

Acute Kidney Injury in the 2019 Novel Coronavirus Disease

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Keywords

2019 novel coronavirus disease · COVID-19 · Acute kidney injury

Abstract

Background: The 2019 novel coronavirus disease (COVID-19) is a newly defined serious infectious disease caused by the SARS-CoV-2 virus. The epidemic started in Wuhan, China, in December of 2019 and quickly spread to over 200 countries. It has affected 4,258,666 people, with 294,190 deaths worldwide by May 15, 2020. COVID-19 is characterized by acute respiratory disease, with 80% of patients presenting mild like flu-like symptoms; however, 20% of patients may have a severe or critical clinical presentation, which likely causes multiple organ injuries (e.g., kidney, heart, blood, and nervous system). Among them, acute kidney injury (AKI) is a critical complication due to its high incidence and mortality rate. Here we present a review of the current understanding of AKI in COVID-19. **Summary:** COVID-19 is a catastrophic contagious disease caused by the coronavirus, and the AKI induced by COVID-19 significantly increases the mortality rate. In this review, we summarize the clinical characteristics of COVID-19 induced AKI by focusing

on its epidemiology, pathogenesis, clinical diagnosis, and treatment. **Key Messages:** Multiple studies have shown that COVID-19 may involve the kidneys and cause AKI. This article reviews the characteristics of COVID-19-induced AKI largely based on up-to-date studies in the hope that it will be helpful in the current global fight against and treatment of COVID-19.

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Introduction

Novel coronavirus disease (COVID-19) is a newly discovered acute infectious disease caused by the SARS-CoV-2 virus, which is mainly manifested as acute respiratory diseases characterized by acute interstitial and alveolar pneumonia and can affect multiple organs such as the kidneys, the heart, the digestive tract, and blood [1]. This disease is highly contagious, with diverse manifestations and complications, and poses a threat to public health, just like another 2 coronavirus-induced diseases, i.e., severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Although it mainly presents with acute pneumonia, acute kidney injury (AKI) is

definitely not uncommon and plays an important role in the prognosis of severely affected patients. Therefore, much attention must be paid to the AKI in COVID-19.

Epidemiology

The current outbreak of COVID-19 started in Wuhan, China, in early December of 2019, and it has now spread to over 200 countries [2]. There are 84,464 cumulative confirmed cases, with 4,644 dead in China and 4,174,202 cases with 289,546 dead outside of China by May 15, 2020. In total, about 16–20% of patients present severe or critical cases. The exact incidence of AKI in COVID-19 is still not fully clear. In the first study reported by Huang et al. [3], the incidence of AKI was 7%, and 3 out of 13 (23%) patients in the intensive care unit experienced AKI. In another study of 99 patients with COVID-19, seven cases developed various degrees of kidney injury with elevated serum creatinine (Scr) and/or blood urea nitrogen (BUN) levels, and 3 of them were diagnosed with AKI [4]. Wang et al. [1] reported that 3.6% of patients developed AKI and 2 patients received renal replacement treatment in his 138-patient cohort study. In a larger multicenter study with 1,019 cases, Guan and Zhong [5] showed that the AKI incidence rate was only 0.5%. However, in a single-center study with 710 consecutive hospitalized COVID-19 patients, Cheng et al. [6] reported that the incidence rate of AKI was 3.2%; most strikingly, 50% of the patients with AKI died. Besides, patients with elevated baseline Scr levels tend to develop more severe AKI and have a higher death rate [6]. So it appears that the overall incidence of AKI in COVID-19 is probably lower than that in SARS and MERS [7, 8]. However, a recent study from Yang et al. [9] suggests that the AKI incidence is quite high (15/52; 29%) in critically ill patients. Quite similar results were also reported by Diao et al. [10] in their retrospective study, demonstrating that 27.06% (23/85) of patients experienced AKI, and elderly patients (age \geq 60 years) had a much higher incidence (69.57%) of AKI development [10]. Clearly, AKI in COVID-19 is very common, particularly in patients in severe or critical condition.

Pathogenesis

Our current understanding of the pathogenesis of AKI in COVID-19 is largely assumptive, based on previous studies and 2 important coronavirus infection, i.e., SARS

and MERS. Renal impairment could be directly attacked by the coronavirus or a cytokine storm due to abnormal immunity. Hypotension or dehydration, hypoxemia, sepsis, and nephrotoxic drugs could also be involved in the development of AKI.

Role of Virus Attack

Angiotensin converting enzyme 2 (ACE2), a metallo-peptidase, has been confirmed to effectively bind to the S1 domain of the spike protein on SARS-CoV. Therefore, ACE2 is considered to be a functional receptor of SARS-CoV [11]. Researchers described the full-length genome sequence of SARS-CoV-2 from 5 patients and found that 79.5% of SARS-CoV-2 sequences are homologous to SARS-CoV [12]. Moreover, they share the same functional receptor, i.e., ACE2, and have an affinity comparable that of human ACE2 (hACE2) [12, 13]. Recently the specific structure of ACE2 was discovered by cryoelectronic microscopy and the multiple conformational states of the SARS-CoV-2 S glycoprotein were demonstrated at a 3.0-Å resolution [13, 14]. hACE2 is not only expressed in lung tissue but it can also be detected in the kidneys, mainly in proximal tubules, afferent arterioles, collecting ducts, and the thick ascending limb of Henle [15]. In addition, viral nucleic acid could also be found in urine in 4 out of 58 (6.9%), suggesting that the kidneys might be the target of this novel coronavirus [16]. Recently, Diao et al. [10] demonstrated that SARS-CoV-2 mainly induced acute tubular necrosis by infecting kidney tubules directly. Immunohistochemistry demonstrated that the NP antigen of SARS-CoV-2 was accumulated in the cytoplasm of kidney tubules instead of glomeruli based on the autopsy findings of 6 COVID-19 subjects with renal function impairment prior to death [10]. Besides, Su et al. [17] found the virus particles in the cytoplasm of renal proximal tubular epithelium and podocytes but less so in distal tubules. SARS-CoV nucleoprotein was analyzed in 6 cases, and 3 showed positive granular staining in a nuclear or cytoplasm pattern in tubular epithelium. These results provide direct evidence that the SARS-CoV-2 virus can directly infect the renal tubular epithelium and podocytes, which may induce AKI in COVID-19 patients [17]. Thus, the novel coronavirus can induce kidney injury directly via hACE2 or other receptors like SARS-CoV, but the exact mechanism still needs to be clarified.

Role of immune Activation

Immune activation accompanying the release of a large amount of proinflammatory factors may also play an important role in COVID-19-associated AKI. Previ-

ous studies have demonstrated that SARS-CoV and MERS-Cov infection could lead to a significant upregulation of inflammatory factors and chemokines [18]. It is noteworthy that cytokine storm syndrome (CSS) may play a critical role in multiple organ dysfunction syndrome in severe patients. Laboratory examination showed that patients with COVID-19 have a higher level of TNF- α , IL-1, IL-6, interleukin (IL)-12, and interferon (IFN)- α , suggesting that they may have experienced CSS. Chen et al. Recently a significant upregulation of IL-6 and the IL-2 receptor (IL-2R) was demonstrated in 29 patients with COVID-19 [19]. The exact role of CSS in COVID-19 needs to be further investigated.

Role of Other Clinical Factors

Severely or critically illness patients with COVID-19 often experience hypotension, hypoxemia, diarrhea, dehydration, electrolyte and acid-base balance disorder, cardiac insufficiency, and disseminated intravascular coagulation. Meanwhile, drugs like NSAID, antiviral drugs, antibiotics, and (or) norepinephrine could all be attributable to the development of AKI, specifically in aging patients with underlying diseases like diabetes, cardiovascular disease, or cancer.

Clinical Manifestations of AKI in COVID-19

General Manifestation

COVID-19 can affect a variety of organs and systems, including respiratory, urinary, digestive, cardiovascular, blood, and neurological systems, depending on the severity [1]. The most common symptoms at the onset of the COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, hemoptysis, diarrhea, dyspnea, and lymphopenia. Severe patients may experience a high fever, anhelation, chest distress, cyanosis, hypoxemia, hypotension, etc. The main feature of lung injury is acute interstitial pneumonia, i.e., alveolar pneumonia with a large amount mucinous secretion, which usually causes persistent hypoxemia. There are other relatively rare complications like acute respiratory distress syndrome and acute cardiac injury [2, 3, 20].

Renal Manifestations

Patients with COVID-19 may have various degree of renal dysfunction, characterized by elevation of BUN, creatinine (Cr), and renal structural changes [4]. A study of 59 patients with COVID-19 found that 34% of patients

developed massive albuminuria on the first day of admission and 63% of patients presented proteinuria during their stay in hospital [21]. BUN was elevated in 27% of the patients, and more importantly two thirds of the patients who died presented with increased BUN and Scr over 200 $\mu\text{mol/L}$. Kidney CT scans for showed the density was in the range of 19.5–34.97 HU, which is significantly lower than value in patients without kidney disease (i.e., 35 HU). This result indicates that inflammation and edema of the renal parenchyma may occur in patients with COVID-19 [21]. Cheng et al. [6] recently reported that 44% of patients presented with proteinuria and hematuria and 26.9% had hematuria on admission among 710 consecutive hospitalized patients with COVID-19, and the prevalence of elevated Scr and BUN levels was 15.5 and 14.1%, respectively. Although the incidence of AKI was 3.2%, it is an independent risk factor for in-hospital death [6]. Recent autopsy data demonstrated that tubular epithelial cell necrosis and degeneration, with interstitial hyperemia, microthrombus, or focal fibrosis were the main pathological features, while glomerular lesions are not common [2].

Laboratory Examination

In the early stage of the disease, the number of peripheral blood leukocytes is normal or reduced; the lymphocyte count is reduced as well. Some patients may suffer from liver disorder with abnormally elevated alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase levels. Elevated troponin can be seen in some critically ill patients. C-reactive protein and erythrocyte sedimentation rates increased in most patients, and procalcitonin was usually normal. In severe cases, D-dimer increased and peripheral blood lymphocytes decreased progressively [2]. Chest CT showed multiple small patch shadows and interstitial changes in the early stage, which further developed into multiple ground glass shadows and infiltration shadows in both lungs. In severe cases, consolidation of the lung or white lung may occur, while pleural effusion is rare [2]. Moreover, a study of 52 critically ill patients showed that lymphocytopenia occurred in more than 80% of COVID-19 patients [7]. However, a previous study claimed that 35% of non-critical patients infected with SARS-CoV-2 had mild lymphocytopenia [4], suggesting that the severity of lymphocytopenia reflects the severity of SARS-CoV-2 infection. A recently published case report analyzed the kinetics of immune responses of a nonsevere case of COVID-19, which suggest that immune parameters should be tested in COVID-19. Early effective adaptive immune responses might correlate with better clinical outcomes [22].

Diagnosis

The diagnosis of AKI complicated with COVID-19 is based on the diagnosis of COVID-19 and complied with the criteria of KDIGO [1]. AKI is identified as one of the following: (1) an Scr increase ≥ 0.3 mg/dL (≥ 26.5 $\mu\text{mol/L}$) within 48 h, (2) an Scr increase to ≥ 1.5 times baseline within the previous 7 days; or (3) a urine volume ≤ 0.5 mL/kg/h for 6 h [23].

For diagnosis of COVID-19, epidemiological factors, clinical manifestations, and laboratory examination (including a hemogram, a chest CT, a virological examination, etc.) should be combined [2]. Novel coronavirus nucleic acid detection, gene sequencing, or specific antibodies (both IgM and IgG) are all recommended approaches for confirmed diagnosis [2]. However, false negativity may happen in some cases with a gene detection kit; it should therefore be used carefully and repeat analysis or combined use with other approaches is recommended [2]. Currently, detection kits like Reverse Transcription Loop-Mediated Isothermal Amplification (RT-LAMP) with better sensitivity and specificity are under investigation [24].

Treatment

The main treatment of COVID-19 with AKI includes general management, antiviral therapy, renal replacement therapy, and other supportive therapies.

General Management

All patients with confirmed COVID-19 should be placed in effective quarantine and treated in designated hospitals. Moreover, early admission to an intensive care unit (ICU) is recommended for critical patients. Patients are given rest, supportive treatment such as nutrients, and maintenance of homeostasis. Oxygen therapy should be provided when necessary. Fever is a common symptom of COVID-19, and nonsteroidal anti-inflammatory drugs (NSAID) are given cautiously. The management of critical cases should focus on the prevention and treatment of complications by maintaining hemodynamic stability. In addition, prevention of the secondary infection should also be emphasized. Timely administration of high-flow oxygen, mechanical ventilation, or extracorporeal membrane oxygenation are key approaches for those with ARDS. It should be noted that assessing the patient's psychological situation and relieving the anxiety of patients are also integral parts of coping with this disorder [2].

Antiviral Therapy

Although antiviral therapy is critical, there is currently no confirmed effective antiviral drug for COVID-19. According to the updated version of guidelines recommended by the National Health Commission of the People's Republic of China, aerosol inhalation of IFN- α and lopinavir/ritonavir are suggested for patients [2]. The specific therapeutic value and safety of lopinavir/ritonavir in COVID-19 patients are under investigation (ChiCTR2000029308). The efficacy of the nucleoside analog GS-5734 (remdesivir) has been confirmed both in SARS-CoV and in MERS-CoV [25, 26]. These studies suggested that remdesivir might be considered for a wider range of coronaviruses, including the current COVID-19. Successful treatment with remdesivir has been reported in COVID-19 patients [27], which quickly piqued the interest of Chinese doctors. TA strictly designed clinical trial on the efficacy of remdesivir in COVID-19 patients was started in China on February 3 (NCT04252664 and NCT04257656) and will hopefully be finished in April of 2020.

Blood Purification

Blood purification comprises a group of techniques including plasma exchange, adsorption, perfusion, and continuous renal replacement therapy (CRRT). Among them, CRRT is critical for severe COVID-19 cases due to its unique technical features, specifically for those with AKI, systemic inflammatory response syndrome, multiple organ dysfunction syndrome, and CSS. CRRT is usually recommended for those with hyperkalemia, acidosis, pulmonary edema, or water overloaded [2]. Besides, it should be noted that CRRT may play a crucial role in clearance of overloaded inflammatory cytokines in severe and critical patients [28]. Ghani et al. [29] had showed the efficacy of high-volume hemofiltration (6 L/h) treatment in sepsis, with not only removed inflammatory cytokines (IL-6, $p = 0.025$) but also improved SOFA (Sequential Organ Failure Assessment) scores on day 7. Park JT et al. [30] also demonstrated that a high dose of CRRT could significantly reduce the patient's serum IL-6 and IL-8 levels. In a randomized clinical trial, Zarbock et al. [31] demonstrated that early use of RRT (KDIGO Stage II started in less than 8 h) could significantly reduce the mortality rate in 90 days compared to delayed use (KDIGO stage III started in over 12 h) in critically ill patients [31]. All of these studies suggested that timely use CRRT might be an effective therapy in helping to clear the deadly cytokine storm in severe patients of COVID-19.

Other Therapies

Convalescent Plasma

Preliminary clinical studies in China have showed that early application of convalescent plasma in patients with COVID-19 is an effective approach and could accelerate the patients' clinical recovery [32]. However, van Griensven et al. [33] reported that transfusion of up to 500 ml of convalescent plasma with unknown levels of neutralizing antibodies to 84 patients with confirmed Ebola virus disease did not show significant improvement in survival. The reason for this discrepancy is still unclear. Now 2 trials (an open-label, non-randomized clinical trial [NCT04264858] and a multicenter, randomized, and parallel controlled trial [ChiCTR2000029757]) about the efficacy of convalescent plasma in patients with COVID-19 are ongoing in China.

Monoclonal antibody directed against the RBD domain of the S protein of MERS-CoV has been verified to be effective in vitro [34]. Although the monoclonal antibody against COVID-19 has not been developed, trastuzumab, as a monoclonal antibody against IL-6 receptor, achieved encouraging results in a preliminary clinical observation. The safety and effectiveness evaluation of trastuzumab is ongoing in multicenter randomized controlled trials (ChiCTR2000029765).

Glucocorticoids

Glucocorticoids are usually applied in severely ill patients with a viral infection. In the retrospective study in SARS-CoV, it was found that steroids could reduce the mortality and shorten the hospitalization time [35]. However, the use of steroids is still quite controversial due to its potential inhibition of virus clearance and prolongation of the duration of viremia.

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Conclusion

SARS, MERS, and COVID-19, as the 3 catastrophic contagious diseases caused by coronavirus in this century, pose great threats to public health and the safety of the world. AKI as a complication of COVID-19 could not only significantly increase the mortality rate of COVID-19 but also, in the long run, increase the risk of developing chronic kidney disease. It is therefore important to pay more attention to finding AKI in a timely manner and treat the patients properly when we are fighting COVID-19.

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Conflict of Interest Statement

The authors have no conflict of interests to disclose, and the results in this paper have not been published previously in whole or part.

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Author Contributions

Bi-Cheng Liu designed this study, Jing-Yi Qian carried out this study, Jing-Yi Qian and Bin Wang wrote the draft, and Bi-Cheng Liu revised this paper.

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