



# Covid-19 and kidney; a mini-review on current concepts and new data

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## ABSTRACT

In late December 2019, some cases of acute respiratory illness occurred in Wuhan, Hubei province, China that caused by a virus named “severe acute respiratory syndrome 2” (SARS-Cov2). More susceptible patients to this disease are elderly male patients since these patients with comorbid diseases are disposed to severe infection and more death. The most important comorbid diseases with COVID-19 pneumonia are hypertension, diabetes mellitus, cerebrovascular disease, chronic obstructive pulmonary disease, coronary heart disease. The most common symptoms of SARS-Cov2 infection are dyspnea, cough, fatigue, diarrhea and vomiting. High number of kidney disease in hospitalized patients with COVID-19 has been reported. Furthermore, a large group of patients with COVID-19 pneumonia had signs of kidney disease, with a high level of serum creatinine and blood urea nitrogen that could be justified with different pathophysiologies happened in COVID-19 pneumonia. However, massive differences were found in the prevalence of acute kidney injury (AKI) in patients with acute respiratory distress syndrome (ARDS) secondary to COVID-19 pneumonia, since various studies have shown that AKI correlates with higher mortality rate, upper morbidity and more severe cases of illness. Therefore, we should be informed about the pathophysiology of AKI in COVID-19 pneumonia to find the modalities to decrease the incidence of AKI and subsequent decrease mortality and morbidity of this disease.

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

Renal failure on hospital admission of COVID-19 patients is a poor prognostic factor which increases the mortality rate.

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## Introduction

In late December 2019, a series of unknown origin cases of acute respiratory illness detected in Wuhan, Hubei province, China (1,2). High throughput sequencing showed that the disease was caused by a virus named “severe acute respiratory syndrome 2” (SARS-Cov2) (3). On 11<sup>th</sup> February 2020, WHO officially changed the name of the disease caused by SARS-Cov2 to coronavirus disease 2019 (COVID-19). The disease rapidly spread from Wuhan to other parts of the world. It is reported that COVID-19 has much more infectivity than its ancestors, SARS and Middle East respiratory syndrome (MERS), however it has less mortality rate (4).

Genomic analysis of coronavirus sequence revealed that the amount of similarity between SARS-CoV genome of bats and SARS-Cov2 was about 96.2%. It is suggested

that SARS-Cov2 might be originated from bats (5). Other studies showed that SARS-CoV isolated from pangolin's body while SARS-Cov2 from human have 99% similarity showing that pangolins might be a potential host for this virus (6). According to genomic sequencing studies, SARS-Cov2 has 79.5% similarity to the SARS-CoV virus, suggesting that they might have the same risk factors and mortality (7). The median age of the patients infected with SARS-CoV2 infection was 47 years old. Around 87% of patients with COVID-19 pneumonia were 30-79 years old while 3% were 80 years old or older, and 41.9% of them were female (7, 8). The overall fatality rate in 70-79-year-old patients was 2.3% while it was 14.8% in older than 80-year-old patients (8).

This finding implies that more susceptible patients to this disease are elderly male ones (2). In addition, patients

with comorbid diseases are disposed to severe infection and more death rate (9,10).

The most important comorbid diseases with COVID-19 pneumonia are hypertension, diabetes mellitus, cerebrovascular disease, chronic obstructive pulmonary disease and coronary heart disease (7,11).

Other comorbidities such as cancer, chronic kidney disease (CKD), chronic liver disease, and diseases of gastrointestinal tract and nervous system also have been reported in patients with COVID-19 (11,12).

There is already extensive evidence of extra-pulmonary involvement in Covid-19 pneumonia such as heart, kidney, and liver involvement (12).

The aim of this mini-review is discussing the pathophysiology of COVID-19 and kidney complications caused by it which may affect patient's prognosis.

### Transmission ways of SARS-CoV2

1. Close contact (The most usual way of infection).
2. Transmission via aerosols.
3. Digestive tract could be a possible way of SARS-CoV2 infection (13).
4. SARS-CoV2 has been found in gastrointestinal tissue from COVID-19 patients (14).
5. SARS-CoV2 has been identified in tears and conjunctival secretions of COVID-19 patients (15).

### Clinical manifestations

The most common symptoms of COVID-19 pneumonia are diffuse alveolar damage, acute respiratory failure and also, involvement of other organs in some cases (12).

The most common symptoms of SARS-CoV2 infection are dyspnea (87.9%), cough (67.7%), fatigue (30.1%), diarrhea (3.7%) and vomiting (5%) (2,7,16).

Moreover, in severe cases of COVID-19, the complications pneumonia such as acute respiratory distress syndrome (ARDS), acute lung injury and secondary infections are also common (11). Other complications such as neurological damage (17), ocular surface infection (18), cardiac arrhythmia, renal damage and abnormal liver function tests (12,18-20) are also usual in coronavirus infected patients.

Laboratory examinations in number of patients revealed 82.1% lymphopenia and 33.7% thrombocytopenia. Besides, the elevated levels of C-reactive protein, LDH, and creatine phosphokinase (CPK) were also found in their blood test. The majority of patients had normal leukocyte count, however, leukopenia was detected in 33.7% of them. Accordingly, a minority of patients had a high level of transaminase, or a raised serum creatinine levels (4,21).

In some studies, various types of renal diseases in hospitalized individuals with COVID-19 were observed. Additionally, forty-percent of patients had signs of renal disease, with a high level of blood urea nitrogen and serum creatinine (around 13% of patients) (21,22). However,

many differences were found in the prevalence of acute kidney injury (AKI) in patients with ARDS secondary to COVID-19 pneumonia (23). In some researches on small subsets of patients with COVID-19 pneumonia, they found hematuria and proteinuria were the most common features in 40% of admitted patients (18, 24).

Abdominopelvic CT scan revealed abnormal renal imaging (reduced density) in these patients, suggesting the existence of inflammation and edema in the patient's kidneys (21,25).

### Pathophysiology of renal involvement following COVID-19

1. After lung infection, COVID-19 RNA was detected in the serum of 15% of patients by RT-PCR (reverse transcription-polymerase chain reaction). This finding reveals that the virus may enter the blood and reside in renal tissue due to the high expression of ACE2 in renal cells and then damage to the resident renal cells (12).
2. Underlying inflammatory state in CKD patients might prone them to COVID-19 pneumonia due to pro-inflammatory state with function defect in adaptive and innate immune cell population (26) which increases the risk of pneumonia and also upper respiratory tract infection (27).
3. In COVID-19 pneumonia patients, superimposed infections during intensive care unit (ICU) stay may occur. The lipopolysaccharide expressed on the membrane of gram-negative bacteria metabolized by enzymes in the blood and released endotoxin which can cause septic shock. Secondary bacterial infection occurs in severe COVID-19 pneumonia and induces AKI then acts synergistically with other mechanisms of kidney damage through this mechanism (7). Moreover, low levels of O<sub>2</sub> saturation in secondary bacterial pneumonia cause renal hypoxia and accelerates the development AKI (28).
4. The recent finding has confirmed a close relationship between alveolar and tubular damage (lung-kidney axis) in ARDS. A study on patients with ARDS with no previous acute or chronic kidney disease has detected that the pneumonia is the cause of ARDS in 83% of patients and AKI in 68% of cases. AKI was more severe in older age, higher body mass index, diabetes mellitus, chronic heart failure and higher airway peak pressure (29). ARDS also causes renal medullary hypoxia which makes additional insult to tubular cells (30).
5. Cytokine storm associated with COVID-19 pneumonia has been accompanied by elevated serum levels of interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-2, IL-7, IL-8, IL-9, IL-5, interferon- $\gamma$ , tumor necrosis factor alpha (TNF- $\alpha$ ), G-CSF (granulocyte colony-stimulating factor) and GM-CSF (granulocyte-macrophage colony-stimulating factor) that resulted

in an inflammatory response and subsequently tissue damages such as pulmonary edema (12). Therefore, AKI at this condition could be a result of body inflammation, increased vascular permeability, volume depletion and cardiomyopathy which can lead to cardio-renal response (31). Additionally, these mediators might exert deleterious effect on renal tissue through induction of shock, rhabdomyolysis following tissue hypoxia, and an elevated level of CPK in patients admitted to ICU (1,21,32). This syndrome includes systemic endothelial injury which makes pleural effusion, edema, intra-abdominal hypertension, third space fluid loss, intravascular fluid depletion and hypotension (31).

6. Kidney microscopic specimens from patients with pneumonia of SARS-Cov2 who were accompanied by AKI, had a normal glomerular feature with lack of electron-dense deposits. This finding is against the diagnosis of glomerulonephritis mediated by immune complexes (33). Moreover, it has been reported that in the kidney, ACE-2 receptors are highly expressed in the brush border of the proximal tubular cells and less expressed in podocyte cells but not in the glomerular endothelial and mesangial cells (33). Therefore, it seems that, the virus has less capacity to infect glomeruli and has more capacity to infect tubules and podocytes.
7. Coronavirus binds to ACE-2 receptor via "S" protein on its surface as a cell entry receptor and then cleaved by cellular transmembrane serine proteases (TMPRSS) allowing the virus to release fusion peptide for membrane fusion (34), a condition which is similar to SARS-CoV which was reported in 2003. In this regard, the human tissue RNA sequencing data showed that, the affinity of "S" spike for binding to ACE2 receptor in SARS-CoV2 is above 10-fold higher than SARS-CoV (35,36). Obviously, SARS-CoV was not detectable in any of the analyzed patient's renal specimen which means that renal impairment is likely due to both multiple organ failure and cytokine release syndrome (33,37) rather than active viral infection in the kidney. However, the human kidney is a specific target for SARS-CoV2 infection (38). Recently, the viral nucleocapsid protein was detected in the kidney of infected patients. It was also showed that SARS-CoV2 antigen accumulated in the kidney tubules suggesting that SARS-CoV2 directly infects the human kidney and induces AKI and also contributes to spreading the virus in the body. The difference between the higher renal tropism of SARS-CoV2 versus SARS-CoV could be explained by the increased affinity of SARS-CoV2 to ACE-2 receptor that is allowing greater interfection of the kidney which may act as a viral reservoir (39).

A study on cells of 15 normal kidneys showed high colonization of ACE-2 and TMPRSS on podocytes and in

proximal straight tubule cells, identified the kidney as a candidate host cells (40).

Human RNA sequencing demonstrates that ACE-2 receptor expression in the kidney is about a hundred-fold more than that of the lung (18), however renal involvement in COVID-19 pneumonia is much less than lung involvement (12). The etiology of this discrepancy is because of the lowest expression of AGTR2m-RNA in the kidney's tissue and the highest level in the lung's tissue, since it is a G-protein-coupled receptor which activates with ACE2/ Ag (1-7)/MasR axis (41).

### Outcome and prognosis

Patients with a high level of serum creatinine at the time of admission were more likely to be admitted to ICU and treated by mechanical ventilation, showing that renal failure on admission is a poor prognostic factor and increases mortality rate (21,42).

Generation of angiotensin-(1-7)[Ang-(1-7)], via Ag-II and ACE-II can create a safe environment in the lung for cells that may counterbalance vasoconstriction and pro-fibrotic process (43). Hence, reduced ACE-2 expression increases Ag-II level through AT1R that may aggravate the disease process, induce lung edema and impair respiratory function due to the fibrotic process and inflammation (33,43,44).

### COVID-19 pneumonia and end-stage renal disease

Analysis of a peripheral blood sample in ESRD (end-stage renal disease) individuals infected with SARS-CoV2 showed lower levels of T-cells, T-helper cells, cytotoxic T-cells and NK-cells. Likewise, the serum levels of inflammatory cytokines in ESRD patients were lower than patients with COVID-19 pneumonia and normal renal function (45). Therefore, the prognosis of COVID-19 pneumonia in ESRD patients was much better than others while the rate of ARDS and severe lung involvement was lower which may be attributed to lower severity of cytokine storm. However, it is suggested that hemodialysis patients have a higher chance for SARS-CoV2 infection; therefore additional prevention tools seem logical in handling the epidemic in hemodialysis patients (45). Various infections including viral infections are associated with high levels of oxidative stress and inflammation. Therefore, some antioxidants might be useful in these patients (44,45).

### Conclusion

Various studies have shown that AKI correlates with higher mortality rate, upper morbidity and more severe case of illness. Therefore, we should be informed about the pathophysiology of AKI in COVID-19 pneumonia to find ways to decrease the incidence of AKI and subsequent decrease mortality and morbidity due to this disease.

### Authors' contribution

EK prepared the primary draft. AP conducted the extensive

revision. JSK conducted the final edit. All authors gave final approval for publication.

### Conflicts of interest

The authors declare no conflicts of interest.

### Ethical considerations

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

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