

Thematic Opinion

Acute kidney injury associated with COVID-19: understanding its underlying mechanism

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Abstract: World Health Organization (WHO) has declared coronavirus disease 2019 (COVID-19) outbreak as a global emergency. Kidney involvement is commonly seen in COVID-19 patients with clinical findings ranging from mild proteinuria to acute kidney injury (AKI) in hospitalized patients. In this viewpoint, I would like to discuss about various mechanism contributing to AKI such as, entry of novel coronavirus into host cell, cytokine storm that destroy kidney tissues, increased blood clotting that clogs kidney, and probable direct infection of the kidney.

Keywords: acute kidney injury (AKI); COVID-19; cytokine storm; hypercoagulation

सारांश: हाल विश्वभरी फैलिरहेका नयाँ कोरोना भाइरसको संक्रमणबाट लागेको रोगलाई विश्व स्वास्थ्य संगठनले कोभिड १९ को नाम दिएको छ र यसलाई विश्वव्यापी महामारीको रूपमा घोषणा गरिसकिएको छ । यस भाइरसले सामान्य रुघाखोकी देखि गम्भीर प्रकारको रोग सम्म गराउन सक्दछ । मृगौलाको समस्या सामान्यतया अस्पतालमा भर्ना भएका कोभिड १९ का गम्भीर बिरामीहरूमा देखिन्छन् जसमा बिरामीको पेशाबमा प्रोटीन देखि तीव्र मृगौला क्षति (acute kidney injury) सम्म हुन सक्छ। यस दृष्टिकोणमा, म तीव्र मृगौला क्षति गराउने विभिन्न कारणहरू जस्तै, होस्ट सेलमा कोरोनाभाइरसको प्रवेश, किडनीको ऊतकहरूलाई नष्ट गर्ने साइटोकाइन (cytokine) आँधी, मृगौला अवरुद्ध हुने रगतको थक्का बढ्ने, र मृगौलाको सम्भावित प्रत्यक्ष संक्रमणको बारेमा स्पष्ट विचार राख्न चाहन्छु ।

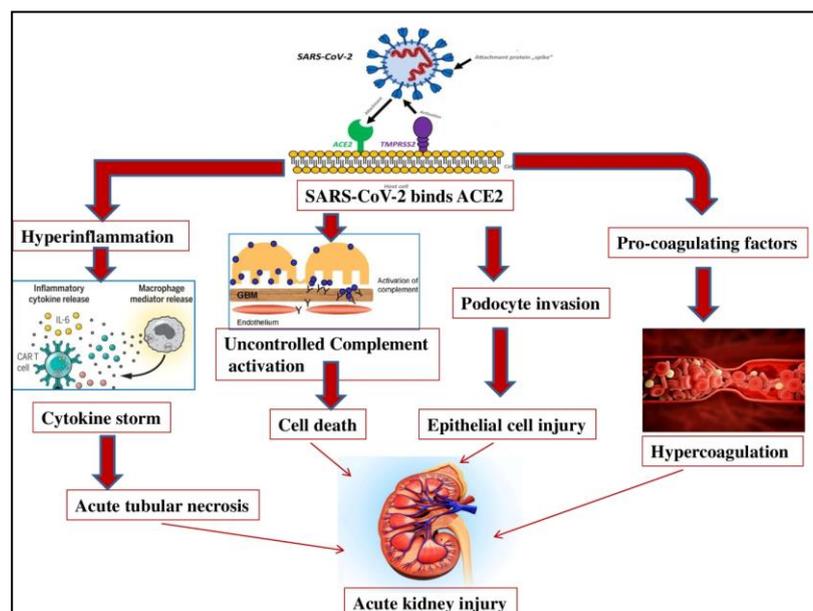


Figure 1. Progression of Acute kidney injury (AKI) in COVID-19

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic is now considered as the global health crisis caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a pathogen responsible for atypical pneumonia that has affected more than 6.6 million people and caused death of more than 390,000 patients (as of June 06, WHO Report 2020, Fanelli 2020). Initially it was known to damage the lungs but, as more people become infected, more understanding of the disease emerges. COVID-19 can also cause severe and lasting harm in other organs, including the heart and kidneys which sometimes leads to death (Ronco 2020). Kidney involvement is commonly seen in COVID-19 patients with clinical findings like mild proteinuria in hospitalized patients, while acute kidney injury (AKI) normally develops at advance stages in critically ill patients and is recognised as a marker of multiple organ failure and disease severity (Cheng 2020). In this Viewpoint, I would like to discuss about various mechanism involved in renal disturbances by COVID-19 infection that are thought to contribute to AKI. The underlying mechanism included SARS-CoV-2 entry into the host cells via ACE2 (angiotensin converting enzyme II) receptors, kidney tubular injury with septic shock, microinflammation by cytokine storm syndrome, increased blood clotting, virus-induced specific immunological effector mechanisms, dehydration, and probable direct infection of the kidney (Valizadeh 2020, Li 2003).

2. Incidence of AKI in COVID-19

The published incidence of COVID-19 induced AKI is highly variable to date. Initial reports from Wuhan, China found only 0.5% of hospitalized patients with confirmed COVID-19 had AKI (Guan 2020), but later on, so many people were affected by this infectious SARS-CoV-2 providing more space to the researchers for their studies. A prospective cohort study of 701 patients with COVID-19 admitted in a tertiary teaching hospital, Wuhan confirmed the 5.1% occurrence of AKI (Cheng 2020). Another study from China showed a 27% incidence of AKI in COVID-19 positive patients (n=85), as defined by a 30% decrease in glomerular filtration rate (Diao 2020). United States data of 5449 patients hospitalized with COVID-19 between March 1, and April 5, 2020, at 13 academic and community hospitals in metropolitan New York has found the 36.6% rate of AKI (Hirsch 2020). Thus, incidence rate of AKI in COVID-19 have now increased in hospitalized patients.

3. COVID-19 entry into kidney epithelial cells via ACE2

To gain entry into host cells, the coronavirus spike (S) glycoproteins that is present on the outer

membrane of the SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) and is activated by transmembrane serine proteases. ACE2 expression in kidney and various parts of gastrointestinal tract like duodenum and small intestine is nearly 100-fold more than that in respiratory organs (lung). SARS-CoV-2 enters apical membrane of kidney tubule by invading podocytes. As a result, the kidney cells are targeted and infected by the coronavirus leading to disruption of whole body fluid, acid-base, and electrolyte homeostasis. Moreover, kidney epithelial cells injury by SARS-CoV-2 also disrupts kidney endocrine production of erythropoietin hormone and vitamin D and impairs blood pressure regulation (Cheng 2020, Valizadeh 2020, Rabb 2020).

4. COVID-19 and cytokine storm syndrome

The dysregulated immune response (hyperinflammation) due to the SARS-CoV-2 can lead to cytokine storm. Cytokine overproduction is involved in lung-kidney bidirectional damage. Cytokines are small signalling proteins that mediate and regulate immune response, inflammation and have specific effect on the interactions between cells. In trying to kill the invading virus, this inflammatory reaction can destroy healthy tissue, including that of the kidneys. Pro-inflammatory interleukins-6 (IL-6) and tumor necrosis factor α (TNF- α) are considered to be the most important causative cytokine in cytokine storm syndrome. These virus-induced cytokines or mediators might also exert indirect effects on renal tissue, such as hypoxia, shock, and rhabdomyolysis (Valizadeh 2020, Ronco 2020, Wu 2020).

5. COVID-19 and dysregulation of complement pathway

Coronavirus-induced glomerulopathy in the family of coronavirus was reported to be low, however deposition of immune complexes of viral antigen or virus-induced specific immunological effector mechanisms (specific T-cell lymphocyte or antibody) may damage the kidney. The complement system is the host immune system's first response to pathogens. SARS-CoV-2 may bind directly to ACE2 expressed on kidney cells, cause cell injury and activate the inflammatory response and the complement cascade locally. This uncontrolled complement activation may contribute to AKI (Chen 2020, Batlle 2020, Noris 2020).

6. COVID-19 and hypercoagulation

In advance stage of SARS-CoV-2 infection, hyperinflammation can cause derangement of hemostasis in patients with sepsis. COVID-19-associated acute disseminated intravascular

coagulation (DIC), decreased platelet count, prolonged prothrombin time, increased D-dimer, low fibrinogen, release of tissue factor and activation of coagulation factors leads to hypercoagulability. Inflammation-induced erythrocyte aggregation and heme-mediated pathology may worsen oxidative stress, inflammation, and complement activation, to aggravate microvascular injury (Batlle 2020, Panigada 2020, Frimat 2013).

7. Conclusions and future directions

The prevalence of kidney disease is 10.6% in Nepal. In this low-income country, poverty and lower socioeconomic status have been specifically identified as independent risks for both kidney disease incidence and rapid progression of such disease. Hemodialysis or renal transplant is needed in advance stage of kidney disease (Singh 2016). People on hemodialysis have weaker immune systems, making it more susceptible to COVID-19 infection. Furthermore, kidney transplant need to take immunosuppressive medicines which work by keeping the immune system less active, thus more prone to infections. In Nepal, we have very few hospitalized COVID-19 cases. Majority of the coronavirus infected patients are asymptomatic. As per the situation update report of 05 June 2020 published by Ministry of Health and Population (MoHP), there was total 2912 COVID-19 confirmed cases, out of which only 11 (0.38%) deaths were reported (MoHP 2020) which indicates low mortality rate in Nepal due to COVID-19 as compared to other countries in the world. It is very difficult to explore AKI incidence in the present context when the hospitalized data are inadequate. Therefore, by increasing the number of tests we can find out more cases to improve our understanding about AKI secondary to COVID-19 and also about its complex mechanism.

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