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Research Paper

Acute Kidney Injury and Hypertension in COVID-19 Infection

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ABSTRACT

The COVID-19 pandemic has affected all the infrastructures of human life and has turned into a global emergency. COVID-19 infection mostly affects the respiratory system but can also cause multi-organ failure, such as acute kidney injury (AKI). The present review aims to assess the relationship between COVID-19 and kidney disorders and hypertension. The six official databases, namely PubMed, WHO COVID-19 database, Academic Search Premier, Science Direct, Google Scholar, and CORD-19, were searched for scientific reports (original articles) using the keywords: “COVID-19”, “Coronavirus”, “SARS CoV-2”, “Kidney disease”, “Acute renal failure”, “Kidney transplant”, and "Hypertension". A total of 58 articles were considered for a full review.

The prevalence of AKI was more than 6% prevalent in COVID-19 patients. Furthermore, AKI and hypertension were associated with higher morbidity and mortality. To control hypertension, there were different opinions and findings regarding the use of angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs); however, most of the studies suggested using these drugs to control blood pressure. AKI is associated with higher morbidity and mortality rates. A simple urinalysis in patients with suspected COVID-19 can reveal renal dysfunction at the earlier onset of complication, which may be very helpful before progressing to late-stage kidney disease. In addition to AKI, hypertension is considered to be accompanied by a worse prognosis. Further studies must be performed to clarify all the aspects of using hypertension medications in COVID-19 patients.

Keywords Acute kidney injury, Hypertension, COVID-19

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Introduction

The coronavirus disease (COVID-19) pandemic turned into a global emergency and has affected all the infrastructures of human life, such as the economy, health, and education; it also caused morbidity and mortality in all age groups. This virus is supposed to be arranged in the same group as middle-east respiratory syndromes (MERS) coronavirus and severe acute respiratory syndrome (SARS) coronavirus; however, COVID-19 has its own special features [1]. After the Spanish flu, COVID-19 has been the most challenging public health issue. It mostly affects the respiratory system causing acute respiratory distress syndrome and severe pneumonia in some patients; despite this, the disease can be mild or even silent and without any symptoms at all [2]. Fever, cough, myalgia, and shortness of breath are the most common symptoms of COVID-19 infection [3]. The incubation period of this disease is about 2-14 days after exposure [4], and the highest potential of person-to-person transmission is when the patient has clinical symptoms [5].

Aged patients, males, and patients with a history of chronic diseases, such as cardiovascular disease (CVD), hypertension, chronic kidney disease (CKD), chronic liver disease, and diabetes, are proven to be infected with a more severe form of COVID-19 [1, 6] and have higher mortality rate [7, 8]. This virus is reported to be the main cause of multi-organ failure in some cases and can finally cause death [9]. Based on the reports, there is a relationship between cardiovascular complications and COVID-19 infection, which leads to myocardial injury, heart failure, and eventually death [10, 11]. Moreover, COVID-19 contributes to renal complications, such as acute kidney injury (AKI), which have been shown to correlate with COVID-19 severity and mortality [12].

The results of various studies have reported multiple organ failure due to COVID-19 infection. For example, almost half of the patients suffered from moderate to severe pneumonia, and one-fifth of them showed acute upper respiratory symptoms, such as nasal congestion, rhinorrhea, sore throat, and cough. Chu et al. showed that 6.7% of the patients developed acute renal impairment at an average duration of 20 days after the beginning of early signs and symptoms [13-17]. Liver dysfunction was reported in about 60% of the patients with the elevation of aspartate-aminotransferase [18].

As discussed, various recent reports show that renal disorder is a common complication in COVID-19 patients [19, 20]. In this review, we aimed to assess the relationship between COVID-19 and kidney disorders and hypertension, as well as the effect of COVID-19 on kidney transplants and the need for kidney replacement in COVID-19 patients.

Materials and Methods

In the present review, three researchers did their searches independently using six official databases: Pubmed, WHO COVID-19 database, Academic Search Premier, Science Direct, Google Scholar, and CORD-19. CORD-19 is a resource consisting of 128,000 scholarly articles, including over 59,000 full-text articles related to COVID-19, SARS-CoV-2, and coronaviruses. The dataset is frequently updated when new research appears in peer-reviewed publications and archive services become available [21, 22].

Filtering the articles was done using keywords, such as "COVID-19", "Coronavirus", "SARS CoV-2", "Kidney disease", "Acute renal failure", "Acute renal failure (ARF)", "Kidney transplant", "Hypertension" and "HTN". About 4,800 articles that matched our keywords were found during our searches and the number of 68 articles were selected to be used for writing this review. The search terms are repeated for all the co-morbidities considered in this paper.

Acute kidney injury

Some studies have shown that COVID-19 infection can damage the kidneys and cause AKI [12]. When the glomerular filtration rate is suddenly reduced and the ability of kidneys to eliminate nitrogenous wastes is compromised, AKI happens [23]. This condition causes disturbed electrolyte balance and homeostasis in the body [24, 25]. AKI has five stages based on the classification of RIFLE (Risk, Injury, Failure, Loss, and End-stage renal failure), and each

one of these has specific clinical manifestations and para-clinical findings [24, 25]. The prevalence of AKI varies from region to region [26]. Based on studies from Asia, 5.5% of hospitalized patients experienced AKI, compared with 28.6% in the USA and Europe. This might be attributed to the varying therapeutic guidelines given to patients and their hospital admission [27-29]. For example, the patients' admission criteria to the hospitalization in China was a positive COVID-19 polymerase chain reaction test [23]; however, in the USA and Netherlands admission personnel only admitted symptomatic patients with moderate to severe disease [27, 29].

AKI and COVID-19 infection

As mentioned before, COVID-19 infection can cause AKI in infected patients; therefore, the mechanism of how SARS-CoV-2 affects renal cells is important. Angiotensin-converting enzyme 2 (ACE2) does not only exist in lung alveolar cells but also in other organs, such as the kidney [30]. ACE2 and dipeptidyl peptidase-4 are expressed in renal tubular cells and help SARS CoV2 and MERS CoV2 bind to renal cells. Viral RNA has been detected in kidney tissue and in the urine in both infections [31]. Regarding this, ACE2 plays an important role in facilitating the virus's entry into target cells and causes target cells to be sensitive to SARS-CoV2 [32, 33]. Therefore, the amount and the pattern of ACE2 expression in different tissues may determine the sensitivity of cells and even the symptoms of COVID-19 infection [34]. Reports have shown that only 6% of patients with SARS CoV2 infection experienced AKI [35], and the prevalence of AKI is 3-9% [36]. Podocytes and proximal straight tubule cells are potential host cells for the COVID-19 virus because these cells express ACE2 genes. According to evidence, ACE2 may have an important role in entering COVID-19 virus into renal cells [37, 38].

Signs and symptoms in COVID-19 patients with renal involvement

The most common signs and symptoms of kidney involvement in COVID-19 patients include proteinuria, hematuria, inflammation, and edema. The results of a recent study demonstrated that of 59 cases admitted to the hospital with COVID-19 infection, 63% developed proteinuria [39]. Furthermore, in patients admitted to hospitals with infection, renal swelling and edema were observed using computed tomography scans [40]. The level of blood urea nitrogen was elevated in 27% of all patients with COVID-19 infection and in 67% of the ceased ones [36].

A recent report by Cheng et al [36] showed that 44% of the hospitalized patients had proteinuria and hematuria and 26.7% had hematuria on admission. A meta-analysis showed that AKI was associated with poor outcomes, such as higher morbidity and mortality, and the severity of COVID-19 infection. The association is not related to age, gender, cardiovascular disease, diabetes, chronic obstructive pulmonary disease, and chronic kidney disease [41]. The result of viral-induced cytopathic effects may cause AKI in COVID-19 patients, especially in patients with viremia. This shows the importance of early monitoring of the condition of kidney function, getting appropriate specimens from COVID-19 patients with AKI, and careful handling of specimens to prevent accidental transmission [37].

Another important issue is disturbed renal function in COVID-19 patients; accordingly, 67% of deceased COVID-19 patients experienced impaired renal function, and about 25% of them had kidney dysfunction. Kidney failure is life-threatening, especially in patients with complications in other organs. Only 15% of the kidney function remained in patients with COVID-19 infection. Kidney involvement can be a crucial sign to differentiate between COVID-19 patients and flu or common cold patients. This means that patients with kidney dysfunction should be checked for COVID-19 in the present and future [42, 43].

Treatment of AKI in COVID-19 patients

After diagnosis of renal involvement in COVID-19 patients, the treatment of this disorder must commence as soon as possible. Treatment of renal failure in patients with COVID-19 infection is not different from that in patients who are COVID-free, and both groups should take the same supportive treatment. Kidney replacement therapy is another option for both groups. By now, no effective antiviral medication is available to treat kidney dysfunction in these patients and new medications cannot be used without confirmed results [44]. All treatments and medications prescribed for hospitalized patients infected with COVID-19 can also be prescribed for

COVID-19 patients with AKI until the current knowledge is updated about COVID-19. This is because this disease is a new phenomenon that turned into a pandemic and with new observations and investigations about this disease, our information will be accurate in the future [45]. Nowadays, the best we know is that COVID-19 is capable of affecting multiple organs, and the kidney is one of the targets of this virus, as discussed before. Acute kidney injury was reported in 5.1% of the patients, and as mentioned before, such a kidney dysfunction may lead to renal failure and even death [13-16].

Kidney replacement therapy in COVID-19 patients

Infection with COVID-19 with just lung involvement as viral pneumonia can be severe enough to be fatal for the patient, especially for aged patients or those with underlying co-morbidities, such as kidney or liver involvement [46]. Kidney transplant patients involved with COVID-19 infection are very fragile and at high risk because of using immunosuppressant medications, renal disorder, and other co-morbidities related to their condition. According to other studies, 81% of hospitalized patients with kidney transplants had co-morbidities, with diabetes mellitus and hypertension as the most common reported co-morbidities. This reveals that patients with a recent history of kidney transplant therapy are at high risk of severe COVID-19 infection, not to mention that this increased risk is related to using immunosuppressive drugs. Kidney transplant recipients and candidates are as a rule at a greater risk for more severe infection because of the higher prevalence of hypertension, diabetes mellitus, obesity, and advanced age in this group [47].

Imam et al. [48] stated that the prevalence of AKI was in 28.2% of hospitalized patients with a recent history of kidney replacement therapy. However, the pooled AKI prevalence was 34.1%. This shows that patients with COVID-19 infection and kidney transplants are at higher risk of having AKI than other groups. AKI has been demonstrated to be associated with higher severity [49]. As a result, kidney transplant patients infected with COVID-19 may have worse outcomes and mortality.

Fever has been reported to be the earliest symptom in 99% of patients with COVID-19 [50, 51]. Nonetheless, 15% of patients with a history of recent kidney transplants showed no signs of fever in their initial symptoms. Additionally, this review found that some unreported symptoms existed in the COVID-19-positive kidney transplant patients, including chest tightness and pain, upper respiratory symptoms, dehydration, conjunctivitis, dizziness, and weight loss [52].

Table 1. Briefly presented the kidney disorders and related clinical outcomes in COVID-19 patients.

Kidney disorders and clinical outcomes	Incidence rate (%)	References
Acute Kidney Injury	0.37	62
Chronic Kidney Disease (CKD)	3.44	62
Other disorders in COVID-19 patients with CKD include:		
Myocardial infarction	8	62
Acute heart failure	8.30	62
Congestive heart failure	19.76	62
Peripheral vascular disease	22.53	62
Cerebrovascular disease	20.55	62
Dementia	13.80	62
Chronic pulmonary disease	35.57	62
Connective tissue disease	11.30	62
Peptic ulcer disease	24.11	62
Mild liver disease	63.63	62
Diabetes mellitus	77.86	62
Hemiplegia	1.97	62
Any malignancy	11.46	62
Moderate to severe liver disease	0.8	62
Metastatic tumor	1.70	62
Acquired immune deficiency syndrome	0.4	62
Hypertension	67.98	62
Mortality	54.24	63

COVID-19 and hypertension

High blood pressure (hypertension) is one of the most common signs in patients with severe COVID-19 infection [53]. In this part, we review some studies about the relationship between hypertension and severe COVID-19. One study has analyzed the UK Biobank to find out the relationship between high blood pressure and increased risk of pneumonia in COVID-19 patients. This study was carried out on 107 thousand hypertensive patients, 3% of whom showed signs of pneumonia [54]. Analysis of data in this study showed that the risk of respiratory disease significantly increased in hypertensive patients. Additionally, patients with hypertension were at higher risk for acute respiratory infection and this risk was not related to age, gender, smoking status, and body mass index. Several studies have recently investigated the variability in the severity of COVID-19 disease in hypertensive patients and its medicinal therapy. In a study conducted by Ip et al. [55], it has been reported

that among 3,017 hospitalized COVID-19 patients, 53% had hypertension. In addition, using ACEIs and angiotensin II receptor blockers (ARBs) to control high blood pressure in hypertensive patients led to a 39% lower mortality rate compared to patients using other kinds of blood pressure medications. Accordingly, it is crucial to use ACEIs and ARBs for the treatment of hypertension in COVID-19 patients, and as a result, to reduce mortality rate. This information was approved by another study that observed 126 COVID-19 patients with hypertension and divided them into two groups of ARB/ACEI takers (n=43) and non-ARB/ACEI takers (n=83) [56]. A group of patients with COVID-19 infection without hypertension was then randomly selected to investigate previous information based on age and gender. The results showed that there were fewer critical patients (9.3% vs. 22.9%, P=0.06) and mortality rate (4.7% vs. 13.3%, P=0.21) in ARB/ACEI takers in comparison to non-ARB/ACEI takers. However, these differences were not statistically significant. Similarly, Liu et al. [57] studied hypertensive patients with COVID-19 infection who used medications to control high blood pressure (ARBs, ACEIs, calcium channel blockers [CCBs], and beta blockers [BBs]), and compared them with patients who did not use any medication for hypertension. This study showed that among 46 elderly patients (>65), patients who were prescribed ARBs had a significantly lower risk of developing a severe disease compared to patients who used no drugs. Although no statistically significant relationship was found, patients using other medications, such as ACEIs, CCBs, and BBs, had a lower risk of developing a severe disease. This could be attributed to the limited number of cases of these medications compared to cases who took ARBs. Nevertheless, in another study, the researchers reported that using CCBs had a significant effect on COVID-19 patients and reduced the rates of morbidity and mortality exactly as same as ARBs and ACEIs drugs [58]. These arguments are not abnormal in this situation given that the COVID-19 virus is a novel phenomenon, and further studies will reveal more about different aspects of this disease over time. Therefore, further studies on CCBs and the efficacy of these types of drug in controlling COVID-19 symptoms is needed. Surprisingly, another study has reported that using ARBs and ACEIs increases the risk of severity and mortality in COVID-19 patients (P=0.063) [59]. Although the results of the mentioned study are not statistically significant, more studies must be carried out for more clarification. In the mentioned study, patients were older and most of them had chronic diseases, such as chronic kidney dysfunction, diabetes, cerebrovascular disease, and cardiovascular disease. Another study reported that using ARBs and ACEIs increased the risk of morbidity and mortality in COVID-19 patients [60]. As mentioned before, a theory suggests that the COVID-19 virus probably enters renal cells using ACE receptors [61], and the hypothesis states that using ACEIs and ARBs up-regulates ACE receptors, and therefore, the virus can enter into renal cells more easily. After all, additional research is required to clarify the effects of these drugs on morbidity and mortality of COVID-19 infection. There is evidence of the involvement of other organs in patients with COVID-19 with kidney damage [62, 63].

The present study had some limitations. Due to the novelty of COVID-19 disease, a complete database of complications related to the disease, such as renal complications, was not available.

Conclusion

A review of 58 selected articles and other resources showed that AKI was accompanied by higher morbidity and mortality rates. It is important to mention that performing a simple urine analysis in patients suspected of COVID-19 can reveal kidney dysfunction at the beginning of the complication. Therefore, a simple urine analysis may be highly beneficial in limiting kidney damage before progressing to the late stage. In addition to AKI, hypertension is considered to be accompanied by a worse prognosis and higher morbidity and mortality rates. Mostly, the reports of articles suggested that using ARBs and ACEIs contributes to the reduction of morbidity and mortality in COVID-19 patients. Further studies are needed to clarify all aspects of using hypertension medications in COVID-19 patients.

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Conflicts of interest

There is no conflict of interest.

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