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# An overview on acute kidney injury following COVID-19

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## Abstract

COVID-19 is a newly emerging infectious disease which first described in December 2019 Wuhan, China. The disease rapidly spread through the world and after a short time of emerging, the World Health Organization (WHO) declared COVID-19 as a pandemic. Since, respiratory system is the main organ affected by COVID-19, the kidney could be involved as well. Given the importance of the kidney involvement in COVID-19, in this study we tried to evaluate and describe the effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on kidney.

**Keywords:** COVID-19, Kidney, Acute kidney injury, SARS-CoV-2

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## Introduction

COVID-19 is a newly emerging infectious disease which first described in December 2019 Wuhan, China. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as a novel member of Coronaviridae family (1). The disease rapidly spread through the world and after a short time of emerging, the World Health Organization (WHO) declared COVID-19 as a pandemic. Recently, WHO has reported almost 445 million COVID-19 cases and more than 5.9 million deaths worldwide. The mean incubation period is estimated to be ranged from 5.6 to 6.7 days. COVID-19 could be presented with a broad spectrum of clinical manifestation rang from asymptomatic infection or mild illness to acute respiratory distress syndrome (ARDS) and multiorgan failure. Among those with COVID-19 infection, elderly patients are at a higher risk of progress to sever disease and death because of a higher prevalence of comorbidities including diabetes mellitus (DM), hypertension, and cardiovascular disease (2).

Respiratory system is the main organ affected by COVID-19, however, other organs including heart, gastrointestinal tract, liver, nervous system, and kidney could be involved as well. Following the lungs, the kidney is the most involved organ with up to 75% incidence rate. Researchers believe that SARS-CoV-2 can affect the kidney directly and indirectly. When the lung is infected, the virus can result in a viremia by entering to the blood circulation and reach the kidneys. In the severe acute

respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) which was happened by the two other agents of the corona family in the past, the kidney involvement was reported in 5%-15% of cases with a high mortality rate about 60%-90% as well. Studies revealed that the kidney involvement in COVID-19 accompanied with higher morbidity and mortality (3). Given the importance of the kidney involvement in COVID-19, in this study we tried to evaluate and describe the effect of SARS-CoV-2 on kidneys.

## Method of search

In this review, we analyzed several articles from the international scientific library databases to evaluate the therapeutic efficacy of curcumin in kidney diseases. We searched PubMed/Medline, Scopus and Google Scholar, using the following key words; COVID-19, kidney, acute kidney injury and SARS-CoV-2.

## Acute kidney injury

Acute kidney injury (AKI) is a medical condition in which the kidney function rapidly decreased and results in an increase in creatinine and nitrogenous wastes concentration and disturbance in water and electrolyte homeostasis. Due to studies, it is one of the worst complications of COVID-19 commonly occurs in patients with severe disease and associated with an increase morbidity and mortality. There are some risk factors which seems to be linked with AKI incidence including;

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### ■ Implication for health policy/practice/research/medical education

COVID-19 is a viral disease that first emerged in December 2019, Wuhan, China. Given the importance of the kidney involvement in COVID-19, we sought to evaluate and describe the effect of SARS-CoV-2 on kidneys.

aging, male gender, DM, hypertension, obesity, chronic kidney disease (CKD), needs for mechanical ventilation, intensive care unit (ICU) admission, higher APACHE (Acute Physiology and Chronic Health Evaluation) score, use of vasoactive drug, higher level of serum creatinine phosphokinase (CPK) and D-dimer, and longer length of hospital stay (4). The incidence of AKI in COVID-19 patients is varied in different studies ranging from 0.5% to 75%. In a study conducted by Guan et al, they demonstrated that only 0.5% of patients had AKI (5). In a case series of 138 hospitalized COVID-19 patients in Wuhan, China, AKI was observed in 3.6% of all patients and 8.3% of ICU admitted patients (6). In contrast, Zamoner et al revealed that AKI incidence is almost 50% of in-patients with COVID-19 (7). However, this amount can reach 75% in patents need mechanical ventilation. This wide variation in AKI incidence may be because of the different national and regional policies such as criteria for hospital admission, different setting of studies, patients' disease severity and risk factors, and also ethnic factors which make the correct comparison and conclusion to be difficult. There is a different idea about the onset of AKI symptoms ranging from time of admission to almost two weeks after the hospitalization. Based on studies, AKI and kidney disease are an independent risk factors for in-hospital mortality. In a study Ng et al found that the mortality rate are 46.4% and 79.3% in COVID-19 patients not requiring kidney replacement therapy (KRT) and those requiring KRT, respectively. Indeed, the 28-day in-hospital mortality is 51% in those with end-stage renal disease (ESRD) who receive dialysis, 49% in those with CKD, and 35% in those without pre-existing kidney disease. In line with these findings, another study demonstrates that the risk of mortality is at least 4 times higher in patients with stage 3 AKI (8).

### Pathogenesis of kidney involvement in COVID-19

SARS-CoV-2 utilize angiotensin-converting enzyme 2 (ACE2) as a receptor to enter the cell. ACE2 is a part of the renin-angiotensin system which has a crucial role in kidney disease. The type 2 alveolar epithelial cells in the lungs, heart, kidney, gastrointestinal system, duodenum, small intestine, nervous system, artery smooth muscle cells, spermatogonia, Leydig cells, Sertoli cells, rectal epithelial cells, and vascular endothelia expressed ACE2. In the kidney, ACE2 is mostly expressed by the brush border of proximal tubular cells and podocytes. The expression level of this enzyme in the kidney is 100 times higher than in the lung (9). This is in line with the studies

that shows the virus particle in the kidney cells. Moreover, transmembrane serine protease 2 (TMPRSS2) is required for coronavirus to enter host cell. Thus, the co-expression of ACE2 and TMPRSS2 is necessary for pathogenicity. In kidneys, we have co-expression mostly in podocytes, proximal convoluted and straight tubules, collecting duct and distal tubule cells. Furthermore, it has been shown that SARS-CoV-2 also invade target cells by CD147 which is frequently expressed in proximal tubular epithelium. CD 147 is a ubiquitously transmembrane glycoprotein that interacts with various protein like cyclophilins, caveolin-1, and integrins. It is believed that CD147 has an important role in some kidney disease via immunoinflammatory responses and dysregulated cell cycle. On the other hand, cyclophilins have a crucial role in corona virus replication cycle. In this sense, cyclophilins' inhibitor like cyclosporine, can efficiently inhibit the intracellular virus replication (10).

### Pathophysiology of AKI in COVID-19

The exact mechanism of AKI in COVID-19 is not yet known, some hypotheses have been stated in the literature. In the following, we will mention some of the theories proposed in the studies.

#### Renin-angiotensin-aldosterone system

As stated above, ACE2 is a part of the renin-angiotensin system which is mostly expressed by the brush border of proximal tubular cells and podocytes. It has crucial physiologic roles in the kidney including: conversion of angiotensin II to angiotensin 1-7, degradation of angiotensin II, nephrin upregulation and preventing the loss of proteins in podocytes, sodium balance and natriuresis in the brush border of proximal tubular cells. When SARS-CoV-2 involve the cells, ACE2-virus complex internalized and may promote an imbalance in the renin-angiotensin-aldosterone system function with increased angiotensin II signaling. This enhancement in angiotensin II signaling can lead to inflammation, fibrosis and vasoconstriction in the kidney (11).

#### Immune system

One of the mechanisms that seem to participate in development of AKI in COVID-19 is cytokine storm. When the SARS-CoV-2 enter the body, innate immune system like pattern recognition receptors detects it. After that, immune cascades start and large amounts of cytokines and chemokines released through activating nuclear factor kappa B (NF- $\kappa$ B) and mitogen-activated protein kinase (MAPK) pathways (12). According to literature, the level of inflammatory mediators such as interleukin-2 (IL-2), IL-6, IL-7, IL-8, IL-10, interferon- $\gamma$  (IFN- $\gamma$ ), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), granulocyte colony-stimulating factor (GCSF), monocyte chemoattractant protein 1, and macrophage inflammatory protein 1 $\alpha$  are significantly higher in patients with severe COVID-19

than in patients with mild disease. These excessive release of pro-inflammatory cytokines is called cytokine storm which can result in harmful outcomes including renal failure, progressive respiratory failure and multiple organ dysfunction (41). Furthermore, kidney injury has a key role in the cytokine storm itself via hyperactivating the immune system which could intensify the processes of fibrosis, apoptosis and changes in the microvasculature. In the other word, the cytokine storm could results in AKI; while, AKI could intensify the cytokine storm. Finally, AKI and cytokine storm are accompanied with disease severity and poor prognosis (13).

### **Coagulopathy**

The other possible reason for AKI development in COVID-19 is coagulopathy. It is shown that SARS-CoV-2 could increase the risk of coagulopathy by raising the blood coagulation factors and blood clotting capability in patients. fibrinogen, thrombin, and tissue factor are the main mediators of blood clotting which act as proinflammatory factors. Fibrinogen expression is increased in COVID-19 and it causes platelet aggregation and immune system activation (14). Furthermore, lung injury by SARS-CoV-2 could result in hypoxia which can accelerates thrombosis via augmenting blood viscosity. Likewise, vascular endothelial injury and complement activation promote hypercoagulopathy by increasing thrombin manufacture and preventing fibrinolysin. All in all, vascular consequence of COVID-19 induced hypercoagulopathy including arterial fibrin thrombi and disseminated intravascular coagulation which can lead to organ damage. In kidneys, this condition causes AKI by glomerular ischemia, acute tubular and cortical necrosis with subsequent fibrinoid necrosis (15).

### **Endothelial dysfunction**

Endothelial dysfunction is the other cause of AKI in sever COVID-19. Based on studies, SARS-CoV-2 can involve the endothelial cells directly by itself and indirectly by activation of immune system and cytokine storm (16). On the other hand, it could be also the consequence of some disease that increase the risk of sever COVID-19 entailed diabetes, hypertension, thrombosis, and kidney disease (17). It means that endothelial dysfunction and injury could be both a cause and/or a result of sever COVID-19. Increasing evidence revealed that abnormality in endothelial cells may be participate in coagulopathy and end organ damages such as AKI in patients with severe disease. Therefore, we can improve the patients' outcomes by preventing the endothelial dysfunction process (18).

### **Fluid challenge**

Small intestine is one of the organs that its cells, enterocytes, highly expressed ACE2. The involvement of enterocytes by SARS-CoV-2 can interfere with ACE2 function and cause diarrhea. Almost 12% of patients with COVID-19

have diarrhea. According to a systematic review and meta-analysis, patients who present diarrhea as one of the symptoms were more likely to have severe form of disease (19). Water loss and fluid challenge are the consequence of diarrhea that may lead to AKI. In addition, myocarditis is one of the other worst complications of SARS-CoV-2 infection. It can mostly occur up to 10-15 days after beginning symptoms (20). Myocarditis and heart failure could result in hemodynamic disorder, which in turn is one of the reasons for AKI as well.

### **Long kidney cross-reaction**

ARDS is considered as a risk factor for AKI in ill patient. In patients with ARDS the disruption in gas exchange result in tissue hypoxia such as renal medullary hypoxia which facilitate the tubular cell injury (21). In a study, **Pei** et al revealed that the severity of COVID-19 pneumonia is associated with kidney injury (22). On the other hand, renal tubular epithelium injury increases the production of IL-6 which promotes the alveolar capillary permeability and pulmonary hemorrhage and, finally, ARDS.

### **Pathologic finding of kidney involvement in COVID-19**

Pathologic findings of kidney injury in patients with COVID-19 are mainly the result of studies carried out on autopsy samples and fewer from kidney biopsy tissue. According to studies, COVID-19 can affect the kidney with a wide spectrum of manifestation entailed acute tubular injury (23), collapsing glomerulopathy (24) noncollapsing focal and segmental glomerulosclerosis (25), thrombotic microangiopathy (26), membranous nephropathy (27), minimal change disease, anti-glomerular basement membrane disease (28), crescentic glomerulonephritis, acute interstitial nephritis (29), oxalate nephropathy, myoglobin cast nephropathy (30), immune complex-mediated glomerulonephritis/lupus nephritis, membranoproliferative glomerulonephritis, infection-associated glomerulonephritis, IgA nephropathy, light chain cast nephropathy, arteritis, brush border loss, vacuolar degeneration, tubular epithelial detachment, and lumen dilation. Furthermore, COVID-19 developed some complication in kidney transplant recipients. Acute rejection via T cell or antibody mediated, collapsing glomerulopathy, atheroemboli, cortical necrosis, and drug induced nephrotoxicity such as calcineurin inhibitor are some reported pathological findings in kidney biopsy studies from kidney transplant recipients with COVID-19. Furthermore, in electron microscopic examination virus-liked particles were seen in vacuoles or cisterns of the endoplasmic reticulum of tubular epithelium and podocytes (31).

### **COVID-19 vaccines and kidney disease**

After introduction of COVID-19 vaccines, many of important nephrology societies including US National Kidney Foundation and the UK Renal Association

have issued a statement to prioritize patients with kidney disease for vaccination. Simultaneously, concerns have been increased that vaccines may induce autoimmunity, flares of prior silent kidney diseases or new diseases. Minimal change disease, antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis, immunoglobulin A nephropathy (IgAN), anti-glomerular basement membrane (anti-GBM) disease, IgG4-related disease, and membranous glomerulopathy are some of the reported vaccine associated kidney disease. Among the vaccines, the most kidney complications have been associated with the first or second dose of mRNA vaccines (Pfizer BioNTech or Moderna). Adenoviral vector vaccine (AstraZeneca) and inactivated virus vaccine (Sinovac) were less likely to be associated with these complications. These side effects are not limited to the COVID-19 vaccine and have been reported for other vaccines as well. According to literature, some cases of MCD flares have been reported after influenza, pneumococcal, hepatitis B, Tdap (tetanus, diphtheria, pertussis), and smallpox vaccines (32). To date, the exact pathogenesis of glomerular diseases after COVID-19 vaccine is not well understood. To develop an effective immune response to COVID-19 vaccine, both B cells and T cells are involved. But due to the rapid onset of glomerular disease after vaccine injection, it seems that T cells are more responsible. T cell activation lead to production of some cytokines like Interferon, tumor necrosis factor, and IL-2 which can result in podocytopathies. This process is similar to what could be happened after SARS-CoV-2 infection itself via activation of different alloimmune and autoimmune diseases affecting the kidneys. Now the question is should patients with glomerular disease be avoided from vaccination? Should they be advised to not use mRNA vaccines? However, we could not say the exact answer, nevertheless we can say that the risk of glomerular disease relapse and AKI after vaccination is likely lower than this risk from SARS-CoV-2 infection (33).

### COVID-19 and commonly administered drugs for the treatment and their renal complication

AKI might occur in patients with SARS-CoV-2 infection due to drug-induced nephrotoxicity (34). Nephrotoxicity from drugs remains a significant health burden. Global data suggests that drug-induced nephrotoxicity is responsible for 19 to 26 percent of all adult hospital stays (34). A cross-sectional national survey of the Chinese population screened 280255 hospitalization cases, from which 1960 were diagnosed with hospital-acquired AKI. Of these, 735 cases (37.5%) were identified as drug-induced AKI (35). Hence, we review drugs which have side effects on kidneys:

#### Azithromycin

Azithromycin is a broad-spectrum antibiotic and a weak base. Due to its anti-inflammatory effects, it has

been widely utilized in treating various infections, such as respiratory infections. Azithromycin interferes with bacterial protein synthesis by inhibiting mRNA translation (36). Some studies have established the efficiency of azithromycin, coupled with hydroxychloroquine, for COVID-19 treatment. Another study found that pre-treatment with azithromycin reduced NF- $\kappa$ B translocation and proinflammatory cytokines in COVID-19 patients. Though this antibiotic fails to directly affect SARS-CoV-2, some researchers believe it is useful in curing severe acute respiratory syndrome in these patients. Given the ubiquitous application of this drug in different healthcare conditions, the increased awareness of physicians regarding its rare but severe adverse effects, including AIN is indispensable (37).

In a case report, the biopsy-confirmed AIN occurred in a 16-year-old girl two weeks after completing a 6-day regimen of 10 mg/kg/d (total dosage of 3 g) azithromycin to treat bronchitis. At presentation, the patient had a serum creatinine concentration (SCr) of 2.6 mg/dL, and dialysis was not carried out, indicating a mild course of AIN. Renal function was completely recovered after treatment with corticosteroids (10 mg/kg/d of intravenous methylprednisolone for three days, followed by 0.5 mg/kg/d of oral prednisone for two weeks) (38).

Woodruff et al reported a 59-year-old man requiring hemodialysis after developing AIN induced by azithromycin. The patient received azithromycin for a 5-day period due to an upper respiratory tract infection. The dosage given was 500 mg on day 1, followed by 250 mg daily on days 2-5 (total dosage of 1.5 g). The patient's SCr level on admission was 7.4 mg/dL (baseline value = 1.3 mg/dL) which increased to 11.4 mg/dL and he required three hemodialysis sessions. The biopsy was taken from the kidney confirmed the presence of AIN. The patient was administered low-dose prednisone of 0.3 mg/kg (30 mg) daily tapered over three months, and his renal function was recovered close to baseline prior to discharge (39).

#### Other antibiotics

Several potential biomechanisms have been introduced for nephrotoxicity induced by antimicrobial agents commonly used to superimpose bacterial infection in COVID-19 patients. Direct cellular toxicity on proximal tubules in vancomycin and daptomycin, direct cellular toxicity on proximal and distal tubules in aminoglycosides, glomerular damages in beta-lactams, impaired creatinine secretion and epithelial sodium channels in trimethoprim/sulfamethoxazole, tubular damage and increased cell immunity in fluoroquinolones are among the proposed mechanisms underlying antibiotic-induced damages, including acute tubular necrosis and acute interstitial nephritis (40).

An observational study in Morocco aiming to determine the predictors of COVID-19 severity identified

azithromycin as the most common antibiotic prescribed in ICU and non-ICU patients. Conversely, the third-generation cephalosporins, quinolones, aminoglycosides, and carbapenem were significantly more prescribed in the ICU ( $P < 0.001$ ) (41).

The findings of an international survey suggested that broad-spectrum antibiotics, including ceftriaxone/cefotaxime plus macrolides and piperacillin/tazobactam, were the most commonly administered antibiotics for COVID-19 patients hospitalized in the ICU (42).

Musavi et al observed that AKI incidence in COVID-19 patients receiving antibiotics against coinfections (AACs) was more than two times higher than in those who did not receive these antibiotics. In addition, AKI was more prevalent in men and elderly patients in both groups. About 28 percent of all participants used at least one AAC, and linezolid was the most widely-used AAC. The AACs greatly affected in-ICU mortality, while AKI was associated with prolonged hospital stay (43).

### Favipiravir

Favipiravir is an antiviral nucleotide analog that is orally administered. Upon cell entry, favipiravir becomes phosphorylated. The phosphorylated favipiravir acts as a substrate for RNA polymerase and enters the newly-emerged virus RNA leading to chain termination and mutation in viral RNA. Thus, favipiravir inhibits viral transcription and replication. This medicine has a broad safety margin and thus can be given in large dosages. The plasma concentration of favipiravir has been shown to reach its peak within two hours after oral administration and then rapidly declines with a half-life of 2-5.5 hours. Favipiravir is metabolized by liver enzyme, aldehyde oxidase, and is excreted by the kidneys. Notably, this drug can enhance its concentration by self-inhibition of aldehyde oxidase. The adverse effects of favipiravir include gastrointestinal effects, increased levels of uric acid, aspartate aminotransferase (SGOT), alanine transaminase (SGPT), triglycerides, and reduced number of neutrophils, and it is contraindicated in people with liver or renal failure. This compound inhibits RNA polymerase, targets both virus shedding and viral load, and contributes to reduced mortality and intubation in patients with COVID-19. Earlier this year, Nasa et al published a case report describing two male patients (38 and 51 years old) with COVID-19 pneumonia and normal renal function at baseline who developed non-oliguric AKI nearly 48 hours after receiving the favipiravir. The dosage of the drug given was similar to the dosage mentioned above. The drug-induced AKI was resolved 24 to 48 hours after favipiravir was stopped, and this was nearly consistent with our findings, except that our patient was a known CKD case (44).

Favipiravir has been proven efficient in treating COVID-19-associated pneumonia in some ESRD patients receiving hemodialysis. The drug-related data and

monographs only recommend general caution regarding the potential worsening of renal parameters and renal function. However, there is a lack of data on adequate dose adjustment based on the current liver or renal function.

### Remdesivir

Remdesivir is a novel anti-viral agent approved by the US Food and Drug Administration (FDA) to treat patients hospitalized with COVID-19. This medicine can shorten the duration of hospital stays and improve mortality in COVID-19 patients. The formulation of remdesivir contains sulfobutyl-ether- $\beta$ -cyclodextrin (SBE-B-CD), which is cleared by the kidneys and produces a degree of nephrotoxicity. For this reason, the clinical studies on this drug exclude the recipients with renal failure and an estimated glomerular filtration rate (eGFR)  $< 30$  mL/min or eGFR  $< 50$  mL/min. The remdesivir-related nephrotoxicity is yet to be fully understood. Thus, renal function needs to be monitored in patients undergoing treatment with remdesivir. A previous study analyzed the adverse effects of remdesivir in COVID-19 patients with or without severe renal disorder (creatinine clearance  $< 30$  mL/min). The authors found that a higher proportion of patients in the severe renal impairment group experienced increased serum creatinine (45).

In their research, Grein et al studied the effects of remdesivir use in 61 patients with COVID-19. The common side effects reported in this study were diarrhea, skin rash, increased levels of liver enzymes, renal failure, and hypotension. Moreover, 12 patients experienced severe complications, including septic shock, multi-organ dysfunction syndrome, and AKI. In a case report, the patients had to discontinue remdesivir three days after using it due to an elevation in their blood creatinine. In this patient, after stopping taking remdesivir and undergoing hemodialysis, the creatinine level reduced on day 16, and the patient was discharged from ICU to the ward (46). Other analysis carried out using the WHO safety database found a significant relationship between nephrotoxicity and remdesivir.

### Hydroxychloroquine

Hydroxychloroquine is a derivative of chloroquine that exhibits anti-malaria and anti-inflammatory activities. It has been considered a component of standard care for COVID-19 patients in some countries, particularly during the first phase of the pandemic. Although the available well-performed meta-analysis have dismissed the potential advantages of treatment with hydroxychloroquine/chloroquine for the prognosis of patients with COVID-19, millions of patients had previously received such treatment. It is revealed that hydroxychloroquine can potentially induce or exacerbate AKI through increasing lysosomal pH and autophagy inhibition. Hydroxychloroquine is shown to inhibit autophagic flux by disturbing lysosome-autophagosome

fusion. Previous studies could not show any strong evidence between the impact of hydroxychloroquine/chloroquine on the increased risk of acute renal damage in COVID-19 cases. So far, no report on the adverse effects of chloroquine and hydroxychloroquine on kidneys is available. However, these drugs must be used cautiously in patients with underlying renal or cardiac illnesses (47).

### Lopinavir and ritonavir

Lopinavir and low-dose ritonavir (LPV/RTV) have been used in protease inhibitor combination therapy with fixed-dose for HIV/AIDS patients. Acute interstitial nephritis has been documented in these patients. The drug-mediated acute interstitial nephritis, after its wide use, is identified as one of the causes in most cases and often manifests as proximal tubular damage (48).

The recent outbreak of SARS-CoV-2 infection, which results in COVID-19, has sparked the interest in LPV/RTV again after preclinical studies (49). Though no superiority was seen for LPV/RTV treatment compared to the standard care. Other randomized controlled trials, including DisCoVeRy (NCT04315948), are being registered. Despite the lack of any systematic pharmacovigilance analysis, LPV/RTV, like other antiviral treatments, has previously been associated with AKI. In the study by Cao et al, the WHO database (VigiBase) was searched to extract all COVID-19 patients who received LPV/RTV combination and had AKI. The authors indicated that eight COVID-19 patients developed AKI type II or III after receiving LPV/RTV therapy on day 2 or 3 of hospitalization in the ICU (50).

### Conclusion

COVID-19 is a viral disease which can affect different human organs including the kidney. The risk of kidney involvement is greater in severe form of disease which worsens the prognosis. However, the exact mechanism of AKI is not yet known, several factors are suggested to be involved entailed immune response, coagulopathy, ischemia, and drugs. Although a lot of studies have been conducted about COVID-19, the lack of studies focused on kidney alterations and biomarkers is felt. This can help us to detect and start the early treatment to decrease the severity and mortality in COVID-19's AKI.

### Authors' contribution

Conceptualization: MRH.

Investigation: MRH and MM.

Writing—original draft preparation: MRH and MM.

Writing—reviewing and editing: MRH and MM.

Supervision: MM.

Project management: MRH.

### Conflicts of interest

MRH is researcher in Nickan Research Institute. However, the process of peer-review was not affected by his job.

### Ethical issues

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

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