoV-2 to ACE2, the expression of this molecule is down-regulated, which leads to increased activity of angiotensin 2 that is unopposed by angiotensin 1-7 (23,24). In normal conditions, angiotensin 1-7 has anti-thrombotic, anti-inflammatory and vasodilator effects that counter the actions of angiotensin 2 through activation of Mas receptors (25–27). It is suggested that the overactivation of angiotensin type 1 (AT1) receptors may contribute to AKI onset mostly due to hemodynamic alterations, such as hypoxia, hypertension-induced proteinuria, and oxidative stress (27,28).

Furthermore, a hypercoagulative state induced by the lack of anti-thrombotic effects of angiotensin 1-7 could cause renal microangiopathy capable of causing AKI (29). Rhabdomyolysis is also a frequent cause of COVID-19 AKI, being responsible for around 7% of the cases (30). The occurrence of skeletal muscle injury is presented in up to one in every five COVID-19 patients, which explains the occurrence of rhabdomyolysis nephropathy in this disease (29).

Cytokine release syndrome consists of an extreme rise of inflammatory cytokines, frequently called a "cytokine storm", caused by a systemic response that can be triggered by a wide variety of conditions (31,32). It has been implied that cytokine storm is a significant component of the disease course of severe cases of COVID-19 (33). The binding of SARS-CoV-2 to ACE2 promotes an inflammatory response with a prominent release of inflammatory cytokines, such as IL-6, IL-8, IL-22 and TNF-α, and chemokines, like CCL2, CCL3 and CCL5 (29,34,35). Lymphopenia, a common feature of SARS-CoV-2 infection, also contributes to the rise of inflammatory cytokines (36).

The crosstalk between kidneys, lungs and cardiovascular system seems to be significant for the development of AKI. Cases of acute respiratory distress syndrome (ARDS) are knowingly associated with a greater risk of AKI onset, including those

related to SARS-CoV-2 infection (37–39). This is likely a result of renal damage triggered by inflammatory mediators that cause tubular injury, which by itself culminates in IL-6 upregulation that harms the lungs (39,40).

The cardiovascular system is another important topic regarding AKI in COVID-19. Acute viral myocarditis and cytokine cardiomyopathy can induce a reduction of the estimated glomerular filtration rate (eGFR) through hemodynamic changes. Type 1 cardiorenal syndrome (CRS) can occur due to a cytokine storm or myocarditis and type 3 CRS can occur after the onset of AKI. Furthermore, on the onset of sepsis, type 5 CRS can occur (41,42). Right ventricular failure caused by pneumonia induced by SARS-CoV-2 and reduction of cardiac output due to left ventricle failure are also possible mechanisms of eGFR diminishment and AKI (43,44).

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

Data available refers to hospitalized patients, since AKI is a complication typical of moderate and severe cases of COVID-19 that require inpatient healthcare (45–50). The incidence of AKI in COVID-19 is highly variable depending on the study analyzed. Our review found results between 5% and 75%, and the article with the largest sample size indicated a frequency of approximately 36%, whilst a systematic review of observational studies found an incidence of AKI of 11% (30,45–49,51–53).

A multicenter study showed that about 45% of the patients had no significant kidney injury caused by the viral illness; that 34% developed AKI without need for renal replacement therapy (RRT), and that 26% developed COVID-19 AKI with need of RRT (AKI-RRT) (44). In contrast, a systematic review found that RRT was used in only 7% of COVID-19 cases with renal manifestations (51). The modality of first choice is usually continuous renal replacement therapy, mostly because it is a suitable modality for hemodynamically unstable patients (54).

In a Chinese cohort study, three quarters of the patients had developed renal symptomatology, including proteinuria and/or hematuria, but only one in every ten patients had an AKI onset (55). Out of all renal clinical findings, the most common ones

were proteinuria, hematuria, elevated SCr and blood urea nitrogen, reduction of eGFR and AKI (46,47,55,58). One study found that three in every four patients that were at least moderately ill had renal involvement to some extent. These levels were as low as 62% in moderately (3.5% being AKI) ill patients and as high as 91% in critically ill patients (43% being AKI). It is suspected that most cases of AKI in COVID-19 occur due to intrinsic rather than prerenal mechanisms (55).

A multicenter American study found that patients who developed AKI because of SARS-CoV-2 infection were older and predominantly male individuals with higher levels of comorbidities associated with more severe cases of COVID-19, such as systemic arterial hypertension, diabetes mellitus and heart failure. Additionally, the same article shows that patients who developed AKI were usually admitted to an intensive care unit (ICU) and were more likely to be on use of vasopressors (52.6% vs. 3.4%) as well as mechanical ventilation (89.7% vs. 21.7% in nonventilated patients), indicating that patients who developed AKI were critically ill. In that sample of AKI patients, about one third of patients died (46). Independent risk factors for the development of COVID-19 AKI include pre-existing renal impairment (such as chronic kidney disease), hypertension and inpatient diuretic use (51,52,57,58).

It is also known that there is an association between ARDS and AKI in general and it also applies to COVID-19 due to the release of inflammatory cytokines, especially IL-6 (37–40). This is clinically notable as well, since patients on mechanical ventilators are more likely to develop AKI with or without need of RRT (45–47). Additionally, abnormal serum urea and serum creatinine values was associated in a bivariate Cox regression model with either ARDS development or progression from ARDS to death (59).

Lab exams show that most AKI patients are admitted with abnormal kidney function, represented by high levels of SCr and low eGFR. Patients who do not develop AKI are admitted with higher levels of SCr and lower eGFR than at discharge, while AKI patients are discharged with worsened kidney function (45–47). Patients who develop stage 3 AKI are usually discharged with a median SCr of 4.0 mg/dL and a

median eGFR of 14.0 mL/min/1.73 m^2, as opposed to a median SCr of 1.19 mg/dL and a median eGFR of 62 mL/min/1.73m^2 at admission (46).

MANAGEMENT AND PROGNOSIS

The management of COVID-19 AKI is a largely discussed theme among intensive care professionals. The 25th Acute Disease Quality Initiative (ADQI) Workgroup defined a few strategies for dealing with COVID-19 AKI (54). The standard measures that have an evidence level of 1B or above include:

Measurement of kidney function through serum creatinine and urine output (57).

Use of dynamic assessment of cardiovascular status to mitigate the risk of AKI and ARDS, avoiding hemodynamic imbalance (57).

Volume expansion with balanced crystalloids to decrease the chances of developing AKI, unless there are indications for the use of other kinds of fluids (57).

Limit the patients' exposure to nephrotoxins whenever possible and monitor their kidney functionality when the use of nephrotoxins is necessary (57).

When contrast media is required, optimize intravascular volume as a means to prevent AKI (57).

Prognosis of COVID-19 AKI and AKI-RRT is arguably poor. AKI was associated with a longer median hospital stay, which was approximately twice as long when compared to non-AKI patients (60). One study found that mortality is about ten times higher in patients with moderate-to-severe COVID-19 who developed AKI in comparison to those who did not (55). Another observational study concluded that AKI is almost 2.5 times more frequent in non-survivors than survivors of critical COVID-19 cases (61). It is also stated that AKI is an independent risk factor for 30-day mortality among COVID-19 patients (52).

Although remission from proteinuria and hematuria is a common outcome for patients with renal COVID-19 manifestations, less than half of AKI patients recover their kidney function (55). Mortality rates were as high as 35% of AKI patients and use of RRT increases the lethality of the disease to levels over 60%. Furthermore,

approximately one in every three RRT patients that were discharged remained RRT-dependent (46,47).

ELECTROLYTE DISORDERS

Patients with COVID-19 may experience diverse electrolyte disturbances with clinical impact. The main disorders are hyponatremia, hypokalemia, and hypocalcemia. The pathophysiological mechanisms are diverse and imply changes in the RAAS as well as immuno-inflammatory phenomena underlying the coronavirus, which are generally associated with kidney and/or gastrointestinal (GI) damage (62). Refer to Table 1 for a general overview of the pathophysiology of the most frequent electrolyte disorders associated with COVID-19.

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 (63). The association between pneumonia and hyponatremia was firstly described in 1962, mainly related to community-acquired pneumonia, which was later reported in other respiratory infections (64). Thus, with the emergence of the COVID-19 pandemic, preliminary studies indicated that hyponatremia was one of the possible complications caused by the viral disease (65). In general, patients with COVID-19 hyponatremia have had more severe forms of the disease, with higher levels of hospitalization, when compared to normonatremic patients, both in infirmary and ICU beds. Most of these patients also had other markers of severity, such as higher levels of C-reactive protein (CRP), ferritin and IL-6; consolidation lesions more present on chest CT; and greater need for oxygen support (66).

The pathophysiology of hyponatremia in patients with COVID-19 is considered multifactorial, but the main cause is the syndrome of inappropriate antidiuresis (SIAD). SIAD is characterized by hyponatremia (serum sodium less than 135mEq/L) and elevated urinary osmolarity (>100 mOsm/kg) compared to plasma osmolarity

(<280mOsm/kg) in euvolemic patients that have normal renal, thyroid, hepatic, cardiac and adrenal functions and are not on use of diuretics (67). Despite its mechanism not being fully understood, SIAD in patients with COVID-19 is apparently related to elevated levels of IL-6, which induce the non-osmotic release of antidiuretic hormone. In addition, these cytokines can damage lung tissue and alveolar cells, generating hypoxic pulmonary vasoconstriction, which may induce SIAD (68). Evidence demonstrates a directly proportional relationship between the serum sodium level and the PaO2/FiO2 ratio and an inversely proportional relationship between the serum sodium level and the IL-6 Level (69). Furthermore, some other factors may contribute to the secretion of this hormone, such as patients who experience fluid loss from vomiting and diarrhea (reported symptoms of COVID-19) (70).

HYPOKALEMIA

Hypokalemia corresponds to the most frequent potassium disorder and is characterized by a serum concentration of potassium below 3.5 mEq/L. The presence of hypokalemia can be variable and data in the literature point to an incidence between 10 and 41% of patients who were hospitalized for COVID-19 (71, 72). Furthermore, in another study carried out in Italy, hypokalemia was associated with a longer hospital stay (72).

There are a lot of factors that can generate hypokalemia, so a precise mechanism for this complication in patients with COVID-19 has not yet been determined. However, some hypotheses can be taken into consideration, such as (a) viral interaction with its input receptor (ACE2), altering the classic renin-angiotensin-aldosterone pathway and stimulating the release of aldosterone, increasing potassium secretion in the urine; (b) volume loss due to gastrointestinal symptoms caused by the viral infection, mainly diarrhea, and (c) secondary to the use of medications, such as diuretics and glucocorticoids (9,72).

The clinical manifestations of symptomatic hypokalemia include muscle weakness and fatigue. However, in more severe cases, low levels of potassium can

cause cardiac arrhythmias with alterations on the electrocardiogram (EKG) tracing, and respiratory muscular weakness (73). Therefore, it is correct to say that hypokalemia can increase respiratory stress and the risk of cardiac injury (62). Regarding coronaviruses, hypokalemia was reported on the onset of SARS-CoV-1 virus infection, back in 2003, and was also described in some preliminary studies during the beginning of the COVID-19 pandemic (72).

HYPOCALCEMIA

Calcium plays an important role in the mechanism of entering a host cell and viral replication, something that was already reported in the pathophysiology of Ebola and SARS-CoV-1 viruses (74,75). In addition, hypocalcemia represents an independent factor for increased mortality among critically ill patients with long hospital stay (76).

In a study carried out in China, the incidence of hypocalcemia in COVID-19 patients was 62.6%. Other lab findings included lymphocytosis and higher levels of CRP, D-dimer and IL-6 when compared to the normocalcemic group. In addition, in that same study, the hypocalcemia group was more likely to have a poor outcome in comparison to the normocalcemic group (47.8% to 25% respectively) (77). In another study carried out in Italy, the incidence of hypocalcemia in patients with COVID-19 was 78.6%, and this electrolyte imbalance also had a strong association with ICU admissions and death when compared to patients with normal calcium levels (78).

Parathyroid hormone (PTH) and vitamin D play a key role in calcium metabolismPatients with chronic hypovitaminosis D and who are affected by Covid-19 are more predisposed to hypocalcemia, as this vitamin alters calcium metabolism by reducing the intestinal absorption of calcium and phosphorus. These patients may have a compensatory tendency to secondary hyperparathyroidism, but this is not always sufficient to prevent hypocalcemia (79).

COVID-19 hypocalcemia has been associated with higher mortality rates when compared to other patients with respiratory conditions that have similar clinical manifestations. Hypocalcemia is also more incident and quantitatively significant in

COVID-19 than in other infections. The main factors responsible for hypocalcemia in hospitalized patients include low dietary intake, hypoparathyroidism, hypoproteinemia, vitamin D deficiency, and drug interaction. However, when it comes to COVID-19, vitamin D deficiency and parathyroid imbalance are identified as the main causes of said electrolyte disorder (76). Parathyroid gland function can be impaired during critical systemic illness and inflammatory response with increased circulating cytokines (79).

CONCLUSION

Besides the respiratory complications caused by the SARS-CoV-2 virus, infected patients are also subject to manifestations regarding other systems, such as the renal system. AKI is a multifactorial and fairly common complication in moderate-to-severe COVID-19. Patients that develop AKI due to COVID-19 are usually older males with other comorbidities and are usually admitted to intensive care units. Clinical management involves measurement of kidney function, cardiovascular status assessment, volume expansion and nephrotoxin exposure limitation, as well as standard AKI care measures. AKI also acts as a risk factor for death in SARS-CoV-2 infected patients, specially concerning those on RRT.

Hyponatremia, hypokalemia, and hypocalcemia are the most relevant electrolyte disorders in hospitalized patients with COVID-19. The cause of these laboratory alterations is multifactorial and may be secondary to renal and gastrointestinal lesions caused by inflammatory response, or even by pathophysiological alterations caused by the entry mechanism of the virus. In patients with COVID-19, electrolyte disorders are associated with worse outcomes, with increased hospitalization length and mortality.

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