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Clinical profile, outcome and management of kidney disease in COVID-19 patients – a narrative review

S. VAHDAT

Isfahan Kidney Diseases Research Center, Khorshid Hospital, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract. – OBJECTIVE: COVID-19 disease can cause damage to various organs, especially the kidneys, so the main purpose of this study was to investigate the effect of different aspects of kidney damages caused by COVID-19 in a narrative review study.

MATERIALS AND METHODS: To conduct this study, all studies related to the topic under discussion during 2020-2021 were reviewed by systematic search in internationally available databases including Web of Science, Science Direct, Scopus, PubMed, and Google Scholar. Finally, 42 completely related studies were selected to extract the results.

RESULTS: The prevalence of acute kidney injury (AKI) varies in different parts of the world and has reached almost 70%. The results showed that, in general, a high percentage of COVID-19 patients had symptoms of renal dysfunction at the time of hospitalization, and the most important of these symptoms were proteinuria, hematuria, and increased serum creatinine. Based on the results, it can be said that AKI most likely occurs early in the disease and in parallel with lung damage. So far, various drugs have been used to control or treat COVID-19 and reduce inflammation in patients. Regardless of their usefulness, some of these drugs may adversely affect kidney function and damage the kidneys. The study results show that chronic kidney disease (CKD) in COVID-19 patients plays a minor role in renal replacement therapy (RRT), and the highest impact on the need for RRT is COVID-19.

CONCLUSIONS: This study showed that one of the major negative effects of COVID-19 on the human body is kidney damage, among which acute kidney injury (AKI) is the most important one. In addition, the prevalence of AKI due to COVID-19 varies widely around the world. Although any medication may damage the kidneys, COVID-19 or anti-inflammatory drugs are not an exception to this rule, but more research is needed to gain more information.

Key Words:
COVID-19, Kidney damage, Acute kidney injury, AKI, CKD.

Introduction

The World Health Organization (WHO) announced on January 30, 2020, the emergence of a new virus that put the whole world in a state of emergency. Then, on March 11, 2020, the WHO formally named the disease caused by the virus coronavirus (COVID-19)[1]. As of November 17, 2021, more than 254 million people were infected with COVID-19, and more than 5 million people died from the disease worldwide. Coronaviruses are a large family of viruses known in humans as the leading causes of respiratory infections including common cold and respiratory diseases, such as pneumonia, bronchitis, and acute respiratory distress syndrome[2].

Of the seven different types of coronaviruses that affect humans, four are very common, while on the other hand, three other types of infectious human coronaviruses, SARS-CoV, MERS-CoV, and SARS-CoV-2, are associated with severe respiratory infections and mortality [3,4]. SARS-CoV-2 is a new type of this family and introduced to the world in late 2019; its related disease has been named COVID-19[5].

The virus is a single-stranded ribonucleic acid (RNA) genome-coated virus that uses the cell receptor of the "angiotensin-2 converting enzyme" to enter target cells[6]. This coronavirus reproduces in large numbers in the upper and lower respiratory tracts, and also causes damage to the lower respiratory tract. Approximately 81% of patients with COVID-19 show mild symptoms, and in 14% of cases, the patient presents with severe symptoms, including pneumonia and shortness of breath. In 5% of cases, the patient's condition worsens, associated with respiratory failure, infectious shock, and failure in other organs of the body[7].

Due to the novelty of this virus in the human population, new reports are published daily regarding its various aspects of pathogenicity. Symptoms,

Corresponding Author: Sahar Vahdat, MD; e-mail: s_vahdat@med.mui.ac.ir

such as fever, cough, fatigue, muscle aches, joint pain, and shortness of breath have been reported as common and clinically confirmed virus symptoms[5,8]. In addition to these symptoms, SARS CoV-2 also affects various body organs, such as the gastrointestinal tract, nervous system, skin, olfactory system, cardiovascular system, liver, kidneys, and eyes[9,10]. However, the manifestations of this disease can vary from asymptomatic to respiratory disorders, insufficiency of various organs, and high mortality[9]. Respiratory failure is the most common feature of COVID-19, and the second organ most affected by COVID-19 is the kidney[10]. Due to the importance of the effect of COVID-19 on the kidneys, different aspects of these effects were evaluated by numerous reviews.

Materials and Methods

A comprehensive search was done in international available databases, including Web of Science, Science Direct, Scopus, PubMed, and Google Scholar in period time 2020 and 2022 to review and extract required results from published articles and reports related to the under-discussion subject. Systematic review using terms "kidney damages", "COVID-19", "kidney injury", "acute kidney injury", "AKI", "COVID patient", "Chronic kidney disease" and "KCD", "Prevalence", "Incidence", "Serum creatinine", "COVID Pandemic", "Proteinuria", "Hematuria" and "Renal replacement therapy", "RRT", "Kidney failure", "Renal insufficiency", "Coronaviruses", "Risk", "Occurrence", "Patients hospitalized", "Mortality", "Outcomes", "drugs", "Anti-inflammatory", "complications", "randomized clinical trial" was performed. For other databases, the same terms were used similarly. The references were thoroughly evaluated to verify that no articles were missed for inclusion in the study (Reference Checking). In addition, the citations from the research were also checked (Citation Tracing) to make sure that the search was thorough and successful[22]. In addition, unofficial reports, articles in a letter to editor format, and unpublished articles and content posted on Internet sites were removed from the list of downloaded files. Finally, the results of 42 published articles were reviewed for the present review.

Results

The obtained result of the present study shows that the prevalence of acute renal impairment (AKI) varies among COVID-19 patients admitted to different parts of the world so that this value varied from 5.1% to 70.7%[12-19]. Based on the finding of the present review, at present, the true incidence of AKI in COVID-19 hospitalized patients is not known, and also, the incidence of AKI is also very high in non-survivors. Besides AKI, chronic kidney disease (CKD) is another important effect of COVID-19 on all COVID-19 patients. Another important finding of the present study was that kidney damage due to COVID-19 is manifested by elevated serum creatinine, proteinuria, hematuria, and AKI. In addition, some patients with COVID-19 require renal replacement therapy (RRT). According to the results of this review study, AKI is consistently associated with increased mortality in COVID-19 patients. According to the results of some studies[19,20], kidney damage is usually seen along with heart damage, probably because both of these complications are predictors of severe disease. Based on the finding of this study, so far, various drugs have been used to control or treat COVID-19 and reduce inflammation in COVID-19 patients. However, some of these drugs may adversely affect kidney function and damage the kidneys regardless of their usefulness.

Discussion

Prevalence and Incidence of Kidney Damage in COVID-19 Patients

The prevalence of acute renal impairment (AKI) varies among COVID-19 patients admitted to different parts of the world. The prevalence of AKI, in various studies, ranged from 5.1% to 70.7%[12-19]. In a review study by Zhu et al[20] with 3062 COVID-19 patients, it was reported that the incidence of renal abnormalities function (as an increase in serum creatinine) is equal to 25.5%.

At present, the true incidence of AKI in COVID-19 hospitalized patients is not exactly known. Based on a study by Cheng et al[13] the incidence of AKI in the cohort of 701 patients with COVID-19 was 5.1%. In the study of Pei et al[14] on 467 patients, it was reported that the incidence of AKI is equal to 4.7%. However, based on the results of a study by Pei et al[14], a retrospective analysis of preliminary data from Wuhan, China, showed that 23 out of 85 hospitalized COVID-19 patients involved AKI.

To date, the most recent results related to the incidence of AKI in patients with COVID-19 were presented in a systematic review and meta-analysis

by Passoni et al[21]. This study reported the results of 30 original research studies related to 18043 adult patients with COVID-19[21]. The results of this review study showed that the incidence of AKI in general and in patients admitted to the ICU was 9.2% (4.6-13.9) and 32.6% (8.5-56.6), respectively. According to the study results, the incidence of AKI in elderly patients and patients with acute respiratory disease syndrome was 22.9% (4.0-49.7) and 4.3% (1.8-6.8), respectively. The incidence of AKI in patients with secondary infection was estimated to be 31.6% (12.3-51.0). In addition, the results of this study showed that the estimated incidence for patients in need of renal replacement therapy (RRT) was 3.2% (1.1-5.4), and the estimated AKI mortality was 50.4% (17.0-83.9)[21].

Apart from this, all reports consistently observed the occurrence of AKI in critically ill patients. For example, based on the results of a study by Yang et al[17] preliminary data showed that 29% of 52 critically ill Chinese patients developed AKI. In Huang et al[16], 23% of patients admitted to the ICU developed AKI, while none in non-ICU care had such a condition[22]. According to Goldfarb et al[23], New York, of the 105 patients with COVID-19 in the ICU, 44 were AKI patients, 40 of whom required renal replacement therapy. In addition, the results of the study by Li et al[18] in China showed that kidney damage was observed in 70% of severe and critically ill patients.

According to two studies[19,18], the incidence of AKI is also very high in non-survivors. For example, in a retrospective study by Chen et al[19], the incidence of AKI was 25% of 113 non-survivors, while in the study of Zhou et al[18] was estimated to be 50% of 54 people. Although the initial symptoms of renal dysfunction were observed much earlier during the disease, AKI developed within 15 days [13.0-19.5] after the disease begun[18]. Based on the results of various studies, including Li et al[24], Cheng et al[13], and Pei et al[14], a high percentage of patients had symptoms of renal dysfunction at the time of hospitalization. According to the results of these studies, 44-65%, 27-44% and 10-14% of patients had respectively proteinuria, hematuria and increased serum creatinine and also symptoms of renal dysfunction[13,14,24].

Pei et al[14] reported that out of 333 COVID-19 patients in China, 251 (75%) had renal complications, including proteinuria, hematuria, and AKI. Therefore, based on the results of this study, it was found that renal abnormalities found in patients are due to COVID-19[14]. Furthermore, based on the results of some studies[14,25], considering that the average time from the onset of the disease to the time of hospitalization was 9 to 10 days, it can be interpreted that renal failure begins even before hospital admission.

In general, based on the results of a review study conducted by Passoni et al[21], the incidence of AKI is high among adult patients admitted with COVID-19. It affects an average of 13.9% of these patients. In addition, one of the important results presented in this study is that AKI most likely occurs early in the disease and is parallel to lung damage[21].

In addition to AKI, another important effect of COVID-19 on all COVID-19 patients is chronic kidney disease (CKD). CKD is a gradual loss of kidney function that can occur for any cause, including diabetes and high blood pressure, recurrent infections, and urinary tract obstruction. CKD impairs the ability of kidney-nephron functional units to treat waste and regulate water and blood acid. Although there may be no signs of CKD in the early stages, the symptoms improve over time. Unlike AKI, which progresses rapidly and is potentially reversible, CKD is a long-term disease in which kidney damage is permanent and progressive. CKD can progress to end-stage renal disease (ESRF), fatal without dialysis or kidney transplantation[26].

Based on the most recent searches performed, important results were obtained in a review study by Liu et al[27] regarding AKI and CKD in patients with COVID-19. In the above review study, 36 trials with a total of 6395 COVID-19 patients were included, and several variables between different patient groups (non-severe, severe and critical groups) using standardized mean difference (SMD) or odds ratio (OR) was examined. In addition, AKI complications (OR = 13.92) and blood urea nitrogen (SMD = 1.18) were significantly increased in the critical group compared to the severe group. This study interpreted that CKD and AKI are prone to occur in patients with severe COVID-19. CRRT is more common in patients with severe COVID-19 is used in non-severe COVID-19 patients, and based on the results of this study, it can be said that the risk of developing AKI in the critical group is higher than the severe group[27].

Specification of Kidney Damage in COVID-19 Patients

COVID -19-induced kidney damage manifests itself in elevated serum creatinine, proteinuria, hematuria, and AKI, which in some patients require renal replacement therapy (RRT)[14]. According to

some scientific reports[13-15,24,28,29] related to kidney damage, AKI was generally defined according to KDIGO criteria, while recently, various other definitions of kidney damage, including eGFR reduction[15] and extended criteria[14] were also used.

Pei et al[16] reported that the first, second, and third stages of AKI were observed in 18%, 32%, and 50% of cases, respectively. Based on the results of this study, high rates of proteinuria and hematuria have been observed in patients with hospitalized COVID-19. Based on the results of the study on 333 patients with COVID-19 hospitalization, proteinuria and hematuria complications were shown in 65.5% and 41.7% of patients, respectively[16]. In addition, various renal pathological changes were observed in patients with COVID-19. Histopathological analysis of six autopsies of patients with COVID-19 with involvement of kidney damage showed viral particles in proximal renal tubules and podocytes, with varipus degrees of acute tubular necrosis and lymphocytic infiltration[25].

Based on the results of Su et al[31] pathological examinations of all patients with COVID-19 showed prominent proximal acute tube damage in the form of vacuolar degeneration, loss of brush border, accumulation of red blood cells without platelets or fibrin plaque, and sometimes even acute tubular necrosis (ATN). Hence, the predominant form of AKI in SARS-CoV-2 infection appears to be intrarenal AKI. Therefore, it can be said that the predominant form of AKI in SARS-CoV-2 infection is intrarenal AKI[31-33].

Outcomes of Kidney Damage in COVID-19 Patients

According to the results of various studies, AKI is consistently associated with increased mortality in COVID-19 patients. A study by Li et al[24] performed on 193 COVID-19 patients found that the mortality rate of patients with AKI was 5.3 times higher than patients without AKI. A cohort study by Cheng et al[13] on 701 patients in Wuhan showed that AKI in stage 2 was independently associated with in-hospital death.

Based on the results of some stcholars[14], apparent renal dysfunction with proteinuria and hematuria without meeting AKI criteria may also predict outcomes. Pei et al[14] showed that the incidence of proteinuria and hematuria in critically ill patients was almost twice as high as in patients with moderate disease (81% *vs.* 44% for proteinuria, 69% *vs.* 33% for hematuria)[14]. Based on the results of the Pei et al[14], among 333 COVID-19 patients, the mortality rate in patients with renal involvement, including hematuria, proteinuria, and AKI, was more than 9 times higher than in patients without renal involvement (11.2 *vs.* 1.2%, respectively).

Menon et al[34] conducted one of the most recent review studies on the association of AKI with disease severity and mortality in COVID-19 when writing the present article. The study included 14,415 patients from different countries. Out of 14415 patients, 3820 developed AKI with a pooled prevalence of 11% (95% CI: 0.07-0.15). In addition, the results of the study showed that AKI was significantly associated with severe COVID-19 disease [OR = 8.45 (95% CI: 5.56-12.56)] and it was significantly associated with mortality in COVID-19 patients [OR = 8.45 (95% CI: 5.56-12.56)].

According to the results of some studies[19,23,29], kidney damage is usually seen along with heart damage, probably because both of these complications are predictors of severe disease. Shi et al[29] reported that the incidence of AKI in patients with heart damage was more than 26 times higher than patients without heart damage. After the high incidence of AKI, after using a ventilator, the use of RTT treatment was the second most common support for COVID-19 patients. In China, Yang et al[19] reported that 17% of critically ill patients with COVID-19 were treated with RTT. Results of the study by Goldfarb et al[23] showed that 38% of COVID-19 patients in the intensive care unit needed RRT.

According to the British ICNARC report (May 1, 2020), 23% of patients with severe COVID-19 (1163 out of 5139) require RTT. Among patients with renal support, approximately 75% died in the intensive care unit. According to the above-mentioned report, only 5.3% of patients who require RRT already had severe kidney disease. So, this indicates that chronic kidney disease (CKD) has played only a minor role in the need for RRT, and the highest impact on the need for RTT has been COVID disease[25]. Other studies[13,18] have reported that the survival rates of patients requiring RTT were significantly lower. Cheng et al[18] reported that 8 out of 9 patients who received RRT did not survive[13], and based on a study by Zhou et al[20], a total of 10 RTT recipients died.

According to a study by Pei et al[14] the improvement of kidney damage among survivors of the disease significantly occurred. According to the results of this study, 68% of patients with proteinuria and 44% of patients with hematuria after recovery of COVID-19 returned to normal status. In addition, 18% of patients with AKI achieved a

complete recovery of renal function with a mean recovery time of 6 days[14]. Based on the results of critical illness was a negative risk factor for recovery from AKI, whereas, at age 60, pre-admission ACEI/ARB treatment and AKI were negative risk factors for recovery of hematuria[14].

The Used Drugs, Kidney Impacts, and Their Complications in COVID-19 Patients

So far, various drugs have been used to control or treat COVID-19 and reduce inflammation in COVID-19 patients. However, some of these drugs may adversely affect kidney function and damage the kidneys regardless of their usefulness.

Remdesivir, a nucleotide analogue, was approved by the US FDA for emergency use in COVID-19[35]. Remdesivir has potent *in vitro* antiviral activity against SARS-CoV-2 due to inhibition of RNA-dependent RNA polymerase[36]. In some cases, remdesivir has been shown to be effective; for example, in 61 COVID-19 patients treated with at least one dose of remdesivir, this became the basis for the FDA's decision to allow the drug. However, early in the onset of pandemics, no dose adjustment was recommended, and the formula contains a vehicle, cyclodextrin, which raises the concern of potential accumulation in renal failure. Therefore, it should be avoided in patients with eGFR <30 ml/min[36].

Lopinavir/ritonavir, an oral combination agent for the treatment of HIV, is another antiviral agent that has also been studied to treat COVID-19 and is widely used for COVID-19 as an off-label treatment[37]. However, in a recent open label randomized clinical trial in 199 patients[38], no benefit was observed. The use of lopinavir/ritonavir for renal insufficiency does not require dose adjustment. Similarly, darunavir/cobicistat is another antiviral drug studied to treat COVID-19 and does not require dose adjustment[37].

Chloroquine and hydroxychloroquine are the most commonly used drugs in the literature since the onset of COVID-19[38], although there are insufficient data to support their effectiveness. They appear to inhibit viral fusion and glycosylation of viral proteins through an unknown mechanism, and their activity against COVID-19 has been demonstrated *in vitro*[36]. However, no convincing evidence for the clinical efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19 was found. Only in a small study by Gao et al[39] from China reported positive outcomes in patients treated with chloroquine; subsequently, small studies involving Borba et al[40] and Jun et al[41] did not observe any effect of hydroxychloroquine on COVID-19 and potential toxicity in critically ill patients.

From the point of view of kidney damage, hydroxychloroquine/chloroquine does not have renal side effects and does not require dose adjustment for short-term use in renal failure. However, both drugs have rare and severe side effects, including QTc prolongation and retinopathy, and should be used with caution[25,36]. Since binding of viral S protein to human ACE2 receptors is essential for the virus to enter cells, recombinant human ACE2 (hrsACE2) could potentially reduce a viral infection agent. Montiel et al[42] reported that hrsACE2 significantly blocks COVID-19 infection, and this drug showed potential therapeutic value for the early stages of infection.

In addition to efforts to use specific adjuvants to control the progression of COVID-19 disease or its treatment, other efforts have been made to provide drugs to reduce inflammation caused by COVID-19. Since the clinical manifestations of COVID-19 range from asymptomatic to multiple organ failure, treatments may focus on preventing disease progression and compensating for systemic damage. Suppression of COVID-19-induced inflammatory is a potential way to prevent the deterioration and development of multiple organ failure. Interleukin-6 (IL-6), a major inflammatory mediator in the development of cardiovascular syndrome (CRS), has been suggested as a therapeutic target for severe and critically ill patients with COVID-19.

Serum IL-6 levels were significantly higher in critically ill patients with COVID-19 than in severe patients. In addition, according to a study by Li et al[16], 74.4% of COVID-19 patients had IL-6 levels above the normal range. Preliminary data on the use of tocilizumab, a human anti-IL-6 receptor antibody that has been used successfully in other types of cytokines storm[43] in severe COVID-19, showed that IL-6 blockade might reduce fatally and the need for mechanical ventilation[44-46]. If tocilizumab is effective, it may reduce severe COVID-19 kidney damage[25].

Although corticosteroids have been tested because they may reduce pneumonia and reduce the incidence of acute respiratory distress syndrome (ARDS), the potential harms, including decreased viral clearance and increased risk of secondary infection, may outweigh the potential benefits[47]. While there is insufficient data on the effect of corticosteroids in COVID-19 patients, current guidelines do not recommend their use[48].

In addition to these efforts to reduce viral infection and control the inflammatory response, the current management of COVID-19 focuses on the management of respiratory, cardiovascular, and thrombotic complications in critically ill patients. Most importantly, limb protection measures taken before limb dysfunction may reduce the high rate of limb dysfunction, i.e., kidney damage, and its detrimental effect on outcome[25].

In this context, the widely used renin-angiotensin-aldosterone (RAAS) system blocking agents need special attention. ACE2, the cellular receptor used by SARS-CoV-2, is an enzyme that converts angiotensin-II to angiotensin 1-7, which has an antitoxic role to angiotensin-II and its inflammatory effects[49]. In addition, Angiotensin 1-7 has vasodilator and anti-inflammatory effects through interaction with Mas receptor[50]. Previous studies[50-52] have shown that ACE2 knockout mice were more susceptible to acid-induced ARDS, endotoxin, and sepsis than wild-type mice. Furthermore, increased severity of ARDS was associated with increased vascular permeability, pulmonary edema, and neutrophil infiltration. Similarly, the administration of recombinant ACE2 protein improved the symptoms of lung injury in both ACE2-knockout and wild-type mice and confirmed the protective role of ACE2 in lung injury[50]. Similarly, ACE2 has a protective role in various kidney diseases, including acute kidney damage[51,52], possibly through its vasodilator, anti-inflammatory, and hypotensive effects angiotensin 1-7.

Conclusions

The present study's finding showed that the prevalence of AKI varies in different parts of the world and has reached almost 70%. The results showed that, in general, a high percentage of COVID-19 patients had symptoms of renal dysfunction at the time of hospitalization, and the most important of these symptoms were proteinuria, hematuria, and increased serum creatinine. Based on the results, it can be said that AKI most likely occurs early in the disease and in parallel with lung damage. So far, various drugs have been used to control or treat COVID-19 and reduce inflammation in patients. Regardless of their usefulness, some of these drugs may adversely affect kidney function and damage the kidneys. The study results show that chronic kidney disease (CKD) in COVID-19 patients plays a minor role in renal replacement therapy (RRT), and the highest impact on the need for RRT is COVID-19. Based on the present study results, it can be concluded that one of the major negative effects of COVID-19 disease on the human body is kidney damage, among which acute kidney injury (AKI) is the most important injury. In addition, the prevalence of AKI due to COVID-19 varies widely around the world. Although any medication may damage the kidneys, COVID-19 or anti-inflammatory drugs are no exception to this rule, but more research is needed to gain more information.

Conflict of Interest

The authors declare that they have no conflict of interest.

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