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Kidney involvement in COVID-19

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Abstract

Since March 11, 2019, SARS-CoV-2 started to spread worldwide and made significant death and global problems. Although it is an acute respiratory infection, it can lead to acute kidney injury (AKI), especially in critically ill patients, and worsen their prognosis. This paper aimed to review prevalence, mortality, mechanism, electrolyte and urinary changes and, laboratory test and imaging findings in AKI. Additionally, investigate the relationship between CKD and COVID-19. Keywords like COVID-19, SARS-CoV-2, acute kidney injury and chronic kidney injury were used to find related articles from PubMed, Google Scholar, and Scopus. Due to studies, the mortality rate of COVID-19 patients with AKI was three times more than other COVID-19 patients. Mechanism of damage includes direct damage, cytokine storm, rhabdomyolysis, volume reduction, and organ crosstalk. Hyponatremia, hypokalemia, hypocalcemia, and hypochloremia were the most prevalent electrolyte changes. Due to activation of the renin-angiotensin system (RAS) system after the entrance of SARS-CoV-2 via angiotensin-converting enzyme (ACE2) inhibitor, blood urea nitrogen (BUN) can increase. In addition, the BUN level and BUN/creatinine ratio were higher in severe cases and can predict survival rates. Researches on AKI due to its high prevalence and mortality was required. Accordingly, it seems that most of these factors reviewed were related to AKI incidence and COVID-19 patients' mortality.

Keywords: Angiotensin-converting enzyme, Coronavirus, Kidney injury, SARS-CoV-2

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Introduction

Coronavirus disease 2019 (COVID-19) is an acute respiratory infection that emerged from SARS-CoV-2 in Wuhan, China, on 11th March 2019 and quickly became a global pandemic and infected nearly 140 million people all around the world (1). Although most of the patients have mild symptoms, it can lead to severe symptoms such as severe acute respiratory syndrome, septic shock, and multiple organ failure in 5% of the cases. One of the most prevalent complications of this virus relates to kidney diseases ranging from mild proteinuria and electrolyte disturbances to acute kidney failure and the need for renal replacement therapy (RRT) (2). Furthermore, the incidence of acute kidney damage seems to be more common in populations with a higher prevalence of chronic kidney disease (CKD) and American populations (3). This review article aimed to discuss the signs of kidney disease in patients with COVID-19 and the pathophysiology of kidney damage after COVID-19 infection.

Acute kidney injury

Most studies indicate that there is a strong association between acute kidney injury (AKI) incidence and COVID-19 disease. However, there is a controversy over the percentage of AKI incidence and COVID-19, ranging from 0.5% to 36% (4-6). The studies of Zahid et al on 469 patients with COVID-19 who were hospitalized in Brooklyn university hospital showed the high incidence of AKI in the patients and their high mortality rate (7). Similarly, Kolhe et al revealed the probability of AKI incidence in patients after being infected by COVID-19. They further postulated that the mortality rate was three times higher in patients suffering from both AKI and COVID-19. In addition, the mortality rate in patients with AKI caused by COVID-19 infection was four times higher than that in patients with AKI caused by other factors (8).

On the other hand, a study by Wang et al on 116 patients in Wuhan, China, showed lower AKI incidence after COVID-19 infection and no relationship between the exacerbation of kidney symptoms and COVID-19 in CKD patients (9). Although the results indicate the higher mortality rate of AKI patients after COVID-19 infection, this can be associated with the higher AKI incidence probability in critically ill patients (10). Acute respiratory distress syndrome (ARDS) patients who are infected with COVID-19 suffer from AKI in half of the cases and can increase the rate of AKI mortality (11). Factors that can predict the high incidence of AKI in COVID-19 patients include acute ischemic tubular necrosis, cytokine storm, direct virus attack on proximal tubule cells and podocyte, hemodynamic instability due to mechanical ventilation, concomitant use of antibiotics and nephrotoxic

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Implication for health policy/practice/research/ medical education

Kidney involvement is one of the complications of SARS-CoV-2 infection. Numerus studies indicated that acute tubular injury is the most common kidney biopsy findings in acute kidney injury patients with COVID-19 infection

antiviruses, and the use of diuretic and higher levels of serum creatinine (10,12).

The mechanisms of kidney damage by SARS-CoV-2

The mechanisms of kidney damage in patients with COVID-19 is not exactly clear, but several probable mechanisms are proposed.

Direct damage

In a recent study, the RNA of coronavirus has been detected not only in patients' blood, but also in their kidney cells and their urine (13). Coronavirus binds to the angiotensin-converting enzyme (ACE2) receptor and then enters the cell through endocytosis. ACE2 receptors are highly expressed in proximal and distal tubule cells (14). These findings postulate that kidney tissue and urinary tracts can be one of the direct targets of SARS-CoV-2. In a study, antibodies were used against virus nucleoproteins (NP), and the results showed the presence of NP virus antigen in kidney tubule, which confirms the idea mentioned above (15).

Cytokine storm

SARS-CoV-2 uses ACE 2 receptors as well as toll-like receptors (TLR) to enter the target cell. TLRs have a vital role in the primary immunity process and are involved in regulating the expression of inflammatory cytokines. TLRs also activate pro-inflammatory cytokines, interferon-alpha, and interleukins (ILs) 6 and 12. It has been reported that there is a relationship between the increase of these receptors and kidney diseases (16,17). On the other hand, the level of some inflammatory factors such as ILs 2, 6, 7, and 10, as well as tumour necrosis factor **α** (TNFα), has been increased in patients with severe forms of COVID-19 (18). These findings indicate that the effect of the virus on the immune system and inflammatory factors can be among the mechanisms of kidney damage. Influencing the endothelial system, cytokine storm reduces blood volume and increases inflammation in kidney tissue leading to kidney damage (19).

Rhabdomyolysis

Rhabdomyolysis is caused by direct damages of the virus or hypoxia due to hyperventilation in these patients. A large amount of myoglobin is released following rhabdomyolysis. Myoglobin has toxic effects on the kidney. Furthermore, it may cause kidney injury through increasing cast formation and decreasing blood supply (20). In kidney autopsy of COVID-19 patients, pigment casts with high creatinine phosphokinase levels have been observed representing rhabdomyolysis (15).

Volume reduction

Many patients experience dehydration at the time of admission to the hospital. This volume reduction can be due to fever or water loss through the gastrointestinal tract (21,22). As a result of the volume reduction, patients may experience pre-renal damage.

Organ crosstalk

There is a relationship between kidney and lung in ARDS patients. The incidence of AKI is increased in ARDS patients and is accompanied by a high mortality rate. ARDS can cause kidney damage through different mechanisms. Disturbance of gas exchange can reduce blood flow in the kidney and increase oxygen consumption in kidney tubules. Following the increase of pulmonary artery pressure, right ventricular pressure increases which leads to the enhancement of venous congestion and intra-abdominal pressure. Furthermore, mechanical ventilation can damage lung and other body organs such as the kidney through increasing cytokines (23-25).

Pathological findings

Kidney biopsy is not routinely conducted on AKI patients with COVID-19 infection, and the majority of the biopsies are conducted because of indication. Thus, the correct percentage of pathological changes is not available in these patients.

Numerous studies indicated that acute tubular injury (ATI) is the most common kidney biopsy findings in AKI patients with COVID-19 infection (26-28). ATI is scarcely the only pathological finding; that is, it goes along with other glomerulus changes. In a multicenter study, AKI was reported in 13 cases out of 14 patients (26). Similarly, in another study, ATI was reported in 12 cases out of 17 patients with COVID-19 infection as pathological changes (27). Sharma et al reported that there was ATI in all 10 patients who suffered from COVID-19 (28). In addition, in a case series study, tubules damage was reported in nine COVID-19 patients through kidney biopsy (29). The evidence indicating ATI in COVID-19 patients include extensive proximal tubule damage, reduced brush border, vascular degeneration, Frank necrosis, and the existence of a cast in tubules lumen (15).

One of the common findings of biopsy in COVID-19 patients, particularly the patients with African race, is collapsing focal segmental glomerulosclerosis (collapsing FSGS). This finding is also true in other cases such as HIV, Epstein bar virus, parvovirus B19, and cytomegalovirus. In a study on six black patients with COVID-19, collapsing glomerulopathy was reported in all cases. By genotypic studies, it was found that all genotype patients had high risk of APOL 1 (30). Furthermore, Magoon et al reported that

both cases of collapsing FSGS with COVID-19 infection had African American race. Moreover, the genotype of both cases for APOL 1 was homozygous (31). Therefore, patients who have African race or have a high risk of the APOL 1 gene are highly susceptible to collapsing FSGS.

Vasculitis is among the complications of SARS-CoV-2 infection. In kidney biopsy of COVID-19 patients, some other types of vessel vasculitis were reported such as immunoglobulin A (IgA) vasculitis and neutrophil anti-cytoplasmic antibody (ANCA)-associated vasculitis with glomerulonephritis. Some reports indicate the deposition of immunoglobulin A (IgA) in glomerulus, which represents IgA vasculitis (32, 33). Uppal et al found two patients with ANCA-associated vasculitis suffering from severe AKI and COVID-19. Both cases were male who had no autoimmune disease history (33). After further investigation and biopsy, ANCA-associated vasculitis with glomerulonephritis was recognized (34). Membranous nephropathy (35), lupus nephritis (27), minimal change disease (26), and interstitial nephritis (26) are other low-prevalent diseases found in kidney biopsy of COVID-19 patients.

Electrolyte changes

Electrolyte changes in COVID-19 patients are more common in forms of hyponatremia, hypokalemia, hypocalcemia, and hypochloremia. These changes can cause dangerous complications for the patients. Since most of the studies indicate a significant association between electrolyte changes and duration of hospitalization, transfer to ICU rate, disease severity, and mortality rate (36, 37), measuring and prompt treatment can improve the prognosis and treatment management in COVID-19 patients.

Previous studies have shown that COVID-19 uses ACE2 to enter the target cells (14). ACE2 is an essential enzyme in the renin-angiotensin system (RAS) which is expressed on the cell surface of different body organs such as lung, liver, and kidney. As the virus enters the cell, the inhibitory effect of ACE2 on RAS reduces, and the system is activated. Following the activation of RAS system, reabsorption of water and sodium increase which enhances potassium excretion (38). On the other hand, diarrhea and vomiting are common in COVID-19 patients causing potassium excretion (39). Hence, potassium changes (hypokalemia) are expected in these patients. In most studies, hypokalemia was reported in COVID-19 patients. Hypokalemia was reported in 12.5% to 37T of these patients which is higher than other people. (3,40). Consequently, hypokalemia should be evaluated and treated in these patients as much as possible; otherwise, it may result in cardiopulmonary complications.

Hyponatremia is the most common electrolyte change in COVID-19 patients reported in 37 percent of the cases (41). In some diseases like pneumonia, inflammatory cytokines such as IL-6 are significantly released by macrophages and other immune cells. IL-6 can cause syndrome of inappropriate antidiuretic hormone secretion (SIADH) through stimulating vasopressin production which consequently leads to euvolemic hyponatremia (42). However, hyponatremia is not caused only by SIADH, that is, other mechanisms are engaged in hyponatremia such as sodium loss through gastrointestinal system which, unlike SIADH, can cause hypovolemic hyponatremia (43). Regarding the differential procedures of treating euvolemic and hypovolemic hyponatremia, it is essential to scrutinize other reasons of hyponatremia other than SIADH. In addition to hyponatremia, hypernatremia is also reported in COVID-19 patients less frequently. Hypernatremia in these patients may be due to iatrogenic effects after saline injection or dehydration (44).

Hypocalcemia is another common electrolyte disorders after hyponatremia in COVID-19 patients. The cause of hypocalcemia in these patients seems to be due to the enhancement of free and unsaturated fatty acids. Free fatty acids can bind to calcium and cause hypocalcemia (45). In addition, hypocalcemia in critically ill patients can be caused by other diseases such as kidney disorders, liver diseases, alkalosis, and pancreatitis (46). On the other hand, the increase of cytokines, particularly IL-6 and IL-1B, influences calcium sensory receptors and consequently increases their sensitivity to calcium in blood circulation (47). Therefore, hypoparathyroidism can be one of the mechanisms causing hypocalcemia in COVID-19 patients. Since the lack of vitamin D is more common in these patients (48), hypovitaminosis D may be another cause of hypocalcemia in COVID-19 patients.

Laboratory biomarkers

Creatinine and blood urea nitrogen (BUN) are produced as a result of nitrogen metabolism and are excreted by kidneys. The changes of these two materials can help the evaluation of kidney function and disease development (49). Based on the aforementioned evidence, SARS-CoV-2 enters the target cells through ACE2 receptors and then activates RAS (5). After the activation of the RAS system and the increase of water reabsorption, BUN is absorbed passively. Furthermore, vascular contraction due to the activation of the RAS system reduces BUN secretion into the nephrons (50).

In a cohort study on 701 COVID-19 patients in Wuhan, China, creatinine level was increased in 14% and BUN was increased in 13% of the cases. High initial creatinine serum level and BUN were reported as the independent risk factors for in-hospital death. In addition, 5.1 percent of the patients suffered from AKI in hospitalization stage, that is, AKI incidence was higher in patients with high initial creatinine serum level (11.9%) than those with normal creatinine serum level (4%). Furthermore, patients with higher initial creatinine serum level became AKI faster than others (51).

BUN level and BUN/creatine ratio in patients with

severe forms of COVID-19 were higher than those with mild forms of the disease (52). In addition, there is a relationship between the increase of BUN/creatine ratio and mortality rate in COVID-19 patients. Thereby, initial BUN/creatine ratio can be used to predict the patients' survival rate.

Cystatin C is a member of cysteine protease inhibitor family produced by many organs and cells in the body (53). Cystatin C clearance is completely conducted by glomerular filtration and is not secreted by kidney tubules. In addition, it is less influenced by factors such as age, gender, and diet than creatinine and BUN. Thus, it can be estimated more accurately in glomerular filtration than BUN and creatinine (54). In a study by Chen et al on 1764 COVID-19 patients without CKD, the increased cystatin C (% 11.5) was reported (55). The increased cystatin C level was an independent risk factor of disease severity; however, it did not have any influence on mortality rate. Therefore, Cystatin C can be a helpful factor in measuring disease severity in COVID-19 patients.

Urinary changes

Chemical urinary tests are economical quick tests, that is, their parameters can be used to detect kidney disease and to investigate treatment response (56).

Proteinuria and hematuria are detected in COVID-19 patients more than the others. The incidence rate of proteinuria in COVID-19 patients, regardless of AKI, is between 28 to 84 percent (57-59). This significant difference in proteinuria range may be due to the severity of the disease and the existence of other related diseases. Furthermore, the incidence rate of hematuria in the studies was reported to be different, that is, it ranged from 17 to 26 percent (51,59,60).

In a retrospective study on 153 hospitalized COVID-19 patients, 14% of the patients had proteinuria less than 150 mg, 42 percent had it between 150 and 500 mg, and 44 percent had more than 500 mg proteinuria. Needless to say, 2 patients had more than 3500 mg proteinuria (61). The study indicated that proteinuria increases along with the increase of age and disease severity. In order to investigate the source of proteinuria, the total urinary protein and macroglobulin-a1 amount are measured which revealed that macroglobulin-a1 urinary level was more than 15 mg/g in 90 percent of the patients. Since the level of macroglobulin-a1 level indicates the function of kidney tubules (62), it can be concluded that proteinuria in COVID-19 patients seems to be caused by damage to kidney tubules.

Some studies indicated that proteinuria in COVID-19 patients could be used as an indicator for prognosis and mortality. In a study by Sundaram et al on 110 COVID-19 patients, the relationship between AKI incidence and mortality rate was reported. Moreover, it was reported that the coincidence of proteinuria and hematuria increases the rate of AKI progression in the patients (59).

A cohort retrospective study on 300 patients reported the relationship between proteinuria and AKI incidence at the time of hospitalization. Furthermore, there was a relationship between the level of proteinuria and increased mortality rate. In addition, hematuria incidence at the time of admission increases the rate of hospitalization in ICU and mortality rate (60).

Heavy metals and trace elements are excreted into the urine by kidneys. Excessive exposure to many of these elements can trigger them to accumulate in the kidney and cause kidney disorders (63). In patients with severe forms of COVID-19, the urinary level of these elements, including chrome and copper, increases more than the normal amount. In addition, it has been reported that there is a relationship between the urinary level of these elements, disease severity, and COVID-19 patients' prognosis (64).

Therefore, it can be concluded that using a simple urinary analytical test can predict the probability of mortality rate and kidney prognosis in COVID-19 patients, and this can increase survival rate through the early treatment procedure.

Imaging findings

Renal imaging in COVID-19 patients is not something common, that is, it was used in some cases with abdominal pains, fever, and abdominal infection (65). Since kidney damages increase the risk of contrast-induced nephropathy, contrast scanning, such as CT scan, should be done with more caution. In addition, it is recommended that evaluating kidney function should be carried out before any contrast scanning process (66).

Acute infarction of solid organs such as spleen and liver is one of the complications of SARS-CoV-2 infection. Kidney infraction and perfusion defects are reported in the radiography of COVID-19 patients (67). Since arterial thrombotic events are more common in these patients, kidney infraction can occur because of hypercoagulopathy condition (68). Therefore, kidney infraction can be considered as a probable pathophysiology factor that causes AKI in COVID-19 patients.

Sonography findings indicate that blood flow in small and large blood vessels of the kidney decrease (69). This reduction in blood flow is not due to the impaired right or left ventricular function. Thus, AKI in COVID-19 patients seems to be happened because of vascular effects, that is, the cause of the pathology can be found in the blood flow of the kidney (69). Another change detected in ultrasound findings is the enlargement of the kidneys in children. In a study on children between 0 to 16 years old who suffered from COVID-19, 33% of the cases had abnormal sonography findings in forms of kidney enlargement, while in 95% of the cases, it was evident in kidneys in both sides. In addition, ultrasound did not indicate any signs of echogenicity or reduced corticomedullary differentiation (70).

Kidney parenchyma CT scan indicated that 106 (96.3%) out of 110 COVID-19 patients had abnormal results. These results confirmed the higher probability of kidney parenchyma edema and inflammation in COVID-19 patients (71).

Furthermore, kidney imaging at the time of hospital admission can give information about the function and the structure of the kidney. This information helps to diagnose the possibility of disease progression to AKI and its mechanism in COVID-19 patients.

CKD and dialysis

Patients undergoing hemodialysis for CKD appear to have milder symptoms due to a weaker immune system and decreased cytokine storms after COVID-19 infection; however, they have a higher risk for COVID-19 infection. Thus, dialysis centers must take preventive and protective measures (72). Studies indicate that different CKD mechanisms such as oxidative stresses, inflammation, and microcirculation changes cause critically ill patients to experience a high incidence of AKI, increasing the mortality rate (73). In a systematic review study on 42 articles, including 8932 patients, Wang et al reported that the patients who already had CKD might experience severe symptoms of COVID-19 and mortality with high probability (74). However, the rate of symptoms and mortality is lower than that in AKI patients. Furthermore, the four major complications of COVID-19, including ARDS, heart damage, shock, and liver damage, do not have any significant relationship with kidney disease, that is, kidney disorders can be considered as independent risk factors for these patients.

Sachdeva et al conducted a study on 719 COVID-19 patients with end-stage renal disease. They reported that only 11 patients were under peritoneal dialysis (75). The number of patients under peritoneal dialysis was lower than hemodialysis ones due to homecare dialysis and social distance. Three patients out of these 11 patients needed mechanical ventilation, and two of them died. Eight patients out of the survived nine patients were released from the hospital without worrying about electrolyte disturbances and body fluids. This shows that although these patients are more susceptible to the infection due to weak immune system and concomitant conditions that predispose patients to other diseases such as diabetes, blood pressure, and upper ages, they had better performance in dealing with COVID-19. However, making a definite conclusion is not possible on the mortality rate of COVID-19 regarding the study's small sample size.

Renal replacement therapy

Previous studies indicate inadequate long-term survival of the patients after RRT following AKI, which is variable according to disease severity. Furthermore, patients with acute kidney damage on CKD have a worse prognosis and lower renal recovery rate (76). It seems that this is also true for AKI patients following COVID-19 infection.

Most patients with acute kidney damage following COVID-19 are classified into stage 1 of acute kidney damage (5.37%-5.46%); however, the mortality rate in AKI stage 3 is higher, which is considered an indicator of doing RRT on AKI patients.

Studies show that the mortality rate of AKI-RRT patients who are infected with COVID-19 is more than AKI patients without RRT. Other factors influencing the need for RRT include high serum creatinine levels and high C-reactive protein at the time of ICU admission (10). Research and auditing center in England scrutinized 10168 critically ill COVID-19 patients and reported that 26.6% patients needed RRT following AKI.

Gupta et al studied 3000 critically ill adult COVID-19 patients hospitalized in American hospitals. They reported that 63% of AKI-RRT patients died during the hospitalization period. Among survived patients, one out of every three patients relied on RRT at the time of release from the hospital, and one out of every six patients needed RRT 60 days after admission to ICU. Moreover, the findings showed that factors such as aging, oliguria, admission to hospitals with fewer ICU wards, and population with more frequent COVID-19 patients are predictors of AKI-RRT patients (12). In addition, it was revealed that CKD, higher body mass and severe hypoxia during ICU are independent AKI-RRT incidence factors in COVID-19 patients. Generally, RRT indications in patients with acute kidney damage such as acidosis and increased body fluid that do not respond to drug treatment are electrolyte disturbances, particularly hyperkalemia and uremic cases (i.e., encephalopathy and pericarditis). However, because of the higher mortality rate in AKI-RRT patients, further studies seem to be essential for prognosis improvement in these patients. In this regard, Wierstra et al investigated that doing early hemodialysis does not significantly reduce mortality rate or ICU hospitalization in AKI patients (77).

Conclusion

Kidney involvement is one of the complications of SARS-CoV-2 infection. The exact mechanism of kidney damage in these patients is not yet known; however, it seems that several mechanisms may be involved. Although the results on AKI incidence in COVID-19 patients are controversial, it is important because it is associated with higher mortality rate. In addition, electrolyte changes, proteinuria and hematuria, increased BUN and creatinine, and changes in pathological features are reported in some COVID-19 patients. Most of these factors are related to AKI incidence rate and patients' prognosis. Thus, exact evaluation of laboratory parameters and clinical representations at the time of admission and hospitalization can be beneficial in determining disease consequences and better management of these patients.

Authors' contribution

Primary draft by MRR and GGD. Further edit by EM and HN. All authors read and signed the final paper.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Conflicts of interest

The authors declare that they have no competing interests.

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