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REVIEW ARTICLE

Acute Kidney Injury in COVID-19: a Brief Review

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Abstract
The contemporary evolution of the coronavirus disease 2019 (COVID-19) outbreak from the Wuhan, China, with a high rate of transmission will act the global medical emergency with immense morbidity and mortality rate across the world. The cell entry of COVID-19 via angiotensin-converting enzyme 2 receptor (ACE-2 receptor) will damage the respiratory system by the cytopathic effect induced by replication of the virus genome in the host and respond respiratory failure with an elevation of cytokine factor-like interleukin (IL) IL-6, IL-8, tumor necrosis factor-alpha (TNF-alpha), etc. However, the lung-kidney cross talk will evidence the activation of molecular mechanisms from pro-inflammatory cytokines and concerned with kidney damage, though the elevated rate of ACE-2 receptor in the kidney will enhance the possibility of mortality with consideration of acute kidney injury. This review provides relevant information which suggests the rate of mortality in COVID-19 patient associated with acute kidney injury (AKI) which lacks critical monitoring of kidney function with a clinical consideration of intervention to avoid kidney damage in the initial stage of the disease.

Keywords COVID-19 · ACE-2 receptor · Acute kidney injury · Cytokines

Introduction

The novel coronavirus 2019 (COVID-19) resembled with the severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak from the Wuhan, Hubei province, China. This virus belongs to the Coronaviridae family associated with acute respiratory syndrome. In the past years, the epidemic caused by COVID-19 family members was severe acute respiratory syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS), whereas in March 2020, the WHO characterizes COVID-19 as a pandemic with the highest morbidity and mortality rate across the world. COVID-19 primarily targets the respiratory system with a clinical outcome of shortening in a breath.

The genome of SARS-CoV and COVID-19 identical to each other depends on the open reading frame of replication which is about 94.4% similar [1]. However, the S gene encodes spike protein for attachment with ACE-2 receptor of targeted cells having receptor function against the rennin-angiotensin system, whereas TMPRSS2 protease which priming the S protein and induces viral and cellular membrane fusion [2]. The pathological alteration in targeted organs was associated with systemic respiratory failure mediated by replication of the viral genome and destructive immune response.

The changes related to SARS-CoV does not confine to the respiratory system, pervasive to organs identified by the murine monoclonal antibody for SARS-CoV and probe designed for SARS-CoV RNA, which detected SARS-CoV in the lung, stomach, small intestine, distal convoluted renal tubule, etc. [3]. Moreover, the study of 54 patients affected by COVID-19 classify in critical and severe type patients, results as kidney will be the most affected organ after heart and majorly found in critical type patients [4]. However, the conflicting data that defines the lung injury is susceptible to kidney function. In this review, we are focusing on the pathophysiology of COVID-19 that induces lung injury and its effect on the kidney associated with the rate of mortality induced by acute kidney injury.

COVID-19 Induced Lung Injury and Impaired Kidney Function

The ACE-2 receptor is a primary site of interaction for COVID-19. The localization of ACE-2 in macrophages, type

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II alveolar cells, and tracheal cells of the lung [5] induces the access of viral genome in cells. In addition, further experimental studies depict the knockout of the ACE-2 receptor in mice model to reduce the replication of the COVID-19 viral genome [6]. This experimental fact illustrates that ACE-2 is a primary requirement for the entry of the viral genome. However, contradiction among the primary receptor arises with the identification of secondary receptor CD209L identified in a Chinese culture hamster ovary [7]. After COVID-19 infection, the hyperinflammatory response was initiated and associated with an elevation in serum cytokine and inflammatory markers such as ferritin, D-dimer, and C-reactive protein. Moreover, the profiling of cytokines in COVID-19 patients represents an elevation in TNF, cytokines (IL-6, IL-7, and IL-2), and chemokines. Thus, the histology of lung biopsy sample illustrates bilateral diffuse alveolar damage with cellular fibromyxoid and formation of a hyaline membrane which indicates acute respiratory distress syndrome [8].

The lung damage caused by pneumonia and related disorder COVID-19 were associated with the multiple organ failure majorly coupled with cardio-renal malfunction, although the baseline functioning of organs depends on oxygen metabolism. The renal function associated with an exchange of PO2 and PCo2, thus fluid retention dependent on the functioning of lungs, the reduction in oxygen tension from 54 mmHg to 30 mmHg depicts the alleviation in diuresis with a significant decline in Glomerular filtration rate (GFR) and renal plasma flow (RPF) throughout the hypoxia, created by lung dysfunctioning [9].

Meanwhile, impairment of pulmonary function due to COVID-19 causes the acute hypercapnic acidosis which affects the renal function by increasing glomerular filtration rate (GFR) with a change in concentration of tubular fluid through excretion of urinary sodium and results in elevation of plasma renin by effecting renin-angiotensin system with controversy on impairment of renal function [10]. In a study by Bratel et al. [11] which concluded that long term lung dysfunction induced hypercapnia responsible for the failure of renal function by alleviating GFR.

The lung injury of COVID-19 patient classically was associated with acute respiratory distress syndrome (ARDS) which requires a ventilator for breathing. However, natural breathing creates negative pressure in the lung to pursue breathing. But ventilators create artificial positive pressure and affect the intrathoracic pressure which decreases the cardiac output and decreases the GFR. Moreover, lung injury induces a cytokine-mediated response, similar to COVID-19 induce cytokine, which generates pro-inflammatory markers such as TNF-alpha, IL-6, IL-8, and IL-beta and affects the renal function that induces AKI [12].

Association of AKI with COVID-19 and Lung Injury

The AKI patients effected with COVID-19 having a high rate of mortality which depicts the function of the kidney is directly proportional to lung function, as an outcome it enhances the rate of lung damage. The relationship between the kidney and lung characterizes the electrolyte balance and regulates the acid-base balance responsible for the transfer of oxygen to the tissue. The co-relation among oxygen transfer in the tissue illustrates that the kidney is directly dependent on the function of cardiac output and lung function. In addition, production of erythropoietin regulates the oxygen-carrying capacity in the body. Though, clinical studies verify disturbance in nitrogenous waste affected by AKI gives a negative clinical outcome by alleviate the rate of monoxide diffusion interpret the marker of pulmonary function [13].

Moreover, AKI curbs the respiratory system by pulmonary edema which might be cardiogenic. The cardiogenic pulmonary edema arises from the damaged cardiac function. The hydrostatic force and oncotic force are responsible for steady fluid flow inside the capillary lumen, whereas impaired cardiac response elevates the hydrostatic, and oncotic force leads to the invasion of fluid from capillary to alveolar site. The normal kidney function inhibits the process by dieresis [14, 15]. Meanwhile, normal kidney function regulates the acid-base firmness by establishing equilibrium among bicarbonate, carbonic acid, and carbon dioxide. Fluctuation in the pH of oxygenated blood initiates the deviation of equilibrium which is critical to lung function. Thus, reabsorption of bicarbonate by kidney controls the deviation of equilibrium en route to acidosis and similar to alkalosis.

AKI patients upregulate the expression of cytokine which induce the lung damage, the data from animal and patient studies suggest that the IL-6 associated with CXCL1 chemokine induce lung injury in AKI by increasing the endothelial CXCL1 production and promotes the neutrophil accretion by upregulation of IL-8 through IL-6 receptor using gp130 on the endothelial cell of the lungs [16]. Although, certain inflammatory mediators identified with their mode of mechanism which induces lung injury see Table 1. In addition, 66 genes were identified in the ischemic mouse model which liable for apoptosis, out of them 6 stands for tumor necrosis factor receptor and lead to AKI mediate pulmonary apoptosis. Thus, cas-3 mediated apoptotic pathway induces lung injury that takes place at endothelial cells [17]. This evidence represents that the survival analysis of kidney dysfunction patients with COVID-19 had a 5-fold higher mortality risk [18] and AKI brings out the distant organ injury like lung damage [19].

COVID-19 and Effect on Kidney

The ACE-2 responsible for rennin angiotensin regulation depends on the conversion of angiotensin II into angi(1–7) and interacts with the Mas receptor. ACE-2 is a homolog of ACE (AT1R) receptors. Moreover, during the development of

Table 1 AKI induced cytokine and their mechanism on lung injury

S. No.	AKI induced cytokines	Mode of action on the lungs
1	NFκB	Responsible for programmed cell death in lung tissue, ensuing lung inflammation [20, 21]
2	TNFR1-induced and caspase-3 mediated apoptosis	TNF act as a ligand for TNFR1 receptor at endothelial cells of lungs which initiate the cascade of signaling and induce cas-3 mediated apoptosis [21, 22]
3	IL-6	Serum IL-6 initiates the cascade of signaling responsible for lung damage by the interdependence of IL-8 and IL-6 receptor in the endothelial cells [23]
4	T cells	AKI commences T cell migration at the respiratory site and initiates the cas-3 mediated apoptosis which affects the endothelial cell of lung [24]
5	TLR4 and HMGB1	HMGB1 is a nuclear protein that binds with the TLR4 receptor and initiates the accumulation of neutrophils in alveolar space [25]
6	IL-8	Activated by IL-6 mediated gp130, responsible for the accumulation of neutrophil and inflammation in the lung [26]

NFκB nuclear factor kappa B, *TNF1* tumor necrosis factor receptor 1, *IL* interleukin, *AKI* acute kidney injury, *TLR4* Toll-like receptor 4, *HMGB1* high mobility group box 1, *gp130* glycoprotein 130

kidney, the expression of ACE-2 upregulated [27] and promote sodium and water excretion. Thus, ACE-2 is not solely curbed to the COVID-19 primary targeting site. However, deviation in developmental renin angiotensin system (RAS) is associated with the downregulation of ACE-2 in tubule due to hypertension [28]**.** The localization of ACE-2 was found within the vascular tunica media layer, whereas ACE was found in the endothelial layer. A study suggests that the administration ACE blocker given for cases with comorbidities such as hypertension results in overexpression of ACE-2 in renal arterioles and a decrease in ACE/ACE-2 ratio marked by mRNA data [29]**.** Although, the clinical data from the study shows that throughout the initial phase of viral infection, patients having signs of kidney dysfunction identified which show 59%(Proteinuria), 44%(hematuria), 14% (Upregulation of urea) and 10% increased level of creatinine. In the later phase of infection, it turns into worst with the reducing level of albumin in COVID-19 patients [18]. Hence, the abundance of renal ACE-2 receptor can be liable for COVID-19 induced kidney dysfunction due to maximum exposure.

In addition, MERS-CoV belongs to a family of coronavirus and associated with kidney dysfunction. The replication of viral genome in the host significantly altered the expression of genes. Thus, the upregulation of Smad7 and FGF2 (fibroblast growth factor 2) induces cas-3 mediated apoptosis and result in kidney dysfunction with lung injury [29]. Furthermore, in another study, the overexpression of Smad7 by adenoviral in primary cultured rat mesangial cells depicts the cas-3 mediated apoptosis followed by TGF-β [30]. Moreover, COVID-19 induces tubular pathogenesis by CD68+ macrophage and C5b-9 complement which directly infects the human kidney [31]. This evidence suggests that COVID-19 can induce smad7 mediated cas-3 apoptosis and affect the GFR which results in kidney dysfunction.

Conclusion

Patients with COVID-19 with acute kidney injury exhibit the lung as the primary site of involvement which subsequently leads to kidney-lung cross talk. The COVID-19 angiotensin-converting enzyme-2 receptor not solely presents in the respiratory system, although expression of angiotensin-converting enzyme 2 receptor elevated in the kidney; thus, it represents renal tubular damage. Therefore, mortality rate is slightly higher in COVID-19 patients associated with acute kidney injury and defines a negative marker for survival. In addition, proteinuria, hematuria, as well as blood urea nitrogen and creatinine are considered for the extant of kidney activity in COVID-19 patients. The emphasis should be on very close observation of kidney functions with the involvement of potential cytokine inhibitor to evade the enforcement of inflammatory cytokine from lung damage to alleviate the mortality of COVID-19–associated acute kidney injury patients.

Data Availability Not Applicable.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethics Approval Not required, the manuscript does not contain clinical study or patient data.

Consent to Participate Not applicable, the review article does not contain any patient data.

Consent for Publication The authors transfer to Springer the non-exclusive publication rights, and they warrant that their contribution is original.

Code Availability Not Applicable.

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