

Review

Inflammatory stress in SARS-COV-2 associated Acute Kidney Injury

Junzhe Chen^{1,2}, Wenbiao Wang^{1,3}, Ying Tang², Xiao-ru Huang^{1,4}, Xueqing Yu⁴, Hui-Yao Lan^{1,5}✉

1. Departments of Medicine & Therapeutics, Li Ka Shing Institute of Health Sciences, and Lui Che Woo Institute of Innovative Medicine, The Chinese University of Hong Kong, Hong Kong, China.
2. Department of Nephrology, The Third Affiliated hospital, Southern Medical university, Guangzhou, China.
3. Guangdong Key Laboratory of Virology, Institute of Medical Microbiology, Jinan University, Guangzhou, China.
4. Guangdong-Hong Kong Joint Laboratory for Immunity and Genetics of Chronic Kidney Disease, Guangdong Academy of Medical Science, Guangdong Provincial People's Hospital, Guangzhou, China.
5. Guangdong-Hong Kong Joint Laboratory for Immunity and Genetics of Chronic Kidney Disease, The Chinese University of Hong Kong, Hong Kong, China.

✉ Corresponding author: Hui-Yao Lan, Departments of Medicine & Therapeutics, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, China. E-mail: hylan@cuhk.edu.hk.

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Abstract

Increasing clinical evidence shows that acute kidney injury (AKI) is a common and severe complication in critically ill COVID-19 patients. The older age, the severity of COVID-19 infection, the ethnicity, and the history of smoking, diabetes, hypertension, and cardiovascular disease are the risk factor for AKI in COVID-19 patients. Of them, inflammation may be a key player in the pathogenesis of AKI in patients with COVID-19. It is highly possible that SARS-COV-2 infection may trigger the activation of multiple inflammatory pathways including angiotensin II, cytokine storm such as interleukin-6 (IL-6), C-reactive protein (CRP), TGF- β signaling, complement activation, and lung-kidney crosstalk to cause AKI. Thus, treatments by targeting these inflammatory molecules and pathways with a monoclonal antibody against IL-6 (Tocilizumab), C3 inhibitor AMY-101, anti-C5 antibody, anti-TGF- β OT-101, and the use of CRRT in critically ill patients may represent as novel and specific therapies for AKI in COVID-19 patients.

Key words: COVID-19; AKI; cytokines; inflammation; mechanisms

Introduction

COVID-19 is a progressive viral pneumonia with a broad spectrum of clinical manifestations, ranging from asymptomatic to mild (80%), severe (10-15%) or critical and death (2-5%) [1, 2]. Among critically ill COVID-19 patients, acute respiratory distress syndrome (ARDS) and multiorgan failure including acute kidney injury (AKI) are the most common co-morbidities [3-5]. In this review article, we are focusing on SARS-CoV-2-associated AKI. The possible mechanisms and pathways related to SARS-CoV-2-associated AKI are discussed.

Epidemiology of AKI in COVID-19 patients

Increasing evidence shows that there is high prevalence of AKI in COVID-19 patients [6, 7]. The manifestations of AKI are diverse, from proteinuria,

hematuria, elevated serum creatinine (Scr) or blood urea nitrogen (BUN) levels to acute renal failure. A meta-analysis shows that more than half (57%) of COVID-19 patients develop proteinuria, accompanied by elevated serum levels of Scr (9.6%-15.5%) and BUN (13.7-14.1%) [5, 6]. The CT scan also shows renal inflammation and edema [8]. Pathologically, diffuse proximal tubule injury with loss of brush border and frank necrosis is found in COVID-19 patients with AKI [9, 10].

Compared to patients with Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) in which the incidence of AKI is 6.7% and 42% respectively [11, 12]. The incidence of AKI in COVID-19 patients is highly variable. In the early reports from China, COVID-19 patients with AKI was rare [13, 14], but increased to

10% in a later study [15], and became more severe with the incident rate of 25%-29% in those admitted to ICU [16, 17]. The large cohort studies in the western countries revealed that the incidence of AKI was 27%-37% [18, 19] and became more severe (68%) in critically ill COVID-19 patients who were admitted to ICU in the New York city [20]. Nevertheless, it is now clear that the incidence of AKI in COVID-19 patients is associated with the age, smoking, the cytokine storm, the severity of disease, the ethnicity, and the history of diabetes, hypertension, and cardiovascular disease [7]. Thus, AKI is an independent risk factor for the poor long-term renal outcome and mortality in critically ill COVID-19 patients [21, 22]. During the follow-up study, AKI is a major cause of in-hospital mortality. In addition, the complete kidney recovery rate of AKI in COVID-19 infection is only about 30-45% based on the recent reports [15, 20, 23]. Thus, AKI is one of severe complications and mortality of in-hospital COVID-19 patients, however, mechanisms of COVID-19-associated AKI remain largely unclear and need further studies.

Inflammation may be a mechanism of AKI in COVID-19 patients

Multiple factors such as direct virus infection, cytokine storm, hypoxia, sepsis shock, hemodynamic instability and rhabdomyolysis, hypertension, and diabetes may be associated with AKI in COVID-19 patients. Of these factors, inflammation stress may be a mechanism of AKI in COVID-19 patients, which is discussed below.

Angiotensin II (Ang II) and hypertensive stress

Kidney is a target organ of SARS-COV-2 virus infection due to the high expression levels of angiotensin-converting enzyme 2 (ACE2), a receptor for SARS-COV-2 virus [24], in the kidney tissues, particularly in renal tubular epithelial cells (TECs) [25-27]. Thus, SARS-COV-2 may be able to directly bind to ACE2 and infect kidney cells, which is supported by high levels of SARS-COV-2 spike (S) and nucleoprotein (N protein) in COVID-19 patients with AKI [9, 10, 28]. In the kidney, renin-angiotensin-aldosterone system (RAAS) maintains renal hemodynamic and regulates renal sodium transport in both normal physiological states and pathological conditions. Ang II and Ang 1-7 are the two major effectors of RAAS and are tightly controlled by two major enzymes of ACE and ACE2 [29]. Ang II acts via its receptor-1 (AT1) to mediate renal inflammation and fibrosis by activating NF- κ B and Smad signaling crosstalk pathways, whereas Ang 1-7 binds receptor Mas to counter-regulate these pathological effects of Ang II [29]. The primary

function of ACE2 is to covert Ang II to Ang 1-7 to exert its anti-inflammatory, vasodilatory and natriuretic properties [30] (**Figure 1**). After binding to ACE2, SARS-COV-2 significantly downregulates ACE2 expression [31, 32], resulting in a inhibition or loss of Ang 1-7 while enhancing Ang II-AT1-dependent renal inflammation, vasoconstriction, thrombosis and anti-diuresis effects [33] (**Figure 1**). It has been well documented that Ang II is a key mediator of AKI [34-36], whereas, the ACE2-Ang-1-7-Mas axis is renoprotective [37]. Thus, SARS-COV-2 viral infection to the kidney may downregulate ACE2-Ang1-7-Mas signaling while promoting the Ang II-AT1 signaling to mediate renal inflammation and AKI. A similar mechanism is also found in patients with ARDS [38]. Thus, the interaction between SARS-COV-2 virus and ACE2 may eventually impair the ACE2-Ang 1-7 while enhancing Ang II signaling, resulting in hypertension and inflammatory stress both systemically and locally in the kidney. This may well explain that hypertension is an independent risk factor in COVID-19 patients [39]. However, the role of Ang II signaling in COVID-19 patients with progressive renal injury remains yet to be determined.

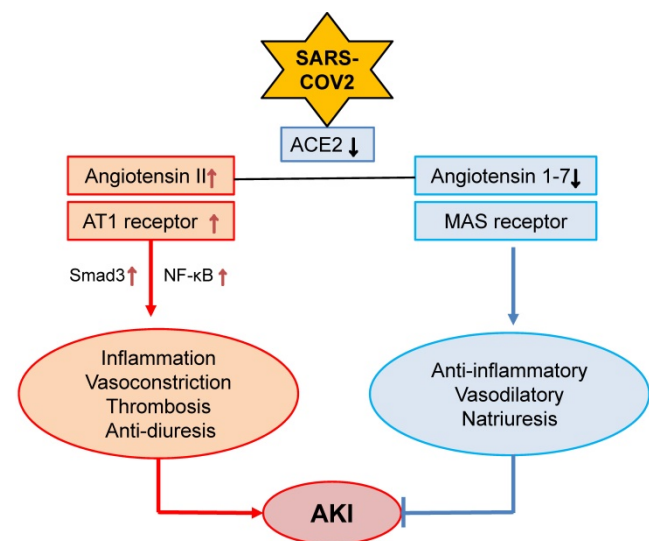


Figure 1. Alterations of Ang II and Ang 1-7 signaling in COVID-19 associated AKI. SARS-COV-2 binds and downregulates ACE2, which may result in downregulation of Ang 1-7 while upregulating Ang II-AT signaling to promote AKI.

Diabetes and metabolic stress

Diabetes is also a risk factor for AKI [40]. Patients with diabetes are associated with the severity and death in pandemic influenza (H1N1) [41], SARS-COV [42] and MERS-COV [43]. Recent studies also reported that COVID-19 patients with diabetes have higher AKI and mortality rate than those with non-diabetes [14, 44]. This is also confirmed in a recent meta-analysis in 5497 COVID-19 patients [45].

It is now well accepted that metabolic stress including hyperglycemia, obesity, insulin resistance and high levels of glycosylation end products (AGEs) in patients with diabetes can trigger the production of pro-inflammatory cytokines and promotes the oxidative stress [46]. Hyperglycemia is a risk factor for AKI in patients with diabetes [21]. The I κ B kinase- β (IKK β)/NF- κ B axis is a key inflammatory pathway in diabetes in response to hyperglycemia and insulin resistance [47]. AGEs can also induce activation of NF- κ B, resulting in production of pro-inflammatory cytokines [48]. By comparing with non-diabetic COVID-19 patients, COVID-19 patients with diabetes have significantly higher levels of IL-6 and CRP [49]. In addition, patients with diabetes also develop hypertension, which is associated with activation of Ang II-AT1 while inhibiting ACE2-Ang 1-7 signaling [50]. In addition, since ACE2 is also expressed in pancreas, infection of SARS-COV-2 may also damage pancreatic islet β -cells and aggravate hyperglycemia [51]. Thus, enhanced metabolic inflammation in the diabetic kidney may be another mechanism contributing to the development of AKI in COVID-19 patients. However, mechanisms responsible for the metabolic stress in AKI after COVID-19 infection remain yet to be explored.

Cytokine storm

Inflammatory cytokines has been recognized as a critical factor in the progression of COVID-19 [52, 53]. The inflammatory response triggered by SARS-COV, MERS-COV or SARS-COV-2 can recruit and activate monocytes, macrophage and dendritic cells to produce inflammatory cytokines [54, 55], which may be essential in controlling the viral replication and cleaning the infected cells [56]. However, overactive immune responses may cause excessive and persistent cytokine production that leads to cytokine storm and results in multiple organ dysfunction as seen in patients with severe SARS [57], MERS [58] and COVID-19 infection [59]. In these patients, a number of proinflammatory cytokines such as interleukin (IL)-1 β , IL-6, IL-12, interferon γ (IFN- γ) and monocyte chemoattractant peptide (MCP-1) are associated with extensive lung damage in SARS patients [60]. The blood levels of IL-10, IL-15 and TGF- β 1 are also positively correlated with the disease severity in patients with MERS [61]. In COVID-19 patients, levels of IL-1 β , IL-1RA, IL-7, IL-8, IL-9, IL-10, granulocyte colony stimulating factor (G-CSF), IFN- γ , interferon γ inducible protein (IP)-10, tumor necrosis factor-alpha (TNF- α) and MCP-1 are also increased over the healthy controls and become worsen in those admitted to ICU with severe acute lung injury [62, 63].

Cytokine storm can also trigger AKI under

various clinical conditions including secondary haemophagocytic lymphohistiocytosis (sHLH) [64-68]. sHLH is also found in patients with SARS and COVID-19 [69, 70]. In addition, cytokine storm may also result in the development of antiphospholipid syndrome in AKI patients with COVID-19 [71, 72]. Of these inflammatory cytokines, IL-6 has been recognized as a key mediator in COVID-19 patients, which is further described below.

IL-6

Many studies have demonstrated that among the inflammatory cytokines, IL-6 is a most strong and important mediator in COVID-19 patients [73, 74]. Meta-analysis involving 12681 COVID-19 patients confirms that IL-6 is significantly higher in those with severe disease conditions [75, 76]. Indeed, serum levels of IL-6 positively correlate with the severity of COVID-19 [75, 77, 78] and also predict the mechanical ventilation need for COVID-19 patients [79]. In COVID-19 patients with older age, IL-6 is an independent risk factor for in-hospital mortality [80].

IL-6 is also a predictor for AKI in patients under various clinical conditions including cardiovascular disease, kidney diseases and liver transplantation [81-83]. This is also found in ischemic AKI animal model [84]. In response to injury, IL-6 is upregulated and released from renal TECs and plays an important role in the pathophysiology of AKI [85]. Increasing evidence shows that IL-6 is not only a biomarker but also a mediator for AKI as mice lacking IL-6 are resistant to HgCl₂-induced AKI [85-88]. In patients with COVID-19, serum levels of IL-6 are elevated in those with AKI [89], and become further increased in those with critically ill [71, 90]. In addition, serum levels of IL-6 can also predict the clinical outcomes of AKI as it is significantly reduced in those when AKI is recovered after effective treatment [91]. Mechanistically, JAK-STAT3 is a downstream signal transduction of IL-6-membrane-bound-IL-6 receptor (mIL-6R)/soluble-bound-IL-6 receptor (sIL-6R). The IL-6-mIL-6R/sIL-6R-JAK-STAT3 signing pathways are activated during cytokine storm in severe COVID-19 patients [54], which is outlined in **Figure 2**. However, the functional role and molecular mechanisms of IL-6 in the pathogenesis of COVID-19 associated AKI remain largely unclear.

C-reactive protein (CRP)

CRP, produced by liver and many inflammatory cells, is an acute phase protein. It has been widely used in clinical settings as an acute inflammation biomarker. CRP is proved as a predictor of postoperative AKI in patients undergoing Coronary Artery Bypass Graft (CABG) [92]. High sensitive CRP

is associated with AKI in patients with acute myocardial infarction [93, 94]. Meanwhile, it is an independent predictor for AKI among ST elevation myocardial infarction patients undergoing primary percutaneous intervention [95]. Increasing evidence has suggested that CRP is also a pathogenic factor contributing to the development of inflammatory diseases including atherosclerosis [96] and AKI [97-101]. The mechanisms of CRP in the progression of AKI include stimulating macrophage activation [97], inducing cell death by causing G1 cell cycle arrest and autophagy [99], and promoting inflammation [101] (Figure 3). The activation of NF-κB/p65 and TGF-β/Smad3 signaling pathways are the major mechanisms through which CRP mediates AKI [98, 100, 101].

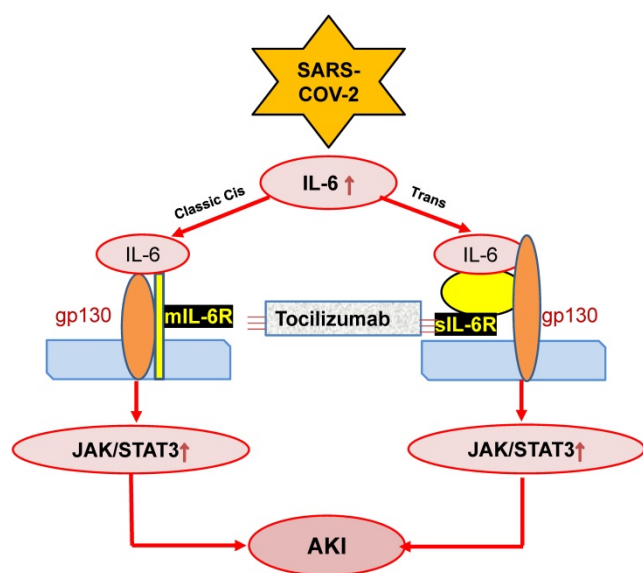


Figure 2. Possible mechanisms through which SARS-COV-2 may induce AKI by stimulating IL-6 signaling. SARS-COV-2 may activate IL-6-mIL-6/sIL6-JAK-STAT3 signaling, resulting in AKI, which can be blocked by Tocilizumab antibodies.

COVID-19 patients with AKI show higher levels of serum CRP over those without AKI [102]. Serum levels of CRP are also a risk factor of AKI in COVID-19 patients [103]. Tan et al. reported that serum levels of CRP are significantly elevated after SARS-CoV-2 infection, which becomes further increased when the disease is progressive but declines dramatically when COVID-19 is recovered [104]. Thus, levels of serum CRP may be a predictor for the clinical outcomes of COVID-19 patients. Meta-analysis confirms this notion that in contrast to mild and survival subgroup of COVID-19 patients, high levels of CRP are associated with severe and death subgroup of COVID-19 patients [75, 76, 105]. In addition, CRP is also an indicator for renal replacement therapy and the need for mechanical

ventilation in COVID-19 patients [106]. Thus, elevated CRP is independently associated with poor clinical outcomes in COVID-19 patients [107, 108]. However, the pathogenic role and mechanisms of CRP in COVID-19-associated AKI remain largely unknown.

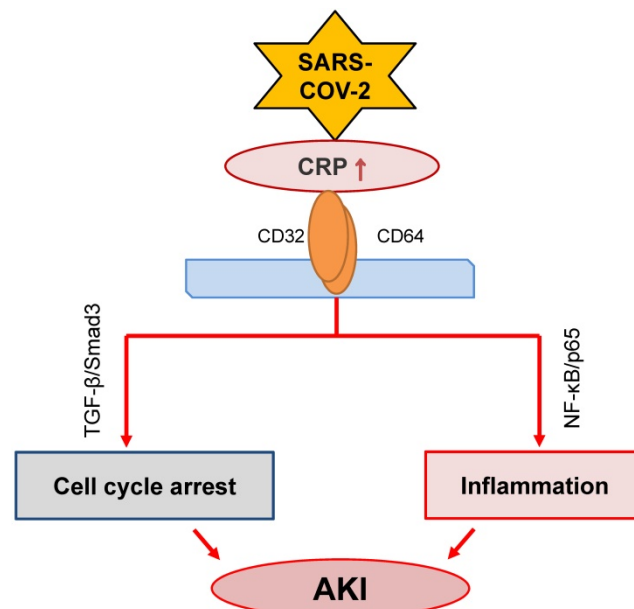


Figure 3. Possible role of CRP signaling in COVID-19-associated AKI. SARS-COV-2 infection may activate CRP signaling to cause AKI via TGF-β/Smad3-mediated G1 cell cycle arrest and NF-κB-dependent renal inflammation.

TGF-β

TGF-β is a pleiotropic cytokine and signals through its downstream canonical and non-canonical pathways to diversely regulate renal inflammation and fibrosis [109, 110]. It has been reported that SARS-COV nucleocapsid protein can interact with Smad3 to activate the canonical pathway [111]. Whereas, the non-canonical TGF-β signaling pathway is also activated by the papain-like protease of SARS-COV by inducing expression of TGF-β1 [112]. In COVID-19 patients, plasma levels of TGF-β are significantly elevated and associated with the disease severity and poor clinical outcomes [113, 114]. Elevated TGF-β2 mRNA is also found in the bronchoalveolar lavage (BAL) fluid of COVID-19 patients [115], which may contribute to lung inflammation and fibrosis because TGF-β1 is also a growth factor associated with fibrosis [109,110]. It is reported that SARS-COV-2 encoded microRNAs are able to target TGF-β signaling pathway to induce TGF-β-dominated adaptive immune response [116]. Upregulation of TGF-β1 in COVID-19 patients is responsible for the recruitment of neutrophils into the site of inflammation [117]. TGF-β can also induce MCP-1 to activate macrophage-dependent inflammation in the diabetic kidney via a

Smad3-dependent LRNA9884 [118]. Induction of IL-6 production by TGF- β 1 also leads to systemic inflammation and “cytokine storm” [119]. Furthermore, TGF- β can induce IgA class switching, which may contribute to vasculitis in critically ill patients with COVID-19 [120]. Thus, TGF- β may significantly contribute to the immediate and long-term effects of COVID-19.

Although the role of TGF- β in COVID-19 associated AKI is still unclear, recent findings that conditional deletion of TGF- β receptor II from renal proximal tubules protects against mercuric chloride and cisplatin-induced AKI reveal a critical role of TGF- β signaling in AKI [121, 122]. Furthermore, mice specifically lacking bronchial epithelial TGF- β 1 (epTGF β KO) are protected against influenza-induced weight loss, airway inflammation, and viral replication [123], suggesting the impact of TGF- β in viral infection. Mechanistically, TGF- β 1 may act via Smad3 to cause AKI as genetic deletion or pharmacological inhibition of Smad3 can block AKI in ischemic mice with or without high human CRP conditions [124]. Indeed, Smad3 can be activated by both TGF- β -dependent and independent mechanisms including Ang II, advanced end products (AGE), and CRP under various disease conditions such as hypertension and diabetes [125-127]. Thus, activation of Smad3 signaling may account for the clinical notion that patients with diabetes and hypertension are high risk for COVID-19 [7]. Mechanistically, Smad3 promotes AKI by directly binding to p21/p27 to

suppress CDKs/cyclin E to cause the G1 cell cycle arrest [128, 129] (Figure 4). Thus, it is highly possible that TGF- β /Smad3 signaling may contribute to COVID-19-associated AKI, which is warranted for further investigation.

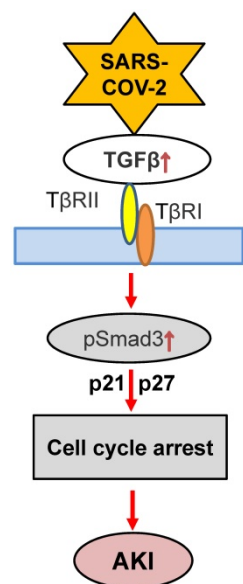


Figure 4. Proposed TGF- β signaling in COVID-19-associated AKI. SARS-COV-2 may induce G1 cell cycle arrest and cell death via TGF- β /Smad3-p21/p27 mechanism.

Complement activation

The complement system is the first response of host immune system that recognizes and eliminates virus, such as SARS-COV or SARS-COV-2 [7, 130]. There are several pathways involving in systemic complement activation including the lectin pathway, classical pathway, and alternative pathway [130, 131]. The lectin pathway is triggered by the binding of mannan-binding lectin (MBL)

with SARS-COV spike (S) protein [132], which leads to the activation of mannan-binding lectin-associated serine protease 2 (MASP-2). The N protein of coronavirus is also associated with the severity of lung injury according to MASP-2-mediated complement overactivation. Thus, alteration of MASP-2-binding motif or blocking the MASP-2-N protein interaction attenuates lung injury [133]. The classical pathway is activated by the binding of antibodies, which forms the immune complexes with viral antigens to complement C1 complex [130, 131]. The classical, lectin and alternative pathways resulting in the formation of C3 convertase to activate the complement system, which is observed in the lung after SARS-COV infection [130, 131, 134]. The role of C3 in SARS-COV-induced lung injury is confirmed in C3 deficient mice in which deletion of C3 protects against ARDS with lower levels of cytokine and inflammatory monocytes infiltration [135].

The complement system is activated during the progression of COVID-19 [136]. The activation of complement system is related to the disease severity and the respiratory failure in COVID-19 patients [134, 136, 137]. It has been shown that the C5a-C5aR1 axis plays an important role in the development of ARDS in COVID-19 [138], whereas, C4d and C5-9 are colocalized with the SARS-COV-2 S protein in the lung and skin vasculature [139].

The activation of alternative pathway of complement also participates in the pathogenesis of AKI [140, 141]. It has been reported that local synthesis or deposition and activation of complement by renal epithelium is an important cause of AKI [142, 143]. In addition, strong C5b-9 staining has been demonstrated on the apical brush border of TECs of the kidney with SARS-COV-2 infection [10]. Activation of the classical complement pathway is also observed in the AKI kidney in critically ill children with COVID-19 [90]. However, the functional role and mechanisms of complement activation in COVID-19-associated AKI remain largely unclear.

The lung-kidney crosstalk pathway

The crosstalk between the lung and kidney has been observed in patients with AKI and ARDS [144]. Clinically, acute lung injury and AKI are complications often encountered in patients with critical illness [145]. Mechanical ventilation can improve lung function but is a risk factor for AKI in critically ill patients [146, 147]. It has been reported that positive pressure of mechanical ventilation can increase the risk of AKI by almost 8-fold [106], which is associated with systemic hemodynamic and neurohormonal changes and biotrauma [65, 148, 149].

ARDS can trigger AKI via mechanisms associated with systemic hypoxia, hypercapnia, systemic inflammatory response syndrome (SIRS), and mechanical ventilation. Severe hypoxemia in ICU patients is associated with AKI required for renal replacement therapy [145]. Kidney is susceptible to hypoxic injury due to the high rate of oxygen consumption [65, 150]. Thus, hypoxia can induce AKI and tubular necrosis or apoptosis [149]. Hypercapnia in COVID-19 patients can also affect the renal blood flow by stimulating renal vasoconstriction [151]. More importantly, the lung-kidney cross-talk is also associated with the cytokine storm [152]. The inflammatory reaction caused by the lung injury can damage the kidney to release abundant inflammatory cytokines, which, in turn, promotes the damage in the lung [8]. Thus, the approaches to limit ventilator-induced lung injury and decrease the duration of mechanical ventilatory support to protect against AKI in critically ill patients are proposed for treatment of critically ill COVID-19 with acute lung and kidney injury.

Therapeutic potential for COVID-19-associated AKI

Continuous renal replacement therapy (CRRT)

CRRT is an advanced approach to treat patients with AKI by improving overload water status and removing inflammatory factors [153], particularly in those with septic AKI [154]. CRRT has been utilized in AKI patients with severe MERS and in critically ill COVID-19 [155]. However, whether the early initiation or high intensity of CRRT can improve the progression of AKI COVID-19 patients remains to be determined.

Tocilizumab (TCZ)

TCZ, a recombinant humanized monoclonal antibody against the human membrane and soluble IL-6 receptors, is widely used for treatment of immunoinflammatory rheumatic diseases [156, 157]. TCZ has been shown to block the IL-6/NF- κ B/JNK pathway to have a protective effect against sepsis-induced acute lung injury and AKI [158]. As IL-6 is important in COVID-19, TCZ has been used to treat COVID-19 patients clinically (**Figure 2**). The early treatment with TCZ has been shown to effectively improve the oxygen status in COVID-19 patients [156]. The meta-analysis of TCZ studies in a total of 1675 and 6279 COVID-19 patients with critically ill shows that TCZ treatment can significantly reduce the in-hospital mortality rate, although patients remain the need for hemodialysis

and ventilation [159]. Thus, the therapeutic efficacy of TCZ on COVID-19-associated AKI needs to be further studied.

Complement inhibitor

A C3 inhibitor AMY-101

AMY-101 is a highly selective and potent C3 inhibitor and is currently tested in Phase II clinical trials in patients with sepsis, hemodialysis-induced inflammation or malarial anemia [160-163]. It is reported that treatment with AMY-101 is safe and can significantly improve the clinical manifestations in severe COVID-19 patients [164]. Further Phase II and III clinical trials are still going.

An anti-C5 antibody

An anti-C5 antibody has been clinically used in patients with C3 glomerulopathy and several types of AKI including atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria [165]. Treatment with the anti-C5 antibody has shown to improve the kidney function and ameliorate the intra-renal complement activation and systemic inflammation in ischemia reperfusion-induced AKI mouse model [165]. The first result of anti-C5 treatment has also revealed a rapid and promising effect on COVID-19 patients [166]. However, more clinical trials are needed for the conclusive results of the anti-C5 antibody treatment on COVID-19 patients with AKI.

Anti-TGF- β treatment

As SARS coronavirus can upregulate TGF- β and patients with coronavirus infection have elevated levels of TGF- β [113, 114], it has been proposed that TGF- β could be a valid target for the treatment of COVID-19 [167, 168]. In a recent Phase II clinical trial, inhibition of TGF- β expression by OT-101, an anti-sense to TGF- β 1, has been shown to suppress SARS-COV and SARS-COV-2 replication and allow patients to recover without going into respiratory crisis [169], suggesting that COVID-19 can be treated with TGF- β inhibition. However, it should be noted that TGF- β has diverse roles in renal inflammation and fibrosis [109, 110] and targeting the upstream of TGF- β may also cause adverse effects. Our recent studies showed that TGF- β can trigger AKI via the Smad3-dependent mechanism and treatment with Smad3 inhibitors such as SIS3 or a natural product of Traditional Chinese Medicine Quercetin can effectively suppress AKI even under high human CRP conditions [100, 170]. These findings suggest that targeting Smad3 specifically, rather than the entire TGF- β signaling, may represent as a novel and effective therapy for AKI in COVID-19 patients

clinically.

Conclusion

AKI is a common complication in critically ill COVID-19 patients. Inflammation may be a key mechanism triggering this process. Many inflammatory stress molecules and pathways including Ang II-associated hypertensive stress, diabetes-related metabolic stress, cytokine storm, high CRP, overreactive TGF- β signaling, complement activation, and lung-kidney crosstalk may promote AKI in COVID-19 patients. Thus, treatments by targeting these molecules and pathways may represent as a novel and specific therapy for AKI in COVID-19 patients.

Abbreviations

ACE2: angiotensin-converting enzyme 2; Ang I: Angiotensin II; AKI: Acute kidney injury; ARDS: acute respiratory distress syndrome; BUN: Blood urea nitrogen; CRP: C-reactive protein; CABG: Coronary Artery Bypass Graft; CRRT: Continuous renal replacement therapy; G-CSF: granulocyte colony stimulating factor; IFN- γ : interferon γ ; IKK β : I κ B kinase- β ; IL-6: Interleukin-6; IP: inducible protein; MASP-2: mannan-binding lectin-associated serine protease 2; MCP-1: monocyte chemoattractant peptide; mIL-6R: membrane-bound-IL-6 receptor; RAAS: renin-angiotensin-aldosterone system; Scr: serum creatinine; sIL-6R: soluble-bound-IL-6 receptor; TCZ: Tocilizumab; TNF- α : tumor necrosis factor- α .

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Author Contributions

J.C. and W.W. wrote the manuscript and Y.T and X.R.H collected and analyzed data. X.Y. and H.Y.L. designed and revised the manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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