Acute kidney injury due to cytokine storm in patients with COVID-19 infection

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MINI REVIEW

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or COVID-19, nowadays, has stood in the center of attention and arisen a pandemic situation throughout the world. As it then cleared, the first transmission of COVID-19 occurred in seafood markets (1,2). Firstly, the pathogen reported in Dec 2019 in Wuhan, China, and then, spread rapidly in other countries. The COVID-19 related symptoms or even disease severity may be different interestingly in each person, however, the respiratory tract tends to be most affected. The cardinal manifestations of COVID-19 infection often mimic an influenza-like syndrome including fever, dyspnea, non-productive cough, and myalgia. Infection is more severe in the elderly group (3). Additionally, based on next further investigations in hospital settings it has illustrated that kidneys are also one of the main sites of disease invasion accompanying higher morbidity, therefore, it gains serious clinical attention (4).

ABSTRACT

Patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or COVID-19 represents usually a variety range of symptoms related to influenza-like syndrome and respiratory tract infections. Likewise, kidney involvement and acute kidney injury (AKI) were reported in many previous studies. Although a hypovolemic circulation would be the most common reason in patients with AKI, some strong proofs are suggesting a cytokine storm due to immune system exaggeration and inflammation-mediated tubular injury in COVID-19 infections. The inflammatory response in cytokine storm leads to the high release of cytokines mostly including TNFα, IL-1β, IL-6, INFγ, IL-2, IL-7, and endothelial mediators. The main culprits in the AKI and consequent organ failure are resident leukocytes in specific tissues, activated following the cytokine release, and systemic inflammatory response. AKI management and cytokine profile evaluation should be highly emphasized in patients with COVID-19 to prevent the progression of chronic kidney disease or permanent renal failure. Treatment options in COVID-19 regarding no specific drugs should be supportive and based on stabilizing the patients; however, combination therapy with different antiviral have shown promising outcomes. As a result, utilizing the anti-TNFα and anti-IL-1 agents should be noticed if indicated. Additionally, the hematopoietic stem cell transplantation is a curative approach.

Implication for health policy/practice/research/medical education:
We are willing to convey the fact that COVID-19 patients need to be more concerned about the renal system complications and acute kidney injury, in particular. Evidentially, it has been suggested that the severe inflammatory response triggered by COVID-19-mediated infection may have a crucial role in tissue damage in kidney and renal failure development. Hence, the lethal renal complications should be minded, especially in elderly who met the COVID-19 infection.

and Web of Science to collect current data about our title. The search was conducted using various keywords or their equivalents: COVID-19, angiotensin-converting enzyme 2 receptor, acute kidney injury, cytokine storm, cytokines, end-stage renal disease, hyperinflammatory syndrome and hemophagocytic lymphohistiocytosis.

**Kidney as a site of involvement in COVID-19**

Following further molecular and physiological exploration about the manner that the COVID-19 virus could adhere and invade to the cells, a body of evidence suggests ACE2 (angiotensin-converting enzyme 2) receptors which are located in the lungs and kidneys act as the main bridging of virus entrance. ACE2 receptors not only mediate the COVID-19 receptors binding but also help the other respiratory viruses to enter into the cell, evidentially. ACE2 receptors have been demonstrated to contribute the angiotensin I conversion to angiotensin II and have a crucial role in hemostasis maintenance. As a result, we can see the kidney involvement trace in COVID-19 infection (5–7). An observational clinical study in China on COVID-19 patients suggested evidence of kidney involvement by referring to laboratory findings including proteinuria, hematuria, high serum creatinine, and azotemia-associated acute kidney injury (AKI) (8). Concerning acute kidney failure, although the patient may not be diagnosed with AKI in the early stages of admission, a fraction of those will disclose the clinical and laboratory evidence of an overt AKI. COVID-19-related AKI has a remarkable tendency around five times to progress to end-stage renal disease (ESRD) and death. Besides, previous studies have demonstrated the occurrence of acute renal dysfunction, AKI, and high mortality rate even ranges between 60%-90% in other members of Coronaviruses family such as SARS-CoV and MERS-CoV which bold the importance of the exact renal management in these patients (9,10).

**Clinical and laboratory findings in COVID-19-associated AKI**

There is a clinical turning point around a week after admission which patients may experience symptoms more exaggerated. Paraclinical findings suggest a considerable increase in IL-6, ferritin, and C-reactive protein representing an ongoing inflammatory process that can lead to sepsis and consequent multi-organ damages such as kidney failure (11). There is a broad controversy about the exact mechanism of AKI in COVID-19; However, it seems that an underlying occult viral sepsis can develop a cytokine storm and progresses to kidney injury (12).

**Cytokine storm and AKI in COVID-19**

Cytokine storm is introduced as a category of potentially lethal hyperinflammatory syndromes that promote a hemophagocytosis reaction. Secondary hemophagocytic lymphohistiocytosis (sHLH) includes as a subtype of cytokine storm which is characterized by non-remitting fever, hyperferritinemia, cytopenia, organomegaly and hypertriglyceridemia (13). A common form of sHLH is a virus-associated hemophagocytic syndrome which introduced by Risdall in 1979. Viral pathogens like herpes viruses and Epstein–Barr virus particularly are the most commonly associated with infection-induced sHLH. However, bacterial, fungal, and parasitic pathogens may have a role in this phenomenon (14). Infrequently, the influenza virus could have a role in developing sHLH in children (15). A severe cytokine release syndrome like what have seen in HLH can develop AKI in patients (16). Moreover, there is a strong link between HLH and organ failure, including kidney failure. AKI is the most common consequence of HLH, for a variety of reasons. The most common mechanism described for AKI is an increase in capillary permeability and pre-renal azotemia. Surprisingly, patients with HLH have normal hemodynamics while there is severe tubular damage pathologically due to the infiltration of leukocytes. During AKI, the tubular component is more affected than the glomerular one, yet glomerular dysfunction can occur rarely followed by the destruction of podocytes structures by TNFa. After binding to receptors, TNFa mediates the accumulation of granulocytes and resident lymphocytes in the tissue, then activating apoptotic signaling kinase-1 (ASK1) in tubular cells, and eventually tissue injury (17–19).

**Pathogenesis of kidney failure due to cytokine storm**

The detrimental inflammatory response in cytokine storm may develop the organ dysfunction which usually progresses in the early and late phases. Both the pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, INFγ, IL-2, IL-7, granulocyte colony-stimulating factor, monocyte chemoattractant protein 1 and macrophage inflammatory protein 1-α, and also inhibitory cytokines (IL-10) are found in cytokine storm (20,21). After the onset of a cytokine storm, almost always excessive pro-inflammatory factors release from leukocytes which boost the activation of endothelial vascular cells. Endothelial cells lining the vascular bed in vital organs produce free mediators including endothelial leukocyte adhesion molecule 1/vascular cell adhesion molecule 1. These released mediators of endothelial cells, in turn, activate neutrophils, macrophages, and other types of leukocytes to adhere and help them to pass through the vascular wall called diapedesis and initiate the production of secondary inflammatory mediators such as prostaglandins and proteases to expand the tissue damage. Finally, in the advanced stage of undiagnosed cytokine storm that
can be significantly lethal, the circulating inflammatory mediators particularly reactive oxygen species and T cell cytokines arouse a systemic inflammatory response, pass within the bloodstream, and activate the resident innate leukocytes including CD8+ T cell and NK cells in specific organ tissues which are the main culprits for specific organ failure (22) (Figure 1).

Treatment
AKI advancement and the permanent sequelae leading to chronic kidney disease are more common in ICU-hospitalized COVID-19 subjects. Hence, as mentioned earlier, the kidneys function needs to be paid more attention clinically (10). Of all involved cytokines, IL-6 and TNFα are more likely to have a certain role in promoting the symptoms of cytokine storm. Therefore in a clinical view, the hyperinflammatory reactions due to cytokine storm or related causes have addressed with TNFα inhibitors and anti-IL-6 receptor antibodies (20,23,24). Additionally, one of the most helpful therapeutic strategies to harness the cytokines uprising is CD8+ T cell-derived INFγ inhibition and IL-1β antagonists (25). Steroid (dexamethasone) and topoisomerase 2 inhibitor (etoposide) combination therapy can be a treatment approach according to previous researches. After the T cell silence, the patient is a candidate to receive the certain curative hematopoietic stem cell transplantation (26–28). Promising therapeutic response of familial HLH to ruxolitinib as a JAK1/2 inhibitor which reported by Maschalidi et al (29) and Das et al (30) may be considered for clinical perspectives by prohibiting T cell signaling pathways. Secondary hemophagocytic lymphohistiocytosis either occurs in viral infection or 3.7%-4.3% of sepsis cases (21). Besides the right management of cytokines profile and inflammatory indices, patients with COVID-19 infection usually need to receive respiratory care conventionally. Additionally, if needed, kidney replacement therapy should be considered for a patient with AKI or impendent kidney failure due to the cytokine storm. No specific vaccine or drug has been developed for this disease so far, and further trials continue. In addition to antiviral treatments including antiretroviral agents like lopinavir and ritonavir, nucleoside analog drugs like remdesivir have been shown to be effective as an anti-rheumatoid drug (31,32).

Conclusion
The impact of COVID-19 infection on the renal system needs to be considered, particularly in the elderly which represent the kidney impairment signs more severe. AKI in the context of tubular injury taught to be caused by a systemic inflammatory response; therefore, besides the supportive management and oxygen regulation, anti-inflammatory agents such as anti-TNFα, anti-IL-1, and anti-IL-6 should be administrated if necessary.

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Authors’ contribution
AHD, SE and HB were the principal investigators of the study. AHD and SE were included in preparing the concept and design. All of researchers 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.

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