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# Relationship Between Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the Etiology of Acute Kidney Injury (AKI)



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## ABSTRACT

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since it was first recognized in December 2019, it has resulted in the ongoing worldwide pandemic. Although acute hypoxic respiratory failure (AHRF) and acute respiratory distress syndrome (ARDS) are the main features of the disease, the involvement of other organs needs to be explored. There has been a growing concern regarding the association between acute kidney injury (AKI) and poor outcomes in SARS-CoV-2 patients. Based on current observational data, AKI is the 2<sup>nd</sup> most common cause of morbidity and mortality behind ARDS in SARS-CoV-2 patients. Angiotensin-converting enzyme 2 (ACE2) receptor has been shown to be the cornerstone of SARS-CoV-2 infection and possibly plays a significant role in the occurrence of renal injury. The pathogenesis of AKI is likely multifactorial that involves not only direct viral invasion but also dysregulated immune response in the form of cytokine storm, ischemia to kidneys, hypercoagulable state, and rhabdomyolysis, among others. We performed a literature search of the Pubmed and Google Scholar database from 1996 to 2020 using the following keywords: severe acute respiratory syndrome coronavirus 2, coronavirus disease 2019, angiotensin-converting enzyme 2 receptor, and acute kidney injury to find the most pertinent and highest-quality of evidence. Any cited references were reviewed to identify relevant literature. The purpose of this review is to discuss, explore, and summarize the relationship between AKI in SARS-CoV-2 patients, with a focus on its epidemiology, association with ACE2 receptors, and pathophysiology of AKI.

**Key Indexing Terms:** COVID-19; Severe Acute Respiratory Syndrome Coronavirus 2; SARS-CoV-2; Acute Kidney Injury; Etiology. [*Am J Med Sci* 2021;361(3):287–296.]

## INTRODUCTION

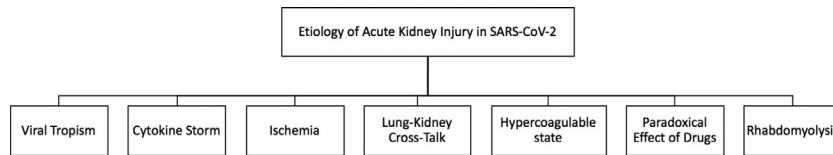
Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since it was first identified in December 2019, it has spread globally, resulting in the ongoing worldwide pandemic.<sup>1</sup> SARS-CoV-2 belongs to the same coronavirus family responsible for respiratory illnesses such as the severe acute respiratory syndrome (SARS-CoV), and Middle East respiratory syndrome (MERS-CoV) that were responsible for the 2003 and 2012 epidemic, respectively.<sup>2</sup> SARS-CoV-2 has 80% similarity in genetic sequence to SARS-CoV but only 50% similarity when compared to MERS-CoV. The clinical presentation of SARS-CoV-2 can range from asymptomatic infection or self-limited flu-like illness to life-threatening illness in the form of sepsis, acute hypoxic respiratory failure (AHRF), acute respiratory distress syndrome (ARDS), coagulopathy, and multi-organ failure.<sup>3,4</sup> Pulmonary involvement with AHRF and ARDS has been the primary focus of the disease in patients with SARS-CoV-2 due to its high prevalence between 40 to 85%.<sup>3–5</sup> However, similar observational reports have highlighted that AKI is also

relatively common in SARS-CoV-2, with prevalence between 3 to 29% in SARS-CoV-2 infections.<sup>3,5,6</sup> There is a growing interest in identifying whether there is an association between the pathophysiology of SARS-CoV-2 and the emergence of AKI in an attempt to alter the disease course and overall prognosis.

This review aimed to describe how the novel SARS-CoV-2 cause AKI based on the current evidence in the literature (Fig. 1). An electronic search was performed through Pubmed and Google Scholar database from 1996 to 2020 using the following keywords: severe acute respiratory syndrome coronavirus 2, coronavirus disease 2019, angiotensin-converting enzyme 2 receptor, and acute kidney injury. All relevant English language articles were included in this review.

## EPIDEMIOLOGY

AKI results from an abrupt loss of kidney function and is strongly associated with an increase in morbidity and mortality. During the SARS-CoV epidemic in 2003, the incidence of AKI was reported to be 6.7% in 536 patients.



**FIGURE 1.** Etiologies of Acute Kidney Injury in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

However, the mortality rate for those with renal impairment was 91.7%, as opposed to 8.8% in those without renal impairment.<sup>7</sup> According to retrospective studies in China, the prevalence of AKI was around 3% in hospitalized SARS-CoV-2 patients that increased to 29% in those who are critically ill.<sup>3,5,6</sup> Cheng and colleagues assessed 701 SARS-CoV-2 hospitalized patients in China, and they observed that the incidence of AKI was 5% but significantly doubled to 12% in those with a history of chronic kidney disease (CKD).<sup>8</sup> Among those with CKD, their in-hospital mortality increased by up to 34% from 13% in those without a history of renal impairment. A study of 28-day mortality after ICU admission among 52 SARS-CoV-2 patients by Yang and colleagues showed that the prevalence of AKI was 38% among non-survivors compared to 15% among survivors.<sup>5</sup> A multi-centered study by Li and colleagues demonstrated that SARS-CoV-2 patients who developed AKI had a 5.3-fold increase in mortality compared to those without AKI.<sup>9</sup> Studies by Yang and Li further demonstrated that AKI was the 2<sup>nd</sup> most common cause of death behind ARDS in critically ill SARS-CoV-2 patients.<sup>5,9</sup> The findings of these studies supports our suspicion that AKI is an emerging cause of morbidity and mortality in SARS-CoV-2 in a similar fashion as ARDS.

## THE ASSOCIATION BETWEEN SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 AND ANGIOTENSIN-CONVERTING ENZYME 2 RECEPTORS

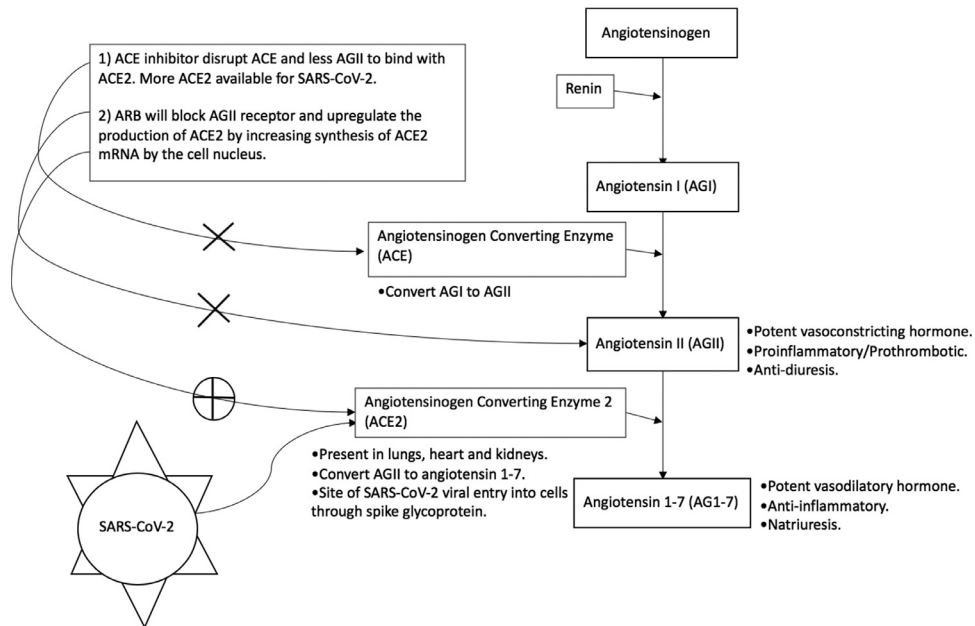
The renin-angiotensin-aldosterone system (RAAS) is an elegant cascade of vasoactive peptides that mastermind key processes in human physiology. SARS-CoV-2 interface with RAAS and cause infections similar to other coronaviruses such as SARS-CoV by exploiting the same membrane-bound protein of angiotensin-converting enzyme 2 (ACE2) receptor.<sup>10,11</sup> The transmission of SARS-CoV-2 is commonly in the form of aerosolized droplets and direct contact with respiratory secretions.<sup>12,13</sup> The respiratory system is the primary point of entry for SARS-CoV-2 into the body as ACE2 receptors are expressed by the epithelial cells along with the nasopharyngeal, oropharyngeal, and bronchial mucosa before the virus finally settle in the lung alveoli.<sup>10,14</sup> ACE2 receptor is expressed in abundance not only in the upper and lower respiratory tract but also in the heart, intestines, and epithelial apical brush borders of the proximal renal tubules, as well as podocytes but less intensity.<sup>15</sup> The primary function of ACE2 (membrane-bound aminopeptidase) is to convert angiotensin II (AGII) to form

angiotensin 1-7 (AG1-7), which has a vasodilatory, anti-inflammatory, and natriuretic properties (Fig. 2).<sup>14,16</sup> AGII, which is a potent vasoconstricting hormone, is synthesized from angiotensin I (AGI) by angiotensin-converting enzyme (ACE). Other than its vasoconstrictive properties, AGII plays a vital role in RAAS, where it displays proinflammatory, prothrombotic, and anti-diuresis effects. AGII will also stimulate the secretion of other hormones such as aldosterone and vasopressin.<sup>14,17,18</sup> AGI is a product of angiotensinogen (amino-acid protein), that is secreted by the liver and metabolized by enzyme renin.<sup>14</sup> SARS-CoV-2 can binds with angiotensin-converting enzyme 2 (ACE2) receptor via spike glycoprotein on its cell membrane that allows the virus to gain access in the targeted human cells where it will intracellularly replicate and display its cytotoxic properties.<sup>2,13,19,20</sup> Moreover, SARS-CoV-2 not only utilizes ACE2 to gain entry into a cell, but it will also downregulate ACE2 expression. Therefore, the level of AGII will increase due to the lack of a negative feedback mechanism involving ACE2 to degrade it into AG1-7. The elevated levels of AGII, which itself is a pro-inflammatory marker, will promote an increase in neutrophil infiltration of organs, production of cytokines, and vascular permeability, causing end-organ injuries.<sup>21,22</sup>

## ETIOLOGY OF AKI IN SARS-COV-2 PATIENTS

### Viral Tropism

SARS-CoV-2 was initially suspected to involve the kidneys based on reverse transcriptase-polymerase chain reaction (RT-PCR) testing of the urine that showed the presence of SARS-CoV-2 in a cohort of infected patients.<sup>3</sup> Moreover, computed tomography (CT) scan of the kidneys in SARS-CoV-2 patients has even demonstrated reduced Hounsfield density that suggests underlying inflammation with edema in patients with AKI.<sup>9</sup> Autopsy findings of 26 kidneys in SARS-CoV-2 patients by Su and colleagues showed diffuse proximal tubule injury with loss of brush border and frank necrosis together with vacuolar degeneration were frequently noted on light microscopy.<sup>23</sup> Under electron microscopy, SARS-CoV-2 was seen in the tubular epithelium predominantly in the proximal tubule and podocyte. These were confirmed on immunostaining testing that showed the presence of SARS-CoV-2 nucleoprotein antibody. We know from previous studies that ACE2 is present in abundance, especially in the proximal tubule but, to a lesser extent, in the distal tubule and podocyte.<sup>14,16</sup> The preference of SARS-CoV-2 towards the kidneys is likely



**FIGURE 2.** Flowchart of Renin-Angiotensin-Aldosterone System (RAAS) with Site of Action of ACE Inhibitors and ARBs, and SARS-CoV-2 Displayed.

due to a low pH environment created by urine and pH-dependent enzyme of cysteine cathepsins (protease responsible for endosomal transport) that thrives in an acidic environment. This will facilitate the entry into the cells by endocytosis after binding occurs between ACE2 receptor and SARS-CoV-2 during periods of viremia.<sup>24</sup> In one observational study, around 15% of SARS-CoV-2 were found to have viremia.<sup>3</sup> Similar pathological findings were noted in the kidneys of patients infected with SARS-CoV that suggest ACE2 receptors play a crucial role in viral infiltration of cells.<sup>25</sup>

Observational studies have reported that 40 to 60% of SARS-CoV-2 patients had an elevated amount of proteins in their urine.<sup>8,9</sup> Podocytes are involved in filtration and synthesizing aspects of the glomerular filtration barrier that prevents proteins from passing through.<sup>26</sup> The presence of SARS-CoV-2 has been seen using light and electron microscopy at the level of the podocytes where effacement of foot process and detachment from the glomerular basement membrane is observed signifying viral-related cell destruction.<sup>23</sup> These findings explain the etiology of proteinuria found in SARS-CoV-2 patients. Other than SARS-CoV-2 causing renal impairment due to its direct cytotoxic effects on cells, SARS-CoV-2 can also trigger the innate immune system to cause indirect cell destruction to the kidneys. Diao and colleagues observed that macrophage, specifically CD68+, together with complement levels of C5b-9, were responsible for innate immune cell-related damage of the kidneys based on their autopsy findings in six SARS-CoV-2 patients.<sup>19</sup> Their report also suggested that the level of destruction was not limited to the proximal renal tubules where the virus was most commonly located at but also affected the

surrounding distal tubules and podocytes. As mentioned above, SARS-CoV-2 will also downregulate the expression of ACE2 after binding to it. The level of AGII will increase due to the lack of ACE2 to degrade it. The elevated levels of AGII will promote neutrophil infiltration of the kidneys, increase vascular permeability, and release of inflammatory mediators causing AKI.<sup>21,22</sup>

Collapsing glomerulopathy, also known as collapsing focal segmental glomerulosclerosis, is an aggressive and distinct variant of focal segmental glomerulosclerosis often associated with human immunodeficiency virus (HIV) infection.<sup>27</sup> However, collapsing glomerulopathy is increasingly recognized in non-HIV patients where it has been described in several case reports of SARS-CoV-2 patients of African descent as a cause of AKI.<sup>28–30</sup> The hallmark of the disease is patients typically present with nephrotic syndrome range of proteinuria define as more than 3 g of proteins daily in the urine and variable degree of renal impairment. Collapsing glomerulopathy can be precipitated by direct SARS-CoV-2 insult and/or alteration to the activity of the immune system by SARS-CoV-2 similar to HIV infection resulting in damage to the glomerular epithelial cells and loss of podocytes integrity.<sup>27,31,32</sup> This will occur in patients with dysfunctional APOL1 protein. APOL1 gene of G1 and G2, which is rampant in individuals of African ancestry, has been identified as a precipitating factor for collapsing glomerulopathy.<sup>32</sup> Segmental or globally collapsed and sclerotic glomerular capillaries, with hyperplasia and hypertrophy of glomerular epithelial cells will be seen on kidney biopsy.<sup>27</sup> Therefore, SARS-CoV-2 causes AKI and proteinuria by direct viral invasion of the renal tubules through ACE2 receptors, triggers indirect cytotoxic damage of renal tubules and podocytes by the



**FIGURE 3.** Pathogenesis of SARS-CoV-2 Causing AKI in The Kidneys.

innate immune system, increases levels of AGII and by collapsing glomerulopathy (Fig. 3).

### Cytokine Storm

Many observational studies in SARS-CoV-2 patients demonstrated the presence of elevated inflammatory markers such as white blood cell (WBC) count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin, lactate dehydrogenase (LDH), ferritin, and D-dimer.<sup>3,4,6,33</sup> In those studies, patients with elevated inflammatory markers had a higher likelihood of developing AKI and poor outcomes. These same cohorts of patients had a higher requirement for ICU admission, vasopressor use, and mechanical ventilation. A study by Zhou and colleagues showed that elevated inflammatory markers were independently associated with poor survival and increasing incidence of AKI up to 50-fold.<sup>33</sup> The elevated inflammatory markers are likely representative of cytokine immune response during SARS-CoV-2 infections, where similar findings were noted during *in vitro* cell experiments done on other forms of coronavirus infections such as SARS and MERS during their respective outbreaks.<sup>34,35</sup> High levels of proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1A (MIP-1A) have been demonstrated to play a significant role in the pathogenesis of ARDS in SARS-CoV patients.<sup>36,37</sup>

Cytokine storm is a form of severe systemic inflammatory response syndrome (SIRS) that can be triggered by any external stimuli such as infections from SARS-CoV-2, which causes massive recruitment of immune cells to an organ resulting in the production of a large amount of cytokines.<sup>38</sup> Cytokine storm is suspected of playing a significant role in the pathogenesis of organ dysfunction and poor outcomes in SARS-CoV-2 patients. In a normal inflammatory phase, cells infected by SARS-CoV-2 will secrete inflammatory mediators (cytokines) and recruit immune cells to destroy it. Once the infected cells have contained the offending pathogens (SARS-CoV-2), the healing phase of inflammation ensues, involving tissue repair and restoration of homeostasis in the body with a reduction in the formation of inflammatory mediators and cessation of recruitment of immune cells. However, in certain circumstances, excessive, delayed, and persistent cytokine response may occur, leading to immune-related damage of not only lung tissues that the SARS-CoV-2 predominantly infects but also surrounding healthy uninfected organs such as

the kidneys, heart, and liver.<sup>38,39</sup> Post-mortem findings by Diao and colleagues supported the notion that innate immune cells, specifically CD68+ macrophages and C5b-9 complement level, were responsible for indirect cytotoxic damage to renal tubules that had been infected by SARS-CoV-2.<sup>19</sup> Similar findings of cytokine storm-mediated AKI has been appreciated in several clinical conditions such as treatment with chimeric antigen receptor (CAR) T cell therapy in patients with hematological malignancies and thymoglobulin treatment in renal transplant patients.<sup>40,41</sup> Cytokine storm has even been suggested to cause collapsing glomerulopathy due to elevated proinflammatory cytokines detected in SARS-CoV-2 patients that result in immune-directed injury to the glomeruli.<sup>27,30</sup>

### Ischemia secondary to hypoperfusion

AKI secondary to impaired perfusion to kidneys can be due to multiple etiologies in SARS-CoV-2. SARS-CoV-2 induced septic shock can also cause hypoxia and ischemia to the kidneys due to a decrease in blood perfusion. Septic shock is the 3<sup>rd</sup> most common cause of death in SARS-CoV-2 patients behind AHRF from ARDS and AKI, where it is the primary cause of multi-organ dysfunction.<sup>4,6,33</sup> Zhou and colleagues also demonstrated that septic shock is commonly seen in up to 70% of non-survivors in SARS-CoV-2.<sup>33</sup> Post-mortem findings by Su and colleagues on SARS-CoV-2 patients, where up to 62% of them developed septic shock revealed diffuse proximal tubule injury with loss of brush border, vacuolar degeneration, and frank necrosis on light microscopy.<sup>23</sup> Acute tubular injury can be seen in either SARS-CoV-2 infiltration of cell or ischemic injury due to hypoperfusion. However, there was also diffuse erythrocyte stagnation in the peritubular and glomerular capillary loops without distinct fragmentation of erythrocytes or platelet noted on autopsy findings. In some cases, there was predominant glomerular loop occlusion by erythrocyte over peritubular capillaries. These findings favored ischemic and hypoxic injury to the kidneys from hypoperfusion over SARS-CoV-2 infiltration of the cell.<sup>42</sup> Other than septic shock, these ischemic events can also be due to high levels of AGII in circulation. SARS-CoV-2 has been shown to downregulate ACE2 upon binding, making more AGII available. AGII has proinflammatory and potent vasoconstricting properties that will cause vasoconstriction of renal vessels that further reduce renal blood flow, causing ischemia.<sup>42,43</sup> In a subpopulation of patients who has CKD, especially those with diabetic and hypertensive kidney disease, the expression of ACE



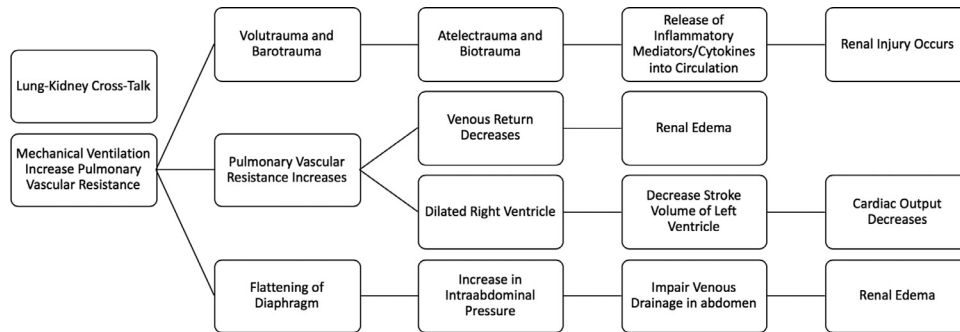


FIGURE 5. Physiologic Changes by Mechanical Ventilation Leading to Acute Renal Failure.

mechanisms of leukocyte infiltration, apoptosis of mesangial, tubular and glomerular cells, endothelial dysfunction, and vasodilatation.<sup>53</sup> Mechanical ventilation will also increase the intrathoracic pressure, pulmonary vascular resistance, and central venous pressure. This will lead to a decrease in venous return and impede right ventricular function causing renal congestion. Dilated right ventricular due to high pulmonary vascular pressure will limit left ventricular filling due to bowing of interventricular septum from right to left (ventricular interdependence) that reduce stroke volume and cardiac output.<sup>54</sup> The rise in intrathoracic pressure and flattening of the diaphragm during mechanical ventilation will create an increase in intra-abdominal pressure and further impede venous drainage causing renal edema.<sup>55</sup> These constellations of physiologic changes will impair perfusion to the kidneys causing AKI (Fig. 5).

**Hypercoagulable/Prothrombotic State**

Several observational studies have shown a marked elevation in D-dimer levels in patients suffering from SARS-CoV-2, and up to 25% was found to have venous thromboembolism events (VTE).<sup>3,4,8,33,56</sup> In these studies, the incidence of multi-organ dysfunction, including renal failure, was noted to be higher in those with elevated D-dimer. Autopsy findings by Su and colleagues noted that in 73% of SARS-CoV-2 patients, D-dimer was markedly elevated.<sup>23</sup> Tang and colleagues revealed that elevated D-dimers were associated with a higher mortality rate (72% in non-survivors versus 0.6% in survivors) in SARS-CoV-2 patients.<sup>57</sup> D-dimer represents the end-products of fibrin clot (generated in any thrombotic state) that has been metabolized by plasmin (antithrombotic) enzyme. The high levels of D-dimer represent not only a prothrombotic state in SARS-CoV-2 but possibly disseminated intravascular coagulation (DIC) process occurring, especially in those with elevated prothrombin time and partial thromboplastin time. Therefore, suspicion exists that micro-thrombosis could potentially play a significant role in the pathogenesis of organ dysfunction in SARS-CoV-2 infections (Fig. 6).

Micro-thrombosis has been demonstrated to occur at the level of small arteries in the lungs of SARS-CoV-2

patients who died of hypoxic respiratory failure.<sup>58,59</sup> The appearance of diffuse and focal segmental fibrin thrombus in the glomerular capillary loops associated with endothelial injury has been observed in autopsy reports of kidneys in SARS-CoV-2 patients.<sup>23</sup> These findings are typically seen in thrombotic microangiopathy-related kidney disease due to complement level dysregulation.<sup>60,61</sup> Magro and Diao have both described the presence of complements C3d, C4d, and C5b-9 together with enzymes of mannose-binding lectin (MBL) and mannose-associated serine protease (MASP2) deposition in the lungs, skin, and kidneys during post-mortem report on SARS-CoV-2 patients.<sup>19,59</sup> C3d is found in the alternative complement pathway, and C4d are core components of the classical complement pathways, whereas MBL and MASP2 are essential enzymes of lectin complement pathway.<sup>62,63</sup> These three distinct pathways are crucial for complement pathway activation to form membrane attack complex (MAC) of C5Bb-9 complements that are likely to cause disruption of cells and microthrombosis seen in organs of SARS-CoV-2 patients. Both the kidneys and lungs have been shown to contain an abundance of ACE2 receptors, which SARS-CoV-2

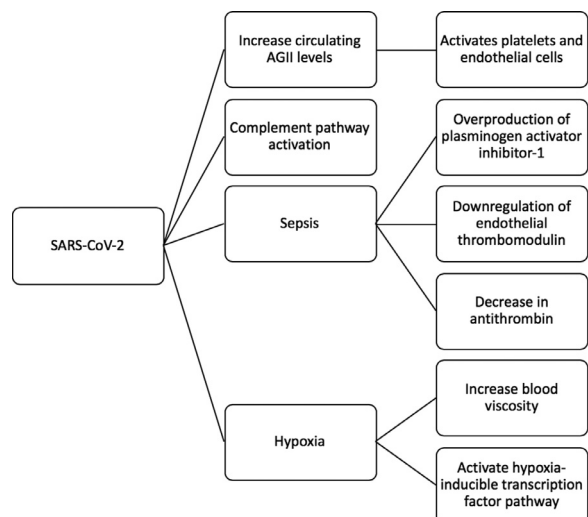


FIGURE 6. Hypercoagulable/Prothrombotic State in SARS-CoV-2.

requires to replicate and thrive. The levels of AGII will be increased in SARS-CoV-2 infection that gives rise to the release of more inflammatory mediators and the recruitment of more immune cells.<sup>18</sup> Many of these inflammatory mediators are prothrombotic that predispose to the development of macro and micro-thrombosis. The elevated levels of circulating AGII and inflammatory mediators will activate the platelets and endothelial cells of the blood vessels to release tissue and clotting factors causing thrombosis.<sup>17,64</sup>

Sepsis can create a prothrombotic state by directly and indirectly affecting coagulation factors and enzymes in our body through three possible mechanisms. 1) Sepsis-related overproduction of plasminogen activator inhibitor-1 enzyme that disrupts the function of circulating tissue plasminogen activator (antithrombotic) enzyme, which is essential to prevent thrombosis. 2) Sepsis-related downregulation of endothelial thrombomodulin proteins, which is required for activation of protein C (anticoagulation) enzyme. 3) The decrease in levels of antithrombin (anticoagulant) enzyme in sepsis due to extravasation in the setting of an increase in vascular permeability and consumption by inflammatory mediators.<sup>57,65</sup> The hypercoagulable state in SARS-CoV-2 can also be triggered by hypoxia that stimulates thrombosis through an increase in blood viscosity and activation of hypoxia-inducible transcription factor pathway.<sup>66</sup> This pathway will stimulate the production of integrin by platelet that allows it to combine with clotting factors and other platelets to form a thrombus. For these reasons using data from observational clinical studies, some medical institutions will recommend considering empirically anticoagulating patients with D-dimer levels of 1.5–3 mg/L and more, as it is a useful marker in predicting VTE in those with confirmed SARS-CoV-2 infections if no contraindications exist.<sup>56,67,68</sup>

### Paradoxical Effect of Anti-Hypertensive of ACE inhibitors and ARBs

Based on current epidemiological data, about 50% of SARS-CoV-2 patients suffer from comorbidities of cardiovascular disease or its related risk factors of diabetes, hypertension, and hyperlipidemia.<sup>3–6</sup> The mortality rate was also significantly higher in those with cardiovascular disease-related comorbidities.<sup>3–5</sup> Many patients with diabetes or cardiovascular disease are either on ACE inhibitors or ARBs due to their reno-protective properties in diabetic nephropathy, and also congestive heart failure.<sup>69</sup> ACE inhibitors and ARBs have major effects on the RAAS, which are essential components of the sympathetic nervous system. These drugs have been shown to disrupt the synthesis and action of angiotensin II (potent vasoconstrictor), decrease the production of aldosterone (anti-natriuresis), and constrict the afferent arteriolar flow in the kidneys causing hypotension, hyperkalemia, worsening renal failure and shock.<sup>70</sup> Therefore in hospitalized patients with sepsis, these medications are typically held due to the increased risk of adverse drug events.

As ACE2 receptor protein plays a vital role in SARS-CoV-2 infection, the use of anti-hypertensive drugs such as ACE inhibitors and angiotensin-receptor 2 blockers (ARBs) have been evaluated in multiple studies. A study by Reynolds and colleagues revealed that in patients with SARS-CoV-2, there was no association that the use of ACE inhibitors and ARBs would lead to a greater risk of SARS-CoV-2 infections or developing severe illness-related to SARS-CoV-2.<sup>71</sup> An autopsy finding in SARS-CoV-2 patients showed that there was no evidence of alteration in ACE2 receptor expression in kidneys despite the use of ACE inhibitors.<sup>72</sup> Mancía and colleagues found that the use of ACE inhibitors and ARBs was more common among those infected with SARS-CoV-2 than those who were not.<sup>73</sup> However, these findings were inconclusive as their observational study did not have sufficient statistical power to prove an independent association.

Animal models of mice have revealed that ACE inhibitors and ARBs upregulate the expression of ACE2 proteins in the heart and kidneys by three to five-fold.<sup>74</sup> ACE inhibitors will bind with ACE and decrease the conversion of AGI to AGII, resulting in more AGII available to link with the SARS-CoV-2 instead (Fig. 1).<sup>16</sup> ARBs will upregulate the expression of more ACE2 for SARS-CoV-2 to bind with by increasing the synthesis of ACE2 messenger ribonucleic acid (mRNA) by the cell nucleus for the ribosomes to produce ACE2 proteins.<sup>75,76</sup> For these reasons, concerns exist that the use of these drugs will predispose to more severe SARS-CoV-2 infections in the form of septic shock and multi-organ failure, including renal failure.<sup>77</sup> As the quality of evidence, has remained constricted to observational studies, the current consensus remains divided on the decision to stop the use of ACE inhibitors and ARBs in SARS-CoV-2 patients versus continuing them in light of their underlying comorbidities.

### Rhabdomyolysis

Rhabdomyolysis is a clinical and laboratory syndrome defined as an injury to the skeletal muscle that results in the leakage of muscle contents, specifically creatine kinase (CK) and myoglobin into the blood and urine.<sup>78,79</sup> AKI is the most common end-organ damage related to rhabdomyolysis, with an incidence of up to 46% reported where electrolyte dysfunction is the most detrimental complications.<sup>78–80</sup> Viral-related cause of rhabdomyolysis has been increasingly reported in the literature where influenza is the most frequent virus associated with rhabdomyolysis.<sup>81</sup> Autopsy findings of kidneys samples of SARS-CoV-2 patients revealed the presence of hemosiderin granules in the tubular epithelium and pigmented casts on light microscopy.<sup>23,79</sup> These suggest rhabdomyolysis as a potential etiology of acute renal failure. Minimum CK levels of 5,000 to 10,000 IU/L has been suggested for the development of acute renal failure.<sup>78,79,82</sup>

The first incidence of coronavirus-related rhabdomyolysis was reported in a case series of SARS-CoV patients where they all developed AKI with peak CK



levels ranging from 7,000 to 330,000 IU/L.<sup>83</sup> Jin and colleagues were the first to describe a 60-year-old man admitted with SARS-CoV-2 pneumonia and subsequently developed rhabdomyolysis on day 9<sup>th</sup> of hospital admission.<sup>84</sup> His peak laboratory values of CK, LDH, and CRP were markedly elevated at 12,000 IU/L, 2,347 IU/L, and 206 mg/L, respectively. Guan and colleagues reported that the prevalence of rhabdomyolysis among hospitalized SARS-CoV-2 patients in China was around 0.2%.<sup>4</sup> The peak levels of CK documented in these patients range from 300 to 2500 IU/L. Hence, peak CK has been shown to have a weak correlation with the development of AKI in the setting of viral-associated rhabdomyolysis.

It is currently unclear if rhabdomyolysis in SARS-CoV-2 patients is related to direct viral invasion as skeletal muscles lack the ACE2 receptors, which are crucial for SARS-CoV-2 invasion of cells. In patients infected with SARS-CoV-2, high values of CK and myoglobin were found in their serum together with marked elevation in their inflammatory markers.<sup>6,85</sup> Chong and colleagues described a 37-year-old man diagnosed with AHRF secondary to COVID-19 pneumonia, AKI, and rhabdomyolysis. His CK on admission was 17,000 and peaked at 35,000 IU/L. His inflammatory markers of LDH (1300 IU/L), CRP (60 mg/L), D-dimer (54 mg/L), and ferritin (1100 ng/mL) were markedly elevated on admission and continued to rise during hospitalization in concordance with his declining renal function, before his demise.<sup>86</sup> These findings suggest that the overactive immune system in SARS-CoV-2 patients is responsible for not only the development of rhabdomyolysis but also AKI as part of multi-organ dysfunction secondary to cytokine storm.<sup>86</sup> There is still a lack of clear clinical evidence that thrombosis can occur in the skeletal muscles due to the scarcity of autopsies being performed during the SARS-CoV-2 pandemic. However, one can only presume that micro-thrombosis is likely to occur at the level of skeletal muscles causing ischemia and rhabdomyolysis from tissue hypoperfusion in a similar fashion to the lungs and kidneys.<sup>23,58,59,67</sup>

## CONCLUSIONS

SARS-CoV-2 is capable of causing multi-organ dysfunction through different processes. While the incidence and prevalence of AKI in SARS-CoV-2 remain underappreciated when compared to AHRF and ARDS, the significant value of recognizing and understanding the pathophysiology of AKI is extremely important to improve the outcome in SARS-CoV-2 patients. Patients with SARS-CoV-2 infections share many similarities where the precipitating factors that cause acute lung injury will also cause AKI. A good understanding of the etiology of AKI will allow more prompt diagnosis and improvement in the management of SARS-CoV-2 patients.

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