Review

Potential Mechanisms of the SARS-CoV-2-induced AKI Progression to CKD: A Forward-Looking Perspective

Zeinab Karimi,[1] Fatemeh Masjedi,[1] Leila Malekmakan,[1] Aida Doostkam,[1] Jamshid Roozbeh,[1] Nasrollah Ghahramani[2]

[1]Shiraz Nephro-Urology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Penn State College of Medicine Division of Nephrology, Hershey, PA, United States

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Coronavirus disease 2019 (COVID-19) was identified in December 2019 and is still expanding in most parts of the world. The wide variety of affected organs is likely based upon the shared expression of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) important entry-receptor angiotensin-converting enzyme 2 (ACE2). For this reason, the broad distribution of ACE2 receptors in different tissues plays a crucial role in the multi-organ dysfunction and fatality due to COVID-19. Because of the high prevalence of acute kidney injury (AKI) in patients with COVID-19, we review the molecular understanding into viral infection mechanisms and implications for AKI. Furthermore, mechanisms of the AKI to chronic kidney disease (CKD) progression, such as the relative contribution of immune cell reaction, fibroblasts activation, endothelial dysfunction, and subsequent hypoxia may contribute to the association of AKI with worse outcomes during this virus pandemic. We highlight the state of the knowledge on SARS-CoV-2-dependent mechanisms for AKI and list the potential management choices for the prevention of AKI aggravation and the impending possibility of CKD. Finally, we intend to provide a much better understanding of why Coronavirus induces AKI and its subsequent progression to CKD in the coming years and further discuss the acute and long-term renal consequences.

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INTRODUCTION

In December 2019, a novel Coronavirus was identified as a microorganism that caused a pandemic of a severe acute respiratory syndrome (SARS)-like condition in Wuhan, China, which was described as Coronavirus disease 19 (COVID-19).[1] Phylogenetic evaluation revealed that the virus responsible for COVID-19 belongs to a unique enveloped RNA beta-Coronavirus genus, which has been called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus has 79% and 50% sequence identity with SARS-CoV and MERS-CoV, respectively.[1,2]

Furthermore, the single-cell RNA sequencing (scRNA-Seq) strategy indicates that the 2019-nCoV invades human cells by cellular receptor the same as SARS-CoV, which is the angiotensin-converting enzyme 2 (ACE2) receptor.[3,4] ACE2 receptors belong to membrane-associated aminopeptidase family and are expressed in the ciliated nasal cells[5] and alveolar epithelial cells (type II) of the lung as well as multiple body organs such as heart, intestines, liver,[6] placenta/decidua,[7] pancreas,[8,9] prostate gland,[10] and the kidneys.[11] For this reason, the wide distribution of ACE2 receptors in the various tissues plays a crucial role in the multi-organ dysfunction and fatality resulting from COVID-19. The kidneys are at high risk for the COVID-19 because ACE2 receptors express on epithelial cells of the proximal tubule with the

proportion at approximately 4%.[12,13]

Epidemiological information has revealed that the mortality rate of SARS-CoV-2 infection is substantially increased in the presence of comorbid chronic illnesses such as cardiovascular diseases, diabetes mellitus, chronic respiratory diseases, hypertension, and cancer.[14,15] Retrospective investigation of patients with COVID-19 showed a particular independent risk factor for mortality with equal importance: kidney dysfunctions, which initially appeared as mild abnormalities and would later be confirmed as clinically diagnosed acute kidney injury (AKI) in a considerable percentage of critically ill patients.[16] The AKI development in patients with COVID-19 is a significant negative prognostic factor for survival, which is not easily remediable by existing interventions, unlike the other well-known negative prognostic factors.

Considerable clinical evidence indicates AKI can be complicated by progressive renal disease. The greater frequency of AKI in hospitalized patients might potentially be one of the leading and influential reasons for end-stage renal disease (ESRD). Although some studies emphasize the concept that AKI can be "treated with defects", whether persistent renal disease is established remains controversial. Furthermore, subsequent to AKI, a range of secondary renal protective pathways are activated that may postpone or prevent severe chronic kidney disease (CKD).[17]

Because of the deteriorating problem of patients with COVID-19 and the lack of sufficient relevant information relating to potential impacts of this disease on kidney function in the future, we have reviewed the risk factors involved in AKI in these patients who may progress to CKD. After recovering from main respiratory infectious disease, these risk factors are likely to influence the kidneys by disturbing other systems such as the immune system, cardiovascular system, etc. This study also aimed to provide practical preventive approaches for CKD in these patients by reviewing and recommending helpful treatment procedures.

SEARCH STRATEGY

International databases including PubMed, Embase, Web of Science, Scopus, and Cochrane Library Databases were used for the search of articles by 10 April 2021. Keywords were nephropathy, COVID-19, coronavirus, renal injury, acute kidney injury, chronic kidney injury, and SARS-CoV-2 or a combination of them in the titles/abstracts.

After the collection of related studies, Mendeley software was used to categorize and eliminate duplicate titles. Then, studies with inappropriate purposes were removed. The selected studies were done on humans and published in English.

PREVALENCE OF AKI DURING SARS-COV-2 INFECTION

AKI is a common clinical syndrome experienced by approximately 10 to 15% of the hospitalized patients. AKI is defined as an abrupt (within hours) decrease in kidney function, which encompasses both injury (structural damage) and impairment (loss of function). Many patients with AKI have mixed etiology where sepsis, ischemia, and nephrotoxicity often co-exist and complicate diagnosis and treatment.[18,19] Several studies have shown that viral infections have induced AKI.[20-22] Although the airway and alveolar epithelial cells are the main targets of 2019-nCoV, kidney damage has also been observed with mild clinical symptoms such as proteinuria, to progressive AKI.[23, 24]

Early clinical studies from China and Italy reported that AKI was developed, ranging widely from 0.5 to 29% in patients with COVID-19.[2,14,25-28] For the first time, Cheng *et al.* reported a relationship between kidney dysfunction and mortality rate in hospitalized patients with COVID-19. In this study, 13% of patients demonstrated kidney disease, approximately 40% of them had mild kidney symptoms and 5.1% progressed to AKI during admitted days.[25] Besides, Hirsch *et al.* performed a cohort study and showed that the frequency of AKI among patients with COVID-19 was higher than earlier studies. However, AKI improved in 1,993 (36.6%) of 5,449 patients admitted with COVID-19 at 13 academic hospitals in metropolitan New York. AKI status was categorized into three stages of 1, 2, and 3, with frequencies of 46.5, 22.4, and 31.1%.[21] Therefore, kidney disease is common and dangerous in COVID-19 hospitalized patients.

MECHANISMS OF AKI INDUCED BY SARS-COV-2 INFECTION

Direct Injury and ACE2 Dependent Mechanisms

Available data indicated that spike (S) glycoprotein of SARS-CoV-2 bind to the ACE2

receptors of the target cells, primed by type II transmembrane protease (TMPRSS2).[29] ScRNA-seq analysis indicated that ACE2 and TMPRSS genes significantly co-express in renal proximal straight tubule cells (S3 segment) and podocytes.[30] Moreover, Huang *et al* reported the entry of SARS-CoV-2 into the systemic circulation is also a vital route that leads to AKI. Therefore, the period between the detection of SARS-CoV-2 in blood samples and AKI manifestation was about seven days.[27] Kidney and lung may be the main target organ for SARS-CoV-2. The basic mechanisms of kidney disease in infected patients with COVID-19 are multifactorial and are not exactly clear. Initial kidney injury and alteration of cell-cell junctions' integrity allow the virus access to ACE2 receptors on the luminal surface.[30]

Although recent studies have shown that SARS-CoV-2 has direct cytopathic effects through the glomerular and tubular epithelial cells, it can cause indirect injury through local and systemic inflammation and organ cross talk (Figure 1).

Local and Systemic Inflammation Induced Renal Injury During COVID-19

The entrance of SARS-CoV-2 to the host cells stimulates the host immune system directly and indirectly. During incubation, the viral infection leads to mild symptoms (the first phase) and causes protective immune responses by a specific adaptive immune system. Response of the adaptive immune system is critical to virus removal and preventing disease development to severe stages.[31]

The adaptive immune system successfully induces antiviral immunity in an infected individual with good health status and a suitable HLA haplotype. While, if immune response to a pathogen is impaired, the virus will cause considerable damage of the invaded tissue, and severe symptoms (the second phase) will occur, mainly in tissue that express ACE2 at a high level, including lung, heart, intestine, and kidney.[30, 31] Furthermore, SARS-CoV-2 activates the complement system in the second phase (severe phase). The complement system is triggered by classical, lectin, and alternative pathways. The nucleocapsid protein of SARS-CoV-2 causes unusual production of C3a-C3b/C5a-C5b through these pathways. These elements induce cell lysis, apoptosis, and cytokine and chemokine production.[32, 33] Damaged cells release intracellular substances that activate the adhesion molecules such as ICAM, VCAM, and CMP-1, subsequently increasing recruitment of neutrophils and macrophages.[34]

Diao *et al.* examined renal tissues from postmortem patients with confirmed COVID-19. Immunohistochemistry data revealed that SARS-CoV-2 NP antigen was accumulated in kidney

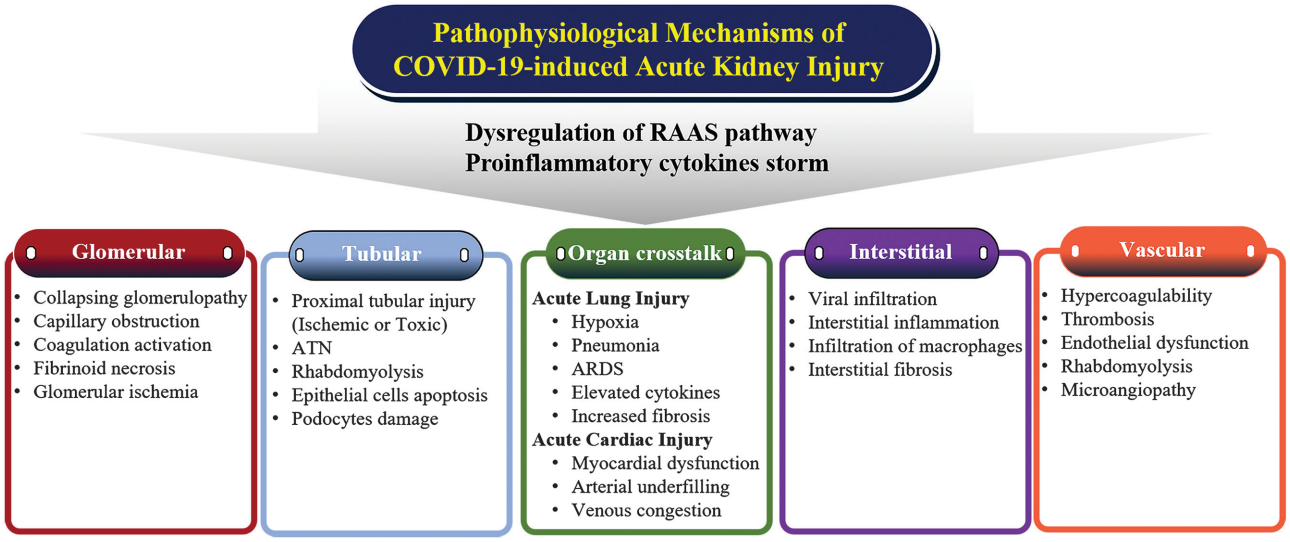

Figure 1. Involvement of multiple dependent pathways in COVID-19 associated AKI. Targeting ACE2 by SARS-CoV-2 results in RAAS dysregulation, innate and adaptive immune pathway activation, and hypercoagulation results in COVID-19-induced AKI. Organ crosstalk between the injured lung and heart with kidneys may further propagate injury (Abbreviations: COVID-19, coronavirus disease 2019; AKI, acute kidney injury; ACE2, angiotensin converting enzyme 2; RAAS, renin-angiotensin-aldosterone system, ARDS, acute respiratory distress syndrome; ATN, Acute tubular necrosis).

tubules. Severe acute tubular necrosis and lymphocyte infiltration have been detected by histopathology examination. Furthermore, SARS-CoV-2 induced infiltration of $CD68^+$ macrophages into tubulointerstitium and increased complement C5b-9 deposition on tubular epithelial cells.[26]

Moreover, Pfister, Vonbrunn, Ries, *et al.*[35] investigated the complement factors C1q, MASP-2, C3c, C3d, C4d, and C5b-9 using immunohistochemistry method and confirmed the involvement of the complement system in kidney biopsies of patients with COVID-19. Their study revealed that the classical pathway (C1q) is difficult to detect in COVID-19 sampling. C3 cleavage products (C3c and C3d) were highly detected in renal arteries and glomerular capillaries of COVID-19 biopsies. The C5b-9 membrane attack complex was mainly deposited on renal arterioles, peritubular capillaries, and tubular basement membrane.

Consequently, different complement pathways were involved in vascular and tubular damages of COVID-19 kidneys, the lectin pathway mainly in peritubular capillaries, the classical pathway partially in renal arteries, and the alternative pathway specifically in tubular compartments.

On the other hand, the renin-angiotensin-aldosterone system (RAAS) has two axes, ACE/Angiotensin II/AT1R and ACE2/Ang-(1–7) MasR axis. ACE2 converts the Angiotensin I (Ang I) to the inactive Ang-(1–9) peptide and also directly converts Ang II to the vasodilatory and anti-inflammatory agent Ang-(1–7).[36] The binding of the SARS-CoV-2 to ACE2, as a cell surface receptor, initiates virus and receptor internalization into the target cells, causing ACE2 down-regulation. Therefore, internalization and down-regulation of the ACE2 decrease the conversion of the total level of Ang II to angiotensin-(1–7).[37, 38] The SARS-CoV-2 prompted an imbalance of ACE2/ACE levels.[39, 40] It appears that increased level of Ang II and stimulation of AT1R have resulted in a pro-inflammatory response.[41] Ang II activated cell signaling pathways of the nuclear factor kappa B (NF-κB)[42, 43] and amplified cellular production of cytokines such as IL-6[44], TNFα, IL-1β and IL-10[45], IL-1, IL-10, IL-12, and TNFα.[46] Therefore, this data indicates crosstalk between RAAS and the complement system. The entry of SARS-CoV-2 to cells activated adaptive and innate immune response, following increased production and release of pro-inflammatory chemokines and cytokines. This condition, termed cytokine release syndrome, is also known as "cytokine storm". The cytokine storm occurred in the COVID-19 like other infectious and non-infectious diseases. For the first time, Wu *et al.* and Huang *et al.* reported cytokine storm in the patients with COVID-19.[27, 47] Therefore, SARS-CoV-2 induced cytokine storm through directly binding to the lung or renal ACE2 receptors or through the induced imbalance of the ratio of Ang II/Ang-(1-7) (Figure 2).

Organ Crosstalk During SARS-CoV-2 Pandemic

Previous studies demonstrated lung–kidney crosstalk in acute respiratory distress syndrome (ARDS).[48, 49] COVID-19 induced alveolar damage and disrupted the blood-gas exchanger barrier. In addition, in the severe condition, these patients showed hypoxemia with less than 93% oxygen saturation in a resting state. Hypoxemia was defined as arterial oxygen partial pressure (PaO2) over inspiratory oxygen fraction (FIO2) of less than 300 mm Hg.[27] Hypoxemia condition might induce renal medullary hypoxia. The clinical and animal research showed that medullary hypoxia and ATP depletion is a common cause of AKI. Lung–kidney cross damage is prompted by a cytokine storm. Gene expression of IL-6 was upregulated in the damaged renal epithelial cells in AKI, associated with higher pulmonary permeability, edema, and alveolar hemorrhage.[50] The endothelial cells of the lung and kidney infected by this novel virus may be another cause of AKI.[51] Additionally, proximal tubule epithelial cells and podocytes are directly infected by SARS-CoV-2 via ACE2 receptors. These interactions promote acute tubular necrosis, collapsing glomerulopathy, and protein infiltration into Bowman's capsule.[52]

As mentioned earlier, the SARS-CoV-2 uses ACE2 as a receptor and causes an imbalance in the ratio between Ang II (vasoconstrictor peptide) and angiotensin 1-7 (vasodilator peptide). A high level of Ang II interrupts the cardiac cycle and promotes cardiac hypertrophy and fibrosis.[53]

Consistent with the cardiovascular undesirable effects of renin–angiotensin system overactivation during infection, a rapidly growing body of evidence recommends a considerable contribution of extrapulmonary cardiorenal indicators, including arrhythmias, acute cardiac injury and AKI[54] (see Figure 1).

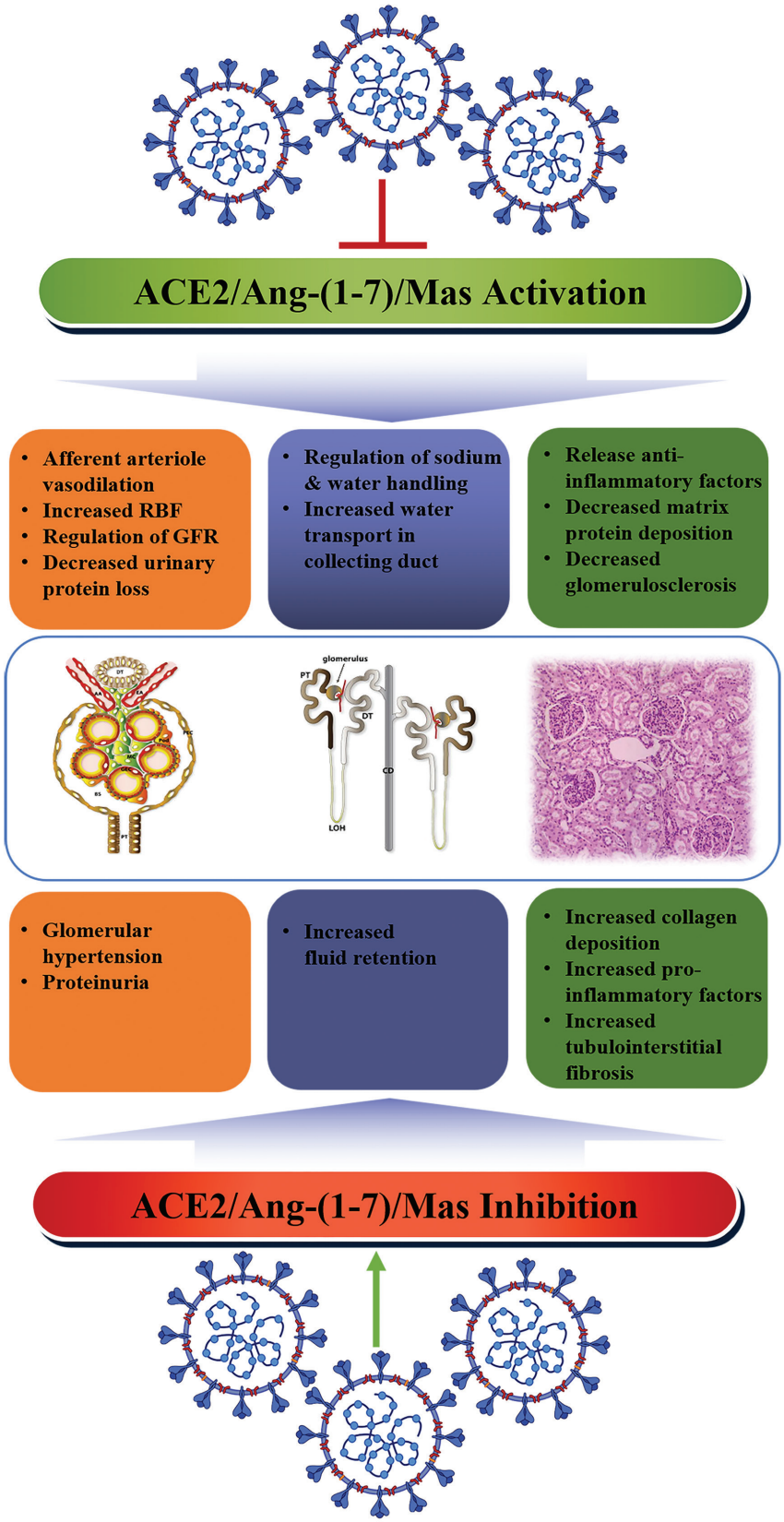

Figure 2. Potential effects of SARS-CoV-2 infection on ACE2-Ang-(1-7)-Mas receptor axis in renal tissue.

In fact, higher levels of troponin and natriuretic peptides play a detrimental role in these events, which can be mediated by RAS imbalance. This phenomenon may complicate the clinical setting through active inflammation, microvascular injury, and endothelial dysfunction.[55] Vascular system inflammation can lead to diffuse microangiopathy with thrombosis. Furthermore, myocarditis, arrhythmia, heart failure, acute coronary syndrome, and even sudden death can occur following inflammatory procedures in the myocardium.[56]

COVID-19-induced myocarditis impairs cardiac output and compromises end-organ perfusion. Moreover, the accompanying right-ventricular problems lead to diastolic dysfunction and venous congestion, which is transmitted back to the kidney and endangers its perfusion. Acute viral myocarditis and cytokine cardiomyopathy can be associated with hypotension, hypoperfusion, and renal vein congestion, which in turn can disturb the glomerular filtration rate (GFR).[57]

Renal congestion and AKI might develop following right ventricular failure secondary to COVID-19-induced pneumonia. Cytokine storm and/or myocarditis in patients with COVID-19 can result in cardiorenal syndrome type 1 (CRS) phenotype. In addition, AKI can induce cardiomyocyte damages and lead to CRS type 3 phenotype, while CRS type 5 phenotype is characterized by simultaneous renal and cardiac injury due to inflammatory response, vascular problems, and microthrombosis.[58,59]

Therefore, there is significant evidence about organ crosstalk between the lung and heart with the kidney during COVID-19.

Role of Hypercoagulability and Thrombosis in COVID-19associated AKI

In general, modified hemostasis because of viral infections usually leads to vascular problems such as thrombosis and/or hemorrhage. Procoagulants, hemodynamic changes, and pro-inflammatory cytokines contribute to the creation of ischemic and thrombotic environment by the virus.[60] The high incidence of acute thrombotic events such as venous thrombosis and pulmonary embolism has also been indicated in patients with COVID-19.[61,62] Interestingly, patients with ARDS induced by COVID-19 exhibited more thrombotic complications than other types of ARDS.[62] In this regard, fibrin deposition in glomerular parts of the kidney[52] generate a dysregulation in coagulation homeostasis that can participate in kidney microcirculatory disturbance and AKI. In a retrospective study, Tang *et al.* revealed that the use of prophylactic anticoagulant therapy was related to a reduced mortality rate in patients with COVID-19.[63] However, no data are available on the direct effects of anticoagulant therapy on COVID-19 kidney complications. As previously mentioned, the high prevalence of pulmonary embolism in the course of SARS-CoV-2 infection and following right heart failure might also contribute to venous congestion and AKI progression.

Rhabdomyolysis During SARS-CoV-2 Infection

Rhabdomyolysis is caused by the rapid destruction of skeletal muscle and following leakage of toxic cellular factors. Direct myocyte damage or energy production deficits that lead to irregularities in intracellular calcium and cellular lysis also contribute to rhabdomyolysis.[64-66] Other etiologies include trauma, some medications, myopathies, metabolic syndrome and also infections.[65] A number of viruses have been implicated in myositis and related rhabdomyolysis. Influenza A and B are typically related, whereas others such as herpes simplex virus, enteroviruses, and SARS-CoV are less common.[66-69] Moreover, rhabdomyolysis was reported as a clinical manifestation of patients with COVID-19.[70, 71] In evaluating autopsy samples of COVID-19 patients, rhabdomyolysis was confirmed by the existence of pigment casts and inflammation.[72]

Mokhtari, Maurer, Christensen, *et al.* [73] reported a high incidence of rhabdomyolysis in critically ill patients with COVID-19 and evaluated the potential independent factors contributing to its development. This study is the first comprehensive research study reporting on rhabdomyolysis in a large prospective cohort of critically ill COVID-19 patients. Almost fifty percent of the studied patient population developed rhabdomyolysis.

One of the common complications of rhabdomyolysis is AKI, occurring in 7 to 10% of cases.[64] The presence of AKI results in increased morbidity and mortality in patients with rhabdomyolysis.[64, 65] In this regard, a recent large cohort study revealed that many patients with COVID-19 had concomitant AKI.[72] There are

some theories to describe AKI as a complication of rhabdomyolysis, including a direct toxic effect of myoglobin on tubular cells, tubular obstruction by myoglobin, or alterations in glomerular filtration rate secondary to kidneys ischemic changes resulting from the release of vasoconstrictive mediators.[74]

For this reason, early recognition and management of rhabdomyolysis in COVID-19 patients may protect against a further decline in renal function and potentially decrease AKI-related mortality.

In general, the pathogenesis of virus-induced rhabdomyolysis is not fully understood, although several mechanisms have been suggested. Viruses could directly invade the myocytes, as seen in influenza and SARS-CoV infections.[66, 69] Immunological mechanisms most likely play the major role. Immune cross-reactivity between viral antigens and myocytes as well as possible viral-related transformation of host proteins might cause a dysregulated immune reaction and muscle injury.[66] Severe immunological response is called a "cytokine storm" and can further lead to diffuse tissue damages, including rhabdomyolysis.[69, 75] Cytotoxic T-cell-mediated invasion has also been associated with viral myositis.[76] Our knowledge of the novel COVID-19 is still progressing, and the precise mechanism of SARS-CoV-2-induced rhabdomyolysis is still unknown, but overproduction of cytokines may be the main effective factor.

Altogether, regular screening of serum myoglobin levels in patients with COVID-19 admitted to intensive care could be somewhat helpful. Contemporary guidelines offer weak evidence-based treatment suggestions to prevent rhabdomyolysis-induced AKI.

POSSIBLE PROGRESSION OF SARS-COV-2-INDUCED AKI TO CKD

For a long time, numerous physicians presumed that AKI was a self-limiting procedure, followed by full recovery of renal function to pre-AKI levels amongst survivors. On the other hand, with the increase in the number of studies, it was confirmed that AKI could trigger or accelerate the development of CKD.[77-79] Investigating animal models of AKI revealed the potential mechanisms of maladaptive repair after AKI, characterized by fibrosis, microvascular rarefaction, tubular injury, glomerulosclerosis, and chronic interstitial inflammation. As a result, kidney aging was accelerated and the functional decline was unavoidable.[80, 81]

Moreover, renal ischemia, toxins, drugs, viral and bacterial infections that induced AKI are associated with various manifestations, including glomerular and tubular cell death/injury, inflammation, and fibrosis. In this regard, renal fibrosis and chronic inflammation are the typical hallmarks of CKD, which occur in some types of AKI.[82] Furthermore, various interactions between tubular, vascular, and immunogenic cells, as well as fibroblasts, have a crucial role in the basic mechanisms, which are involved in the progression of AKI to CKD.[78]

On the other hand, an important reason for the lack of understanding of the long-term impact of AKI is that generally, AKI clinical studies have focused on in-hospital results such as short-term mortality and resource utilization.[83-85] There is no relevant follow-up information on what occurs months to years after discharge from the hospital. As a result, the relationship between AKI and subsequent renal dysfunction during the progression of CKD is challenging to investigate.

However, over a decade of follow-up, two studies showed that AKI had an independent association with ESRD progression [86] and all-cause mortality[87]. Afterward, some studies linked AKI with the development and acceleration of CKD. Typically, patients that experienced AKI had an nearly 9-fold higher adjusted risk of CKD and a 3-fold greater adjusted risk of ESRD progression.[82]

Besides, we already know from the non-COVID-19 literature that the AKI may be associated with more complications. Since the recognition of kidney problems in patients with COVID-19 in recent months, some studies on hospitalized patients have shown that the incidence of AKI is associated with higher rates of acute renal replacement therapy (RRT). Moreover, the mortality rate was greater in patients with AKI compared to those without AKI.[21, 88] It is notable that, of those that developed AKI, only 30% survived and recovered kidney function. In survivors, 46% of patients still had constant AKI (AKD) at the time of discharge.[88, 89] Moreover, all three researches pointed out above found that proteinuria and hematuria (about 70%) are remarkably frequent in COVID-19.

Recent clinical studies demonstrated that the brush border of proximal tubular cells is a target for SARS-CoV-2 invasion. Smaller arterioles and

renal microcirculation are damaged in AKI. In addition, fluorescence microangiography showed a local "no-reflow" area after AKI. These findings demonstrated that AKI not only caused a reduction in the number of peritubular capillaries but also decreased the quality of remaining capillaries, which led to a significant decline in renal blood flow.[88-90] Reduction in renal blood flow causes renal hypoxia, disturbs proximal tubular epithelial cell functions that are highly vulnerable to hypoxic state, and progresses to apoptosis. Hypoxia stimulates collagen production in the renal fibroblasts, which contributes to renal fibrosis. Fibrosis also exacerbates renal hypoxia. This positive feedback triggers a vicious cycle, which has a critical role in AKI to CKD progression.[91, 92] Hypoxemia and systemic hypotension is a common clinical feature of infected patients with SARS-CoV-2. Besides, renal hypoperfusion and medullary hypoxia were kidney manifestations in hospitalized patients with COVID-19.[93]

Therefore, renal ischemia, vascular dysfunction, tubular cell death/injury, chronic inflammation, apoptosis, and fibrosis are the typical hallmarks of CKD, which occur during SARS-CoV-2-induced AKI (Figure 3).

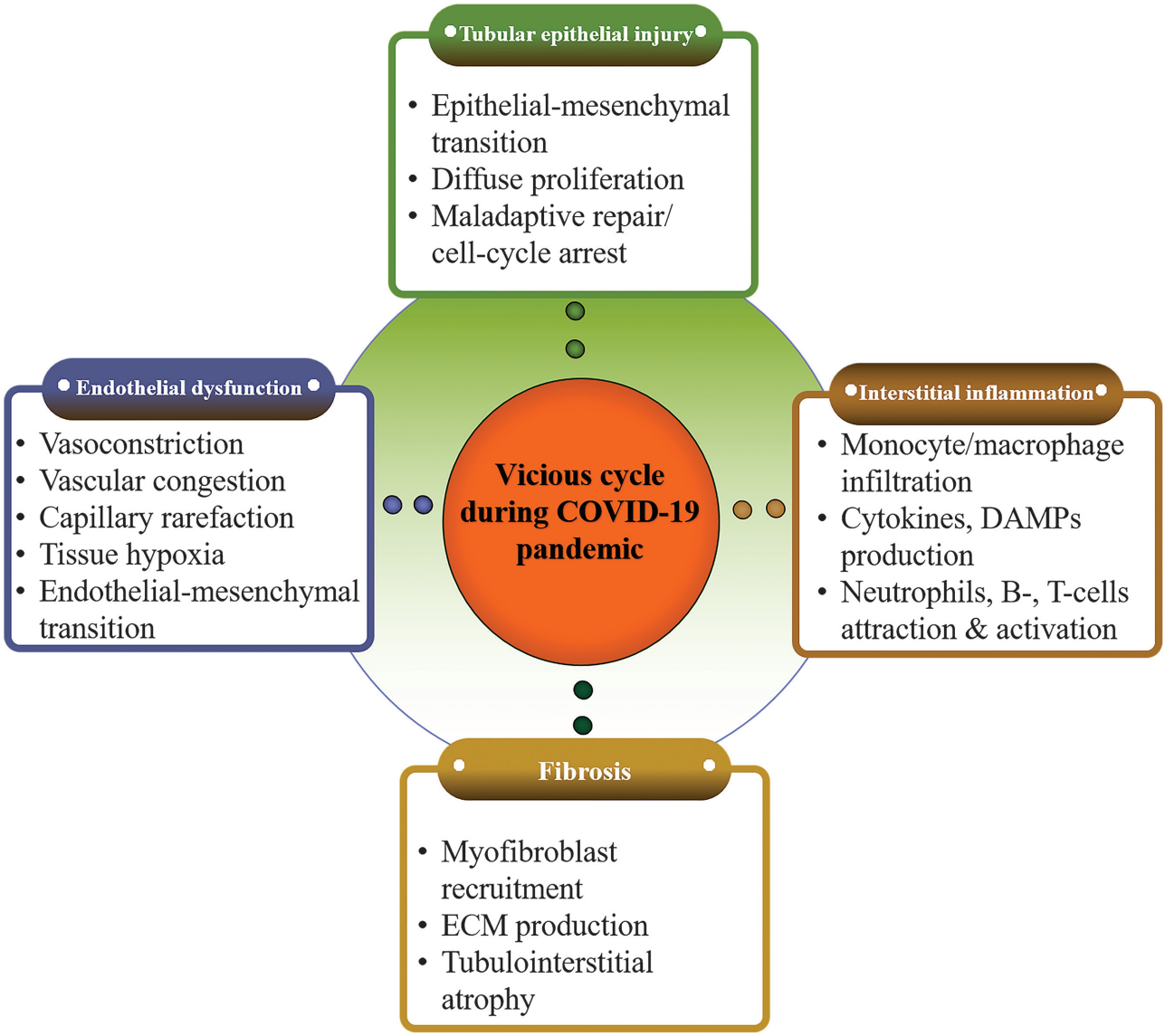

Figure 3. Potential interrelationship between endothelial dysfunction, tubular epithelial injury, interstitial inflammation, and fibrosis is likely to create a vicious cycle that can lead to the progression of acute kidney injury to chronic kidney disease (AKI to CKD) during COVID-19.

PREVENTIVE MANAGEMENT OF AKI TO CKD DURING COVID-19

To date, there is no special definite treatment for COVID-19-induced AKI. A number of trial agents have been discovered for the COVID-19 treatment. The management of AKI appears to be no different than in other setting. In the absence of specific treatment options, the care strategy for patients with COVID-19 in the ICU remains mainly supportive. Given the high prevalence of renal involvement in COVID-19, it is necessary to take into consideration all accessible therapeutic options to maintain renal function and protect against the progression to a chronic state.

Avoidance of nephrotoxins, regular monitoring of serum creatinine and urine output, consideration of hemodynamic monitoring are parts of the KDIGO supportive care guideline that requires improvement and validation in critically ill patients to decrease the incidence and severity of AKI during COVID-19 course.[94]

Improving volutrauma and barotrauma using protective lung ventilation reduces the risk of new onset or worsening AKI by controlling ventilation-induced hemodynamic problems and the cytokine load on the kidney.[95]

Another important decision is the adjustment of fluid balance to recover normal volume to avoid volume overload and minimize the risk of pulmonary edema, right ventricular overload, congestion, and resultant AKI.[96]

It should be noted that some of the patients who experience fever, nausea, vomiting, and possibly diarrhea are susceptible to intravascular volume depletion and prerenal AKI. In these patients, early aggressive volume resuscitation has been shown to prevent extensive acute tubular injury progression.[97]

In the Fluids and Catheters Treatment Trial (FACCT), the incidence of AKI was similar between restrictive and liberal fluid management therapy.[98] Increased intra-abdominal pressure due to progressive volume overload can also contribute to further impairment of renal hemodynamics and function. Furthermore, an accumulating body of evidence has determined positive fluid balance as a independent predictor of poor outcomes in critically ill patients.[99, 100] Besides, venous wall stretching stimulates endothelial activation and generation of inflammatory mediators, which in turn may lead to interstitial damages and functional irregularities such as diminished tubular reabsorption and sodium and water retention.[101] Further supporting this concept is the observation that attaining a negative fluid balance in volume-overloaded patients with sepsis is related to improved survival rates.[102]

The precise monitoring of hemodynamic status and fluid imbalance in COVID-19 associated AKI will help patients achieve better results.

If conventional management fails, RRT should be considered in patients with volume overload, particularly those with refractory hypoxemia. In patients with COVID-19-induced AKI, early initiation of RRT and sequential extracorporeal organ support[103] appear to supply sufficient organ support and avoid disease severity progression. However, this issue requires further investigation in future clinical trials.

Continuous RRT (CRRT) as a preferred modality has been suggested in hemodynamically unstable patients with COVID-19. In CRRT, local citrate anticoagulation is more beneficial than other anticoagulants in extending the extracorporeal circuit lifespan and minimizing the hemorrhage risk.[28] Furthermore, continuous veno-venous hemodialysis modality (CVVHD) supplies a longer filter life-span with reduced internal hemoconcentration in the filter. CRRT should be supplied with a minimum dose of 20 to 25 mL/kg per hour.[94]

Although promising results have been reported, evidence for these treatments is limited at present, so they need to be used in the context of a clinical trial to determine their safety and efficacy.

CONCLUSION

Previous experimental findings concerning endothelial dysfunction, immune cell response, and fibroblasts activation have provided new understanding about the cellular and molecular mechanisms of the AKI to CKD transition. Irrespective of the AKI etiology, endothelial dysfunction and the subsequent hypoxia trigger a cascade of self-sustaining events that lead to myofibroblast activation, extracellular matrix deposition, and interstitial inflammation.

The general view has revealed that all the molecular and cellular mechanisms finally converge on tubular epithelial cell dysfunction. The inadequate recovery of the tubular structure's

integrity sustainsthe events discussed above, promoting renal interstitial injury.

Due to the high prevalence of AKI in patients with COVID-19, the involvement of most of the aforementioned signaling pathways and the lack of definitive treatment for this problem, as well as the involvement of various systems such as cardiovascular, respiratory, and immune during this disease, the possibility of progression to CKD even after recovery will exist. This is likely to increase the burden of disease in the coming years and impose heavy costs.

Based on the literature review finding in the present study, it is necessary to conduct a close follow-up and long-term longitudinal study on survived critically ill patients with COVID-19 associated AKI in the coming years to properly manage and prevent possible risks of kidney failure and subsequent problems.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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Correspondence to:
Jamshid Roozbeh, MD
Full Professor of Nephrology
Shiraz Nephro-Urology Research Center, Muhammad Rasoololah Research Tower, Khalili Avenue, Shiraz, Postal Code: 7193635899, Iran
ORCID ID: https://orcid.org/0000-0002-4268-1727
Tel: 0098 917 111 4021
Fax: 0098 713 628 1563
E-mail: roozbehj@hotmail.com

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