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## Updates on coronavirus (COVID-19) and kidney

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### ABSTRACT

The severe acute respiratory syndrome (SARS) is an infectious disease developed in Wuhan, China, at first. It involves the respiratory system and other organs like kidney, gastrointestinal tract and nervous system as well. The recent reports indicated that renal disorder is prevalent in coronavirus patients. The aim of this study was to provide a review of nephropathy caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and its mechanisms. The Web of Science, Scopus, and PubMed databases were systematically searched. Articles reporting nephropathy, coronavirus disease (COVID-19), coronavirus and the renal injury were included for assessment. Study designs, contrast agents, case reports and results were assessed. Of the assessed studies, suggested mechanisms include sepsis which caused cytokine storm syndrome or perhaps direct cellular injury due to the virus. In patients who were studied, albuminuria, proteinuria, and hematuria as well as an elevation in blood urea nitrogen and serum creatinine were observed. Additionally CT scan of the kidneys showed a decrease in tissue density suggestive of inflammation and interstitial edema. On the other hand, dialysis patients are a high-risk group than the general population. The current treatment for COVID-19 in acute kidney injury includes supportive management or kidney replacement therapy. All patients need to be quarantined. An N95 fit-tested mask and protective clothing and proper equipment are necessary. Some drugs can be effective to inhibit the outcome of this infection such as lopinavir/ritonavir, remdesvir, Chloroquine phosphate, convalescent plasma, tocilizumab, ACEi/ARBs (angiotensin-converting enzyme inhibitor/angiotensin receptor blockers), and hrsACE2 (human recombinant soluble angiotensin-converting-enzyme 2).

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

The severe acute respiratory syndrome (SARS) is an infectious disease was developed in China. It involves the respiratory system and other organs like the kidney as well. The aim of this study was to provide a review of nephropathy caused by SARS coronavirus 2 (SARS-CoV-2) and its mechanisms. According to studies, the suggested mechanisms include sepsis leading to cytokine storm syndrome or maybe a direct cellular injury due to the virus. Albuminuria, proteinuria, hematuria and an elevation in blood urea nitrogen and serum creatinine were observed in patients. Some medications that can be effective for this infection include lopinavir/ritonavir, remdesvir, chloroquine phosphate, tocilizumab, ACEi/ARBs (angiotensin-converting enzyme inhibitor/angiotensin receptor blockers), and hrsACE2 (human recombinant soluble angiotensin-converting-enzyme 2).

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### Introduction

In December 2019 an infection was developed in Wuhan, China (1). This infectious disease presenting as a severe acute respiratory syndrome was known by alveolar and interstitial pneumonia (2). Although the pulmonary system is the target of this virus, it additionally involves other organs like the kidney, gastrointestinal tract and nervous system (2). A study conducted by Li et al indicated

that severe acute respiratory syndrome (SARS-CoV-2) may have neurotropism, which it can involve the respiratory center in the brain stem (3). Laboratory analysis includes viral culture, direct/indirect immunofluorescence assay (IFA), microarray-based assays such as reverse transcription loop-mediated isothermal amplification (RT-LAMP) and reverse transcription-polymerase chain reaction (RT-PCR) method and multiplex nucleic acid amplification (2,4).

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Acute kidney injury (AKI) needs acute renal replacement therapy (RRT) that happens in approximately 15% of all ICU admissions, but this rate is often increased greatly in the setting of acute respiratory distress syndrome (ARDS) (5,6). Recent reports indicate that renal disorder is prevalent in coronavirus patients (7,8). In 59 COVID-19 infected patients who had renal disorders, Li et al showed proteinuria as well as raised values of urea nitrogen and serum creatinine were found in 19% and 27% of the patients, respectively (9). Another clinical finding was the computerized tomography (CT) scan of kidneys from 27 patients which demonstrated inflammation and edema of the renal parenchyma in all patients (100%) (10). Additionally, in another study of 710 coronavirus positive subjects admitted in a hospital in Wuhan (2020), revealed the presence of proteinuria in 44% and hematuria in 26.9% of patients. Further, raised plasma creatinine in 15.5% and blood urea nitrogen in 14.1% of patients were observed in their investigation. Furthermore, acute renal injury was found in 3.2% of patients. The outcomes of this infection are AKI, proteinuria, hematuria, and raised plasma creatinine and urea nitrogen (10). The possible mechanisms of renal injury in COVID-19 consisted of dehydration, which this condition may be due to fever or decreased intake of fluids in patients. Dehydration has various outcomes on the kidney, directing to the decrease of glomerular filtration rate and AKI. Other possible mechanisms consist of sepsis by COVID-19, which directs to cytokine storm syndrome, rhabdomyolysis and hypoxia. Besides, direct virus invasion to the renal tubular cells and glomeruli or interstitial cells is possible as it has been detected previously (11,12). According to a study, coronavirus enters into the cells through ACE2 (angiotensin-converting enzyme II) receptors, which are widely presented in the renal cells. The result of this finding shows that COVID-19 targets and infects the renal cells (8,10–13). The biology of the virus suggests the assumed link between angiotensin receptor blockers (ARBs) and SARS-CoV-2 angiotensin-converting enzyme inhibitors (ACEis) can be justified (11).

## Methods

### *Search strategy*

International databases including Web of Science, Scopus, and PubMed were used for search of English articles by 1 April 2020. Keywords were nephropathy, COVID-19, coronavirus, renal injury or a combination of them in the title/abstracts.

After the collection of related articles, Mendeley software was used to organize and remove the duplicate titles. Then, after browsing titles, studies with irrelevant purposes were removed. The selected studies were done on humans and published in English.

## Clinical features

### *Incubation time*

The incubation time for COVID-19 is thought to be about 14 days following exposure, but most start about 4-5 days after exposure (14,15). Symptomatic infection in children is uncommon; it usually occurs mild, although there are some reports with severe cases (16). In a Chinese report, only 2 percent of infection was in younger people than 20 years old (17). In a study which has conducted in China, with over 40000 confirmed COVID-19 cases, they found the overall case fatality rate (CFR) was 2.3% since age>70 years (CFR 10.2%), cardiovascular disease (CFR 10.5%), diabetes (CFR 7.3%) and hypertension (CFR 6.0%) were the most reported symptoms (18). The most common clinical features at the beginning of sickness were; 90% fever, 70% fatigue, 59% dry cough, 40% anoxia, 35% myalgia, 31% dyspnea and 27% sputum production (19). The less common symptoms were headache, sore throat and rhinorrhea. Furthermore, gastrointestinal symptoms (eg, nausea and diarrhea) have also been reported (7,19).

### *Laboratory findings*

Leukopenia, leukocytosis and lymphopenia have been reported, however, the most common laboratory finding was lymphopenia (7,19). High levels of lactate dehydrogenase and ferritin levels are common and high levels of aminotransferase have been described too (7,19).

### *Imaging features*

Chest CT in COVID-19 patients shows ground-glass opacification which may have abnormalities. The chest CT abnormalities are more likely to be bilateral, have a peripheral distribution, and involve the lower lobes. The other findings which were less common include lymphadenopathy, pleural effusion, and pleural thickening. The chest CT abnormalities show involving the lower lobes and having a peripheral distribution and moreover include pleural thickening, pleural effusion and lymphadenopathy (20,21).

### *Impact of age*

A person of any age may suffer from severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection; however, adults of middle age and older are most commonly affected. In many groups of hospitalized patients with confirmed COVID-19, the mean age ranged from 49 to 56 years (7,19,22).

## Transmission

Person-to-person transmission of SARS-CoV-2 occurs mainly through respiratory droplets, similar to the spread of other respiratory infections like influenza. When an infected person coughs or sneezes, by droplet

transmission, the virus released in respiratory secretions. Besides, this transmission occurs by touching an infected surface and then touches mucous membranes like his or her mouth, nose or eyes. Droplets typically do not travel more than about two meters (23). The RNA of SARS-CoV-2 has been detected in blood and stool specimens (24). The fecal-oral transmission did not appear to be a remarkable factor in the spread of infection (25).

### Kidney involvement in COVID-19

A study of 59 patients with COVID-19 showed on day 1 of illness, 34% of patients have had albuminuria, and 63% of patients have had proteinuria during their stay in hospital (26). Another study by Cheng et al in 2020, indicated that blood urea nitrogen was elevated in 27% overall and in two-third of patients who died (10). A recent report stated that amongst 710 patients with COVID-19, 26.7% have had hematuria and 44% of them had proteinuria and hematuria. The outbreak of elevated serum creatinine was 15.15% and blood nitrogen was 14.1% (10,26,27).

### Mechanism of renal involvement in COVID-19

The mechanism of kidney injury is not clear yet; the suggested mechanisms include sepsis which caused cytokine storm syndrome or direct cellular injury due to the virus. In renal tubular cells, expression of angiotensin-converting enzyme and dipeptidyl peptidase-4 were identified as a binding partner for SARS-CoV and MERS-CoV, respectively (11,28). In a more recent study, it has been indicated that ACE2 is a carboxypeptidase which especially removes carboxy-terminal hydrophobic or basic amino acids (29). Viral RNA has been identified in both infected kidney tissue and urine (8,26). Furthermore, Shi et al, indicated that SARS-CoV-2 interacts with human ACE2 molecules via its spike protein (30). The expression of ACE2 protein beside the respiratory system has been observed in human kidneys as well (31,32). According to a study, it has been shown that ACE2 is expressed in the mouth and tongue, make an easier viral entry in the host. In normal human lungs, ACE2 is expressed on type 1 and 2 alveolar epithelial cells in the lower lungs. After infection, the SARS-CoV-2 entrance starts with the binding of the spike glycoprotein expressed on the viral envelope to ACE2 on the alveolar surface. The binding of SARS-CoV-2 to ACE2 causes the clathrin-dependent endocytosis of the whole SARS-CoV-2 and ACE2 complex, inducing fusion at the cell membrane. A low pH and independent endosomal cysteine protease cathepsins facilitates endosomal cell entry (33). SARS-CoV-2 can cause acute renal failure in COVID-19 patients. The infection has both direct cytotoxicity and initial CD68+ macrophage together with complement C5b-9 as a mediate tubular pathogenesis (34). Scientists

suggested that AKI in SARS patients could be the result of special pathogenic conditions, containing cytokine release syndrome rather than active viral replication in the kidney (35). Indeed, increasing viral infection in alveolar cells results in massive attract of immune cells, which produce a large number of cytokines causing multiple organ failure. Actually, the mechanism which has been described in SARS-CoV infection was discovered by a subsequent study which indicates that an interferon-gamma-related cytokine storm was induced post-SARS-CoV infection leading to severe organ damage (36). The study by Diao et al indicates that the extents of tubular atrophy and interstitial disease are the strongest histological parameters which can be mentioned (34). In six cases during postmortem examination, the glomeruli were intact except for some cases which slight glomerulosclerosis, acute renal tubular damage and lymphocyte infiltration, suggesting that other conditions such as diabetic nephropathy and hypertension may have been involved in the pathogenesis (34). Additionally other studies have been shown that the ACE-2 receptor of SARS-CoV-2 is highly expressed in renal tubules (31,37). Some researchers have reported they have isolated SARS-CoV-2 virus particles from the urine of COVID-19 patients, suggesting the viral particles in the affected kidney can enter the urine through glomerular filtration (34). Hyaline thrombi are found in small vessels in different organs and are of importance to investigate pathological changes in autopsy material (37). According to a study, the mechanism of nephropathy in this disease may due to dehydration, toxic tubular damage induced by cytokine storm, cytopathic action induced by the virus and also drug-induced cytotoxicity (3).

### Dialysis patients

Dialysis patients are a high-risk group than the general population because their routine treatment usually needs three dialysis sessions per week (38). In a study, seven hemodialysis patients died, including six patients with COVID-19 and one of them without the infection. The causes of death were not related to pneumonia. Analysis of their blood samples from hemodialysis patients showed a remarkable reduction in the numbers of killer T cells, T helper cells, NK cells, and also inflammatory cytokines, compared to non-hemodialysis patients with COVID-19. This result may be due to an illness that causes the reduced function of the immune system and decreases cytokine storms (39). Dialysis patients should stay at home in their non-dialysis days. They should use individual transports to and from dialysis departments. Hand hygiene, respiratory hygiene, and cough etiquette should be considered by dialysis facilities. Dialysis facilities should have at least 2-meter space in waiting areas for critical patients. Body temperature should be systematically measured before and

after the dialysis session in all patients. Early recognition and isolation of patients with respiratory infection are necessary. For example; patients should be in a room dedicated to sampling. Likewise, the disinfection of the room after sampling is necessary (38).

## Treatment

The treatment for COVID-19 in AKI includes supportive management or kidney replacement therapy.

### Treatment guideline

#### *General management*

All patients need to be quarantined. An N95 fit-tested mask and protective clothing and proper equipment are necessary. Early admission to intensive-care units is recommended for seriously ill patients. Supportive care, nutritional and fluid support, and preservation of blood pressure and also using oxygen therapy are important procedures. Another measure is preventing secondary infection (26).

#### *Antiviral therapy*

There is no specific antiviral drug for COVID-19 now. The guidelines of the Chinese national health commission recommend using aerosolized inhalation of interferon- $\alpha$  and lopinavir/ritonavir (26). Another effective antiviral drug is remdesivir which has been assessed in patients with COVID-19 in China. This drug is a modern nucleotide analog that has activity against related coronaviruses (including SARS and MERS-CoV) both in vitro and in animal model studies as well as in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro (40,41). Chloroquine phosphate is another one that has been shown to have some efficacy against COVID-19 (42). Both chloroquine and hydroxychloroquine have been reported to inhibit SARS-CoV-2 in-vitro, although according to recent studies hydroxychloroquine has more potent antiviral activity (43). The chloroquine has a positive charge which increases the organelle's pH and this effect can prevent viral-endosome fusion, ultimately inhibit the infection (44). In an open-label study with 36 COVID-19 patients, the use of hydroxychloroquine (200 mg three times per day for 10 days) was associated with a higher rate of undetectable SARS-CoV-2 RNA on nasopharyngeal samples at day 6 compared to non-treated patients (70 versus 12.5 percent) (45). Given the relative safety of short-term use of hydroxychloroquine (with or without azithromycin), the lack of known efficient treatment, and the in vitro antiviral activity, some clinicians assume it is sensible to use one or both of these agents to hospitalized patients with risk for infection, especially if they are not qualified for other clinical trials (46).

#### *Glucocorticoids*

These medications are not recommended by the World Health Organization (WHO) because of the potential inhibition of viral clearance and lengthening of the duration of viremia (47).

#### *Convalescent plasma*

The clinical studies in China have shown that the early use of convalescent plasma in patients with COVID-19 could be useful for recovery (7). Accordingly, tocilizumab—the IL-6 inhibitor for patients with severe COVID-19 and elevated IL-6 levels; the agent is being evaluated in a clinical trial in China (48).

#### *ACEi/ARBs*

ACEi/ARBs are classes of antihypertensive drugs, with clinically benefits in patients with hypertension, chronic kidney disease, and heart failure. Animal model studies actually support the idea that ACEi and/or ARB use could be protective in viral pneumonia, like coronavirus infection, but it needs more studies (49).

#### *Human recombinant soluble ACE2*

According to a new study, human recombinant soluble ACE2 (hrsACE2) can block the early stages of SARS-CoV-2 infection. hrsACE2 can reduce viral growth in some cells like cells Vero E6 and it can significantly inhibit infection in human blood vessel organoids and kidney organoids too (50).

## Conclusion

The recent COVID-19 outbreak has been a global health emergency. SARS-CoV-2 interacts with human ACE2 molecules via its spike protein. The expression of ACE2 protein beside the respiratory system has been observed in the human kidneys as well. There is no specific antiviral drug for COVID-19 at present. Chloroquine phosphate has some efficacy against COVID-19. It has a positive charge which increases the organelle's pH with the abrogation of viral-endosome fusion, ultimately inhibition the infection. On the other hand, hrsACE2 can block the early stages of SARS-CoV-2 infection. The clinicians should be more considerate about renal injuries by some protocols provided by the WHO.

### Authors' contribution

SZA and DM were the principal investigators of the study. SZA, DM, MAN, and YD were included in preparing the concept and design. DM revised the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the

intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

### Ethical considerations

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

### Conflicts of interest

The authors report no conflict of interests.

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