


## REVIEW

# Covid-19 and kidney injury: Pathophysiology and molecular mechanisms

Elham Ahmadian<sup>1</sup> | Seyed Mahdi Hosseiniyan Khatibi<sup>1</sup> | Saiedeh Razi Soofiyani<sup>2</sup> |  
Sima Abediazar<sup>1</sup> | Mohammadali M. Shoja<sup>3</sup> | Mohammadreza Ardalan<sup>1</sup> |  
Sepideh Zununi Vahed<sup>1</sup> 

<sup>1</sup>Kidney Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

<sup>2</sup>Clinical Research Development Unit, Sina Educational, Research and Treatment Center, Tabriz University of Medical Sciences, Tabriz, Iran

<sup>3</sup>Department of Surgery, University of Illinois at Chicago-Metropolitan Group Hospitals (UIC-MGH), Chicago, Illinois, USA

## Correspondence

Sepideh Zununi Vahed and Mohammadreza Ardalan, Kidney Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.  
Email: [sepide.zununi@gmail.com](mailto:sepide.zununi@gmail.com) (S. Z. V.) and [ardalan34@yahoo.com](mailto:ardalan34@yahoo.com) (M. A.)

## Funding information

Kidney Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

## Summary

The novel coronavirus (SARS-CoV-2) has turned into a life-threatening pandemic disease (Covid-19). About 5% of patients with Covid-19 have severe symptoms including septic shock, acute respiratory distress syndrome, and the failure of several organs, while most of them have mild symptoms. Frequently, the kidneys are involved through direct or indirect mechanisms. Kidney involvement mainly manifests itself as proteinuria and acute kidney injury (AKI). The SARS-CoV-2-induced kidney damage is expected to be multifactorial; directly it can infect the kidney podocytes and proximal tubular cells and based on an angiotensin-converting enzyme 2 (ACE2) pathway it can lead to acute tubular necrosis, protein leakage in Bowman's capsule, collapsing glomerulopathy and mitochondrial impairment. The SARS-CoV-2-driven dysregulation of the immune responses including cytokine storm, macrophage activation syndrome, and lymphopenia can be other causes of the AKI. Organ interactions, endothelial dysfunction, hypercoagulability, rhabdomyolysis, and sepsis are other potential mechanisms of AKI. Moreover, lower oxygen delivery to kidney may cause an ischaemic injury. Understanding the fundamental molecular pathways and pathophysiology of kidney injury and AKI in Covid-19 is necessary to develop management strategies and design effective therapies.

## KEYWORDS

acute kidney injury, angiotensin, bardikinin, coronavirus, proteinuria, renal injury, SARS-CoV-2

**Abbreviations:** ACE2, angiotensin-converting enzyme 2; ACKR2, atypical chemokine receptor 2; AKI, acute kidney injury; ANPEP, Alanyl aminopeptidase; APC, antigen-presenting cells; ARDS, acute respiratory distress syndrome; BK, bradykinin; BMI, Body mass index; CKD, chronic kidney disease; Cov, coronavirus; Covid-19, coronavirus disease 2019; CRS, cardio-renal syndrome; CVVHD, continuous veno-venous haemodialysis modality; DAMPs, damage-associated molecular proteins; ENPEP, Glutamyl aminopeptidase; GFR, glomerular filtration rate; HD, haemodialysis; ICU, intensive care unit; IFN, interferon; IL, interleukin; KKS, kallikrein-kinin system; MERS, Middle East respiratory syndrome; NETs, neutrophil extracellular traps; PAMPs, pathogen associated molecular patterns; RAS, renin-angiotensin system; SARS-CoV, severe acute respiratory syndrome coronavirus; TMPRSS2, transmembrane protease, serine 2; TNF, tumor necrosis factor.

Elham Ahmadian and Seyed Mahdi Hosseiniyan Khatibi contributed equally to this work and should be considered as co-first authors.

## 1 | INTRODUCTION

The novel coronavirus (SARS-CoV-2) has turned into a life-threatening pandemic disease (Covid-19). Acute respiratory distress syndrome (ARDS) and diffuse alveolar haemorrhage are the principal manifestations of Covid-19.<sup>1</sup> Although the respiratory system is the major target of COVID-19, other organs in the body might be infected by the virus via the circulating system, including scanty information regarding the renal system. Reports indicate that kidney involvement is frequent and ranges from mild proteinuria to an advanced acute kidney injury (AKI).<sup>2</sup> Clinical evidence has shown the increment of serum creatinine and blood urea nitrogen as well as the appearance of haematuria and proteinuria in 701 Covid-19 cases in a large prospective study in China.<sup>3</sup> These patients showed a lower platelet and lymphocyte count, higher leucocyte count, a higher rate of comorbidities, and an intensive care need compared to patients with normal kidney function. About 5% of the patients were diagnosed with AKI during hospitalization.<sup>3</sup> Studies in Europe and the USA reveal that Covid-19 induces AKI in 20-40% of the patients admitted to intensive care unit (ICU) and AKI is deemed as a negative prognostic factor and an indicator of disease severity.<sup>3-5</sup>

Multiple factors could be involved in the pathogenesis of kidney damage in patients with Covid-19.<sup>6,7</sup> The initial impact might be the direct role of the virus on the renal parenchyma mediated by activating the angiotensin-converting enzyme 2 (ACE2), which functions as a SARS-CoV-2 receptor. ACE-2 and transmembrane protease, serine 2 (TMPRSS2) genes are expressed in kidney cells as much as in lung, small intestine and oesophagus; supporting their role as profound targets of SARS-CoV-2.<sup>8</sup> Moreover, recent studies suggest podocytes and proximal convoluted tubules, which express the ACE2 gene, as important host cells of the SARS-CoV-2, implying that the renal tissue is a possible target of SARS-CoV-2.<sup>9</sup> Beyond functioning as a viral receptor, ACE2 may act as a linker between Covid-19, the renin-angiotensin system (RAS), and the kallikrein-kinin system (KKS),<sup>10,11</sup> Figures 1 and 2.

The second mechanism through which Covid-19 can affect the kidney includes the immune system, which can in turn result in kidney damage. Another mechanism is the occurrence of a cytokine storm after a viral infection that can both influence the kidney directly and indirectly by inducing sepsis, shock, hypoxia, and rhabdomyolysis.<sup>12</sup> Organ interactions between lung, heart, and kidney would be other possible causes of the Covid-19-induced kidney injury. Finally, the generation of microthrombi in Covid-19 patients which can lead to acute ischaemia and AKI is the last proposed mechanism (Figure 3). There is no information regarding the impact of hyperinflammation, proteinuria and/or tubular damage on SARS-CoV-2 viral entry and ACE2 expression in proximal tubules. Theoretically, the replication of the virus in podocytes and further injuries could result in proteinuria.<sup>3</sup> Furthermore, the Covid-19-related microangiopathy and hemophagocytic macrophage activation could result in AKI. However, a result showed that AKI is uncommon in Covid-19 and the viral infection does not either cause AKI or worsen the chronic kidney disease (CKD) in these patients.<sup>13</sup>

In this review, we explore the potential pathways of kidney damage during Covid-19 in more details.

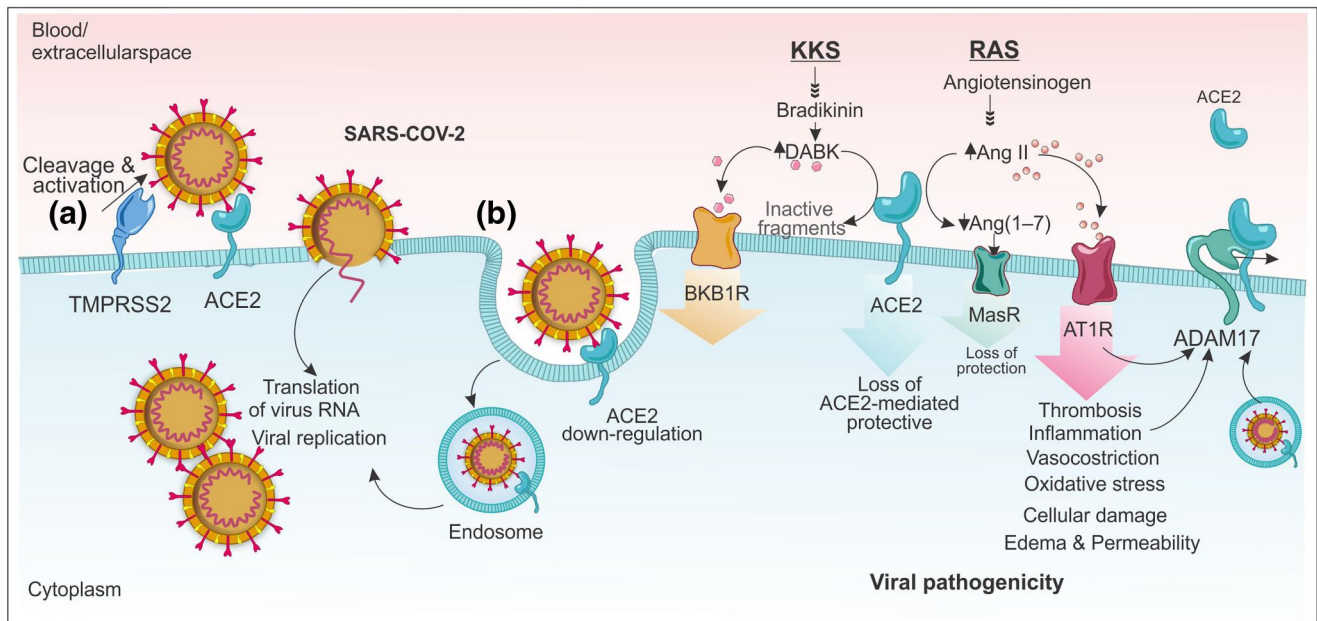
## 2 | THE KIDNEY AS A TARGET OF SARS-CoV-2

Although Covid-19 mainly targets the respiratory and immune systems, AKI is also found in Covid-19 patients. Kidney injury and the subsequent clinical events such as haematuria and proteinuria have been observed in approximately 40% of the Covid-19 patients.<sup>14</sup> This has been speculated to be in close connection with the expression of the ACE2 receptors in the brush border of proximal tubular cells.

The exact impact of SARS-CoV-2 on kidney and the possible induction of acute renal failure have to be investigated.<sup>15</sup> However, recent reports have shown renal dysfunction to be an increasing sign during the disease. Massive albuminuria and the later development of proteinuria have been observed in Covid-19 hospitalized patients.<sup>9</sup> Besides, 27% of affected and two-thirds of deceased patients have shown elevated blood urea nitrogen. From the pathological point of view, inflammation, oedema and a reduced density have been reported in kidney tissues of the sufferers.<sup>16</sup> In a recent study conducted by Cheng et al., 44% of the 710 hospitalized Covid-19 patients showed haematuria and proteinuria, while 27% of them had haematuria on admission.<sup>9,17</sup> Accordingly, kidney involvement appears to be a common event in SARS-CoV-2 infection and AKI is an independent prognostic factor.<sup>18</sup> Despite the amelioration of proteinuria and AKI, kidney complications were linked with exacerbated rates of mortality in Covid-19 patients, three weeks after the commencement of symptoms. The AKI and/or abnormal urine dipstick findings have been observed in approximately 75% of the 333 patients.<sup>19</sup> Urine analysis and postmortem samplings from the kidney tissues of the infected patients show SARS-CoV-2, confirming the kidney to be a novel target of Covid-19.<sup>20,21</sup> Moreover, SARS-CoV-2 nucleocapsid protein antigen accumulates in the renal tubules as observed by an immunohistochemistry examination. Virus-like particles are visible when an electronic microscope is used.<sup>9</sup> Interestingly, collapsing glomerulopathy has been also reported in Covid-19 patients.<sup>22</sup> Altogether, these reports clarify that kidney cells are targeted by SARS-CoV-2 and new strategies are needed to treat Covid-19 to prevent organ infection and dysfunction.

### 2.1 | Coronavirus entry into renal cells

ACE2 receptors are the major binding site for SARS-CoV-2. Alveolar Type II cells, oesophagus keratinocytes, liver cholangiocytes, stomach epithelial cells, colon colonocytes, ileum, rectum and kidney proximal tubules express ACE2 receptors.<sup>23</sup> Kidney expresses ACE2 more than the lung tissue<sup>24</sup> in the proximal tubules' brush border apical membrane and to a lower extent, podocytes express ACE2 in kidney tissues.<sup>24</sup> Thus, it could be hypothesized that the virus enters arteriole and glomerular capillaries and initially infects the glomerular endothelial cells. Then, podocytes are infected and the virus enters



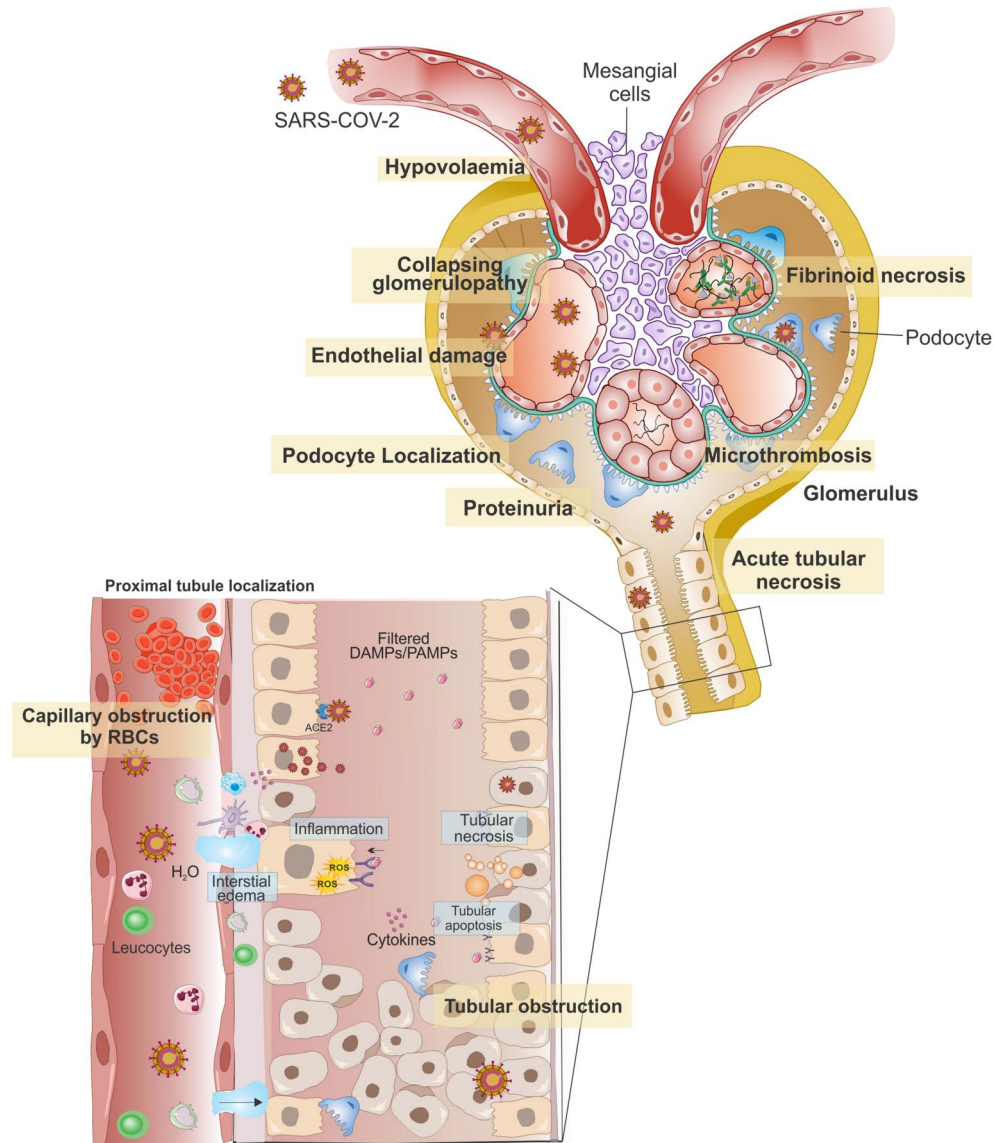
**FIGURE 1** SARS-CoV-2 and ACE2. SARS-CoV-2 enters into the ACE2-expressing cells through two possible pathways. (a) It binds to the host cell membrane-bound ACE2 via its viral spike protein. Moreover, SARS-CoV-2 requires the TMPRSS2 (cellular serine protease) for cleavage of its spike protein and supporting its cell entry. (b) Internalization of the virus can also occur through endocytosis and the cleavage activation of the viral spike protein by cathepsin in endosomes. Virus-induced ACE2 down-regulation may reduce its anti-inflammatory function and activate the harmful Ang II-AT1R axis and bradykinin-BKB1R axis. These events worsen the viral pathogenicity and lead to organ damage. Viral infection and AT1R activation lead to shedding of ACE2 into a soluble form by ADAM17 and its release into the body fluids. ACE2, angiotensin converting enzyme 2; Ang II, angiotensin II; AT1R, angiotensin II receptor type 1; BKB1R, DABK/bradykinin receptor B1; DABK, bradykinin [des-Arg973]; RAS, renin-angiotensin system; KKS, kallikrein-kinin system

the tubular fluid and consequently binds to its receptors in proximal tubules.<sup>25</sup> As depicted in Figure 1, SARS-CoV-2 can enter the host cells through two possible mechanisms: endocytic and non-endocytic pathways (Figure 1).

The fusion of the virus envelope to the host cellular membrane is vital for virus entrance into the renal cells. A specific proteolytic cleavage of the S protein, called the priming step, generates fusion-activated SARS-CoV-2 peptides. The expressions of ACE2, as well as the activity of certain proteases result in cell infection. Except ACE2, other surface receptors including TMPRSS2 and CD147 (basigin or extracellular matrix metalloproteinase inducer) may be involved in the entry of SARS-CoV-2.<sup>26</sup> Single-cell RNA sequencing of 13 human tissues was used to identify other candidate co-receptors of the coronavirus. The results showed that among serine protease dipeptidyl peptidase 4 (DPP4), Alanyl aminopeptidase (ANPEP) and Glutamyl aminopeptidase (ENPEP) receptor, ENPEP can be another potential receptor for human CoVs.<sup>23</sup> On the other hand, the tropism of SARS-CoV-2 may be extended by the unique furin cleavage.<sup>27</sup> In Asian and Occidental groups, the number of renal cells expressing proteases of the TMPRSS family, the SARS-CoV-2 binding site and ACE2 were investigated. As a result, the Occidental showed higher rates of ACE2 and kidney-associated genes in comparison to Asian donors. However, the expression of TMPRSS genes did not show a noticeable difference between them proposing a higher susceptibility of the Occidental group to coronavirus-related renal damage.<sup>8</sup>

## 2.2 | Direct virulence of SARS-CoV-2 on kidney proximal tubule cells

It is assumed that the direct impact of the virus on the renal tubules reflects the kidney damage according to several findings.<sup>28</sup> First, the presence of viral fragments in urine either indicates a direct interaction of the coronavirus with renal tubules or indicates a possible exposure of the tubules to the virus.<sup>29,30</sup> Second, the expression pattern of ACE2 is limited to proximal tubular cells.<sup>29,31,32</sup> Finally, between the second and third week of infection linked with the onset of AKI, SARS-CoV shedding was detected in the urine,<sup>29,33</sup> all implying the plausible role of SARS-CoV-2 in the induction of tubular damages. Since ACE2 receptors are highly expressed in the proximal tubular cell, the entry of SARS-CoV is supported by the activation of these receptors. Despite airway epithelial cells, proximal tubules express low levels of TMPRSS2<sup>34,35</sup>; hence, it is still vague whether other TMPRSS in the proximal tubule can regulate the priming process or not. Distal tubules in the kidney express TMPRSS2 rather than the proximal tubule which in turn primes the SARS-CoV-2 S protein.<sup>27,36,37</sup> This is a crucial step allowing the conformational rearrangement of remaining S2 unit leading to the fusion of cellular membrane. Subsequently, the virus enters the cell, liberates its constituents, replicates, and finally infects the other cells.<sup>38</sup> Recently, it is shown that SARS-CoV-2 attacks target cells through CD147, a transmembrane glycoprotein. CD147 is

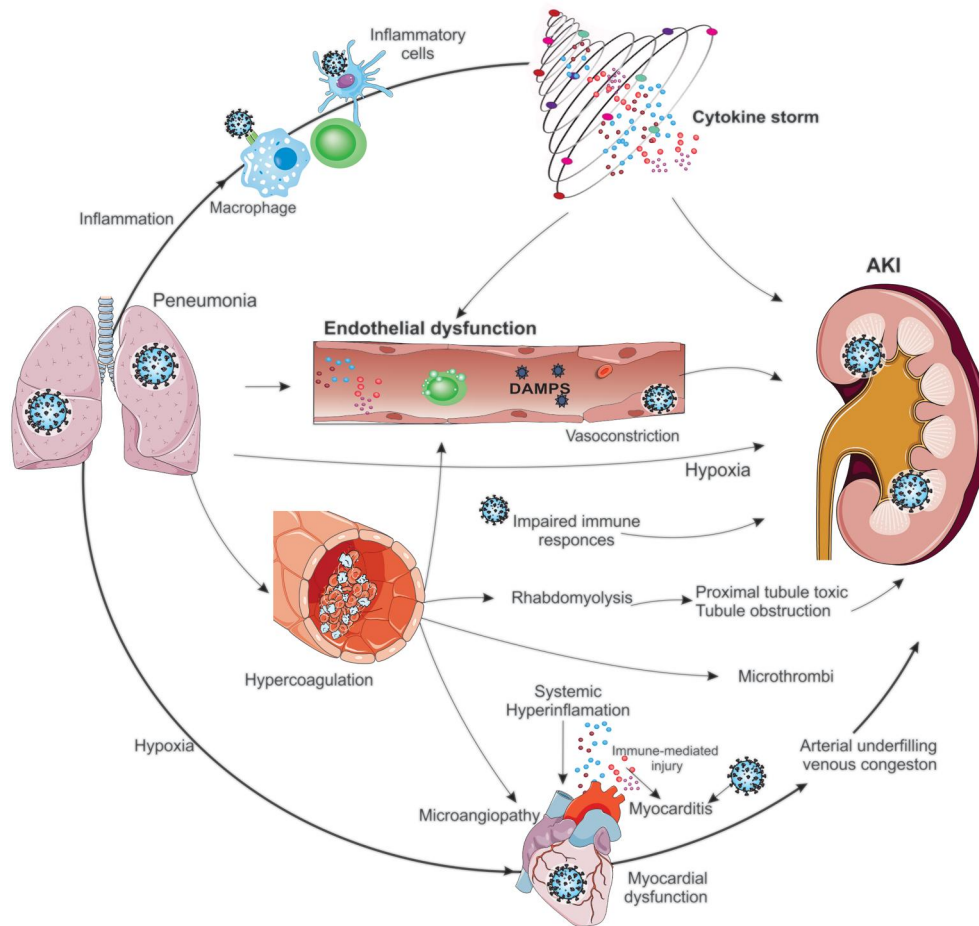


**FIGURE 2** Direct effects of SARS-CoV-2 on kidney injury. Acute renal failure is observed in Covid-19 patients through the direct effect of the virus in kidney tubules and podocytes. The direct impact of SARS-CoV-2 on kidney is mediated by an ACE2 pathway that leads to acute tubular necrosis, protein leakage in Bowman's capsule, collapsing glomerulopathy, and mitochondrial impairment. ACE2, angiotensin converting enzyme 2

highly expressed on the infiltrating inflammatory cells and proximal tubules of kidney and through dysregulation of cell cycle and inflammatory responses exerts important role in different kidney diseases.<sup>26,39</sup> Ample levels of related proteases such as glutamyl aminopeptidase, cathepsin B/L, DPP4 and cysteine are candidate viral S priming proteases expressed in the kidney<sup>23,40</sup> and may be a substitute for TMPRSS2 in proximal tubule cells.<sup>23,41</sup> Although cathepsins could be a potential assistance for ACE2 to enable the entry of SARS-CoV,<sup>42</sup> the role of DPP4 has not been identified in this context.<sup>34</sup> However, it may exert an essential function in aiding Middle East respiratory syndrome (MERS)-CoV entry into the pulmonary alveolar cells.<sup>43</sup> The MERS-CoV and SARS-CoV kidney tropisms have been recognized by their replication in proximal tubule cell culture.<sup>44</sup>

### 3 | PATHOGENESIS OF AKI IN SARS-CoV-2 INFECTION

Although little is known about the involvement of the kidneys in Covid-19, AKI is an observed clinical event.<sup>45</sup> AKI has been reported to be an important non-respiratory clinical manifestation in Covid-19 regardless of any preceding kidney damage in different clinical studies.<sup>46-48</sup> Wang et al. reported that about 4% of the Covid-19 patients had AKI.<sup>48</sup> In another study, 10% of the 41 Covid-19 patients revealed an increased level of creatinine on admission and 7% were diagnosed with AKI.<sup>47</sup> The worsened Covid-19 symptoms, the more progressed kidney damages were reported. In addition, Covid-19 patients have shown similar patterns to SARS cases in the prevalence rate of AKI; a retrospective study reported 6% of SARS patients to suffer also from



**FIGURE 3** Indirect effects of SARS-CoV-2 on kidney injury. SARS-CoV-2 infects alveolar macrophages and lung epithelial cells to amplify viruses and release cytokines and chemokines. Infected dendritic cells and the activated macrophages activate immune response extensively and initiate cytokine storm in the lung. Chemokines release can attract extra inflammatory cells to migrate into the inflammation site that intensify cytokine storm and may have indirect impacts on multi-organ failure, specially kidney, and death. Organ interaction between the damaged lung, the heart and the kidney can deteriorate the viral pathology. Numerous mechanisms including unmasked cardiovascular diseases (CAD), cytokine-induced myocardial damage, microangiopathy and viral myocarditis may clarify the main driver of myocardial damage and/or increased levels of troponin in Covid-19 cases. Endothelial dysfunction, microangiopathy, coagulation dysfunction are also involved in the kidney pathology in Covid-19

AKI.<sup>49</sup> Acute renal dysfunction was developed in about 7% of the SARS patients in an analysis of 536 cases, and this has been linked to a great extent of mortality (91.7%).<sup>50</sup> Also, Covid-19 patients who were admitted to ICU were more prone to the incidence of AKI in comparison with patients who did not receive any care in the ICU.<sup>48</sup>

Rarely has the effect of SARS-CoV-2 in patients suffering from CKD been investigated. However, this condition is accompanied by an elevated risk of severe Covid-19 infection according to a reported meta-analysis.<sup>51</sup>

Different factors could result in AKI during SARS-CoV-2 infection. Direct viral damage and/or disturbed haemodynamics of the kidney might account for AKI in Covid-19. Besides the direct impact of SARS-CoV-2 on kidney cells, other secondary insults, including cytokine storms, hypoxia, drug-associated nephrotoxicity, and secondary infection with other viruses, bacteria, and fungi can be contributed to AKI. Furthermore, sepsis-associated pathways are the probable mechanism for the kidney injury. Since septic conditions can

induce kidney damage as a consequence of altered haemodynamics, it is assumed that some cases of kidney injury are sepsis-unrelated events. The virus influences kidney cells including podocytes and tubules in the latter group.<sup>28</sup> Postmortem studies show lymphocyte infiltration and an extensive acute tubular necrosis in kidney tissues. Angiotensin II (AngII) overactivity, the coagulation system, and innate/adaptive immune and complement pathways, systemic effects, and organ crosstalk determine the severity of AKI and its consequences. We will highlight these factors in the following sections.

### 3.1 | Overactivation of AngII pathway

The majority of ACE2 is in the insoluble form bound to cell membranes. ACE2 in both soluble and insoluble form converts angiotensin II to angiotensin (1-7) which is crucial in controlling different hazardous effects on the body such as inflammation, vasoconstriction

and thrombosis. An enhanced production of angiotensin (1-7) stimulates these counter-regulatory protective impacts through the activation of Mas receptors. However, SARS-CoV-2 entry significantly down-regulates the expression of ACE2 and thus inhibits its protective roles, decreases anti-inflammatory effects, and increases the effects of angiotensin II in infected patients.<sup>10,52</sup> These detrimental effects occur as a result of the binding of angiotensin II to type 1 angiotensin receptors (AT1) that lead to pulmonary inflammation and coagulation (Figure 1). This might result in the activation of AT1 and decreased generation of angiotensin (1-7) and subsequent AKI triggering.

ACE2 deficiency has been reported clinically in SARS-CoV-2 patients with different features such as hypertension, cardiovascular diseases, diabetes, and older age. Thus, the virus-related down-regulation of ACE2 might be particularly harmful to individuals with baseline ACE2 deficit accompanied with the above mentioned status. A further deficiency of ACE2 after SARS-CoV-2 infection may increase the dysregulation between the protective (angiotensin (1-7)) and adverse (AT1) roles of RAS. The dysregulation of these axes in the lungs will lead to thrombotic and inflammatory conditions by the local function of angiotensin II in contrast to angiotensin (1-7).<sup>52</sup> It is plausible that an increased kaliuresis, as a marker of RAS activation, may be connected with a high level of angiotensin II in patients with Covid-19.<sup>53</sup>

Apart from the RAS, ACE2 is connected with the kallikrein-kinin system (KKS) in which bradykinin plays a chief role in the inflammatory process. The active metabolite of bradykinin [des-Arg973] BK (DABK), is hydrolysed and inactivated via ACE2. Decreased levels of ACE2 by the viral infection result in the activation of KKS through the bradykinin B1 receptor (BKB1R) that in turn increases leucocyte recruitment and fluid extravasation in the lungs,<sup>11</sup> Figure 1.

### 3.2 | Dysregulated immune responses in Covid-19

Covid-19 infection affects both naive and acquired host immune responses. SARS-CoV-2 can induce the immune response in two phases: an early specific acquired immune response to eradicate the virus and inhibit the disease progression and an uncontrolled inflammation, as a responsible mechanism for ARDS. The virus propagates and affects tissues under ineffective immune responses.<sup>54</sup> Necrosis or apoptosis of T cells is promoted via the release of a cytokine storm leading to a reduction in T cells,<sup>47</sup> especially in cases with severe disease, lower circulating CD4 and CD8 T cells and higher, IL-10 and tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) levels.<sup>55</sup> Consequently, an unrestrained inflammation harms viral clearance via promoting T cell exhaustion.<sup>56</sup> Almost all patients with Covid-19 have developed lymphopenia as an important marker of immune system disturbance.<sup>21</sup> Kidney macrophages play a pivotal role in immune defence since they are the predominant cells communicating with the virus targets and can activate phagocyte and chemokine signalling.<sup>23</sup> Moreover, the cytopathic effect of the SARS-CoV-2 virus can directly damage renal tubular cells during the

infection and replication steps propagating a complex immune response. Furthermore, chemokine network, activation of complement cascades, and coagulation play potential role in the development of the AKI in patients with Covid-19.<sup>57</sup>

#### 3.2.1 | Cytokine storm, pathological inflammation and COVID-19-induced AKI

Binding of the SARS-CoV to the ACE-2 receptors and viral replication in the lung cells lead to the apoptosis of epithelial and endothelial cell, pyroptosis in lymphocytes and macrophages, vascular leakage, and promotes a cascade of inflammation in the lower respiratory tract<sup>58,59</sup> that is started by antigen-presenting cells. Macrophages as important innate immune cells can sense and react against pathogens and generate inflammatory molecules to remove infectious agents and support tissue repair. The virus enters to the macrophage and they present viral antigen to T-helper 1 (CD4<sup>+</sup> and Th1) cells releasing interleukin-12 to further trigger the Th1 cell. The activated Th1 cells stimulate B-cells to produce antigen-specific antibodies and T-killer cells (CD8<sup>+</sup> and Tk) to target cells containing viral antigen.<sup>60</sup> CD8<sup>+</sup> T cells pose an antiviral effect and induce their cytotoxic effect directly or by cytokine production. T cells trigger pro-inflammatory cytokine production by activating NF- $\kappa$ B signalling pathway. Similar to MERS and CARS-CoV, the cytokines and chemokines levels are increased in Covid-19 patients. Following the secretion of chemokine and cytokines such as IL-21, IL-8, TNF- $\alpha$ , IL-6, IL-1 $\beta$ , CCL-2, -3, -5, the cytokine storm happens being responsible for multiple organ damage.<sup>61</sup> During the Covid-19 infection, the reduction of CD4<sup>+</sup> and CD8<sup>+</sup> cells count and increase in cytokine levels causes inflammation.<sup>62</sup> Conversely, regarding the weight of Covid-19 protein, various subgroups of T cells are activated.<sup>63</sup> Excess cytokine production that results in ARDS is connected with the outcome and severity of Covid-19. SARS-CoV-2-induced hyperinflammatory response has a pivotal role in the severity of infection, AKI development, and death.

In spite of the post-mortem examination of Covid-9 patients showing SARS-Cov2 antigens in the proximal tubules, the impact of cytokine storm in the induction of kidney damages is nevertheless vague.<sup>64</sup> However, the pathophysiology of cytokine storm in understanding Covid-19 has been proposed. The cytokine storm may contribute to the AKI in Covid-19 cases by cooperating with renal resident cells, and promoting tubular and endothelial dysfunction. Even early cases of Covid-19 have shown a cytokine storm where the harmful role of IL-6 is most relevant.<sup>19,65</sup> IL-6 induces renal endothelial cells to secrete pro-inflammatory chemokines/cytokine and induces kidney vascular permeability, playing a part in microcirculatory dysfunction.<sup>66</sup> Pro-inflammatory cytokines can also induce capillary leak syndrome and the production of thrombosis, which may result in disseminated intravascular coagulation.<sup>67</sup> Additionally, cell death and tissue damage can occur due to the presence of high levels of circulating cytokines. Also, erythro-phagocytosis and anaemia are observed since cytokines can activate macrophages; together

(disturbances of vascular haemostasis, anaemia and cytokine-induced injuries) leading to multi-organ failure in kidney.<sup>68</sup>

Haemophagocytosis occurs as a result of this cytokine storm and induces disturbances in kidney. Infiltration of CD68<sup>+</sup> macrophages into tubulointerstitium is induced by a viral infection.<sup>9</sup> Moreover, viral infection leads to infiltration of CD56<sup>+</sup> natural killer cells and CD4<sup>+</sup> T cells into the tubular interstitium and secretion of their pro-inflammatory cytokines that damage tubules.<sup>9</sup> Over-activity of these immune cells might stimulate fibrosis, apoptosis, and micro-vascular alteration after their infiltration into the infected kidney.<sup>69,70</sup> The bioavailability of chemokines also plays a key role in AKI. The pro-inflammatory chemokines like CCL14 and CCL2 have a significant role in pathogenesis of AKI via interaction with atypical chemokine receptor 2 (ACKR2). ACKR2 as a scavenger receptor binds to CC inflammatory chemokines and sequesters them. While it does not transmit normal G-protein mediated signalling messages.<sup>57</sup> Previous studies indicated that ACKR2 limits the infiltration of leucocyte, inflammation, and remodelling of fibrotic tissue following AKI; therefore, avoiding the progression of the disease.<sup>71</sup> Moreover, regarding the preventive role of ACKR2 in limiting kidney injury progression, it might be a promising target for renal inflammatory and fibrotic disease associated with AKI.<sup>72</sup>

As a life-threatening organ dysfunction, sepsis is a serious complication in cases with novel SARS-CoV-2 pneumonia caused by a cytokine storm cascade following the infection.<sup>73</sup> Superimposed infections can occur in cases with elongated ICU stay. The generation of endotoxins via the action of circulatory enzymes in Gram-negative microorganisms can result in septic shock. It has been reported in a cohort study that 6.4% of the 113 patients with severe Covid-19 also exhibit septic shock. It has been speculated that the septic AKI might occur in these patients and synergistically trigger kidney damage.<sup>15,73</sup>

### 3.2.2 | COVID-19 and lymphopenia

Lymphopenia is clinically observed in severe Covid-19 patients.<sup>74</sup> The maintenance of immune haemostasis and the inflammatory cascade is supported by lymphocytes. The expression of ACE2 in lymphocytes turns them into potential targets of SARS-CoV-2, which consequently result in cell death of both CD4<sup>+</sup> and CD8<sup>+</sup> T cells<sup>75</sup> leading to an imbalance in the both innate and acquired immune responses, neutrophils and macrophage hyperactivation and delayed clearance of viruses. There are some potential hypotheses regarding lymphopenia in this context.<sup>76</sup> First is the presence of ACE2 receptors in lymphocytes and the direct role of the virus in lymphocyte death.<sup>77</sup> Second is the propagation of the inflammatory response, which leads to lymphocyte apoptosis and lymphopenia.<sup>78</sup> Finally, destruction of lymphatic organs by virus might be considered. Additionally, post-mortem analyses show a marked lymphocytic apoptosis found in spleen and lymph node of Covid-19 patients. The effects of SARS-CoV-2 on CD169<sup>+</sup> macrophages present in human spleens and lymph nodes have been also reported.<sup>74</sup>

### 3.2.3 | Dysregulation of complement and hypercoagulation

The complement system, a significant component of native immunity, is critical to a rapid response against infections. During acute/chronic inflammation, complement system activation promotes pathogens elimination. The complement system dysfunction leads to acute lung injury following a highly severe viral infection. Covid-19 activates the complement system via lectin and alternative pathways. The complement system produces anaphylatoxins like C3a and C5a. These anaphylatoxins bind to their specific receptors and stimulate the histamine, leukotrienes and prostaglandins which lead to the main symptoms of hypersensitivity like flushing, hypoxia, vasodilation, and hypotension.

The model of Ang II-related kidney damage has been used to investigate the role of complement activation.<sup>79</sup> Assembly of complement C5b-9 through the alternative pathway in tubules apical brush border consequent to their accumulation in tubular lumen leads to tubulointerstitial damages as reported in both clinical and experimental models.<sup>80,81</sup> SARS-CoV-2 commences this assembly and the deposition of the membrane attack complex (C5b-9) in infected patients, proposing a chief role for complement activation in tubular pathogenesis.<sup>9</sup> Laurence et al. showed that anti-complement C5 therapy may be an effective treatment for patients with severe Covid-19.<sup>82</sup> Regarding the complicated role of complement system in acute lung injury pathogenesis, currently clinical trials and studies are conducted to analyse the effect of complement system blockade in critical Covid-19 patients.

The complement activation and procoagulation pathways can stimulate each other. In most of the severe Covid-19 patients the coagulation activity is enhanced and the consequent of coagulation factors consumption is microvascular thrombosis.<sup>83</sup> The activation of macrophages via COVID-19, the onset of cytokine storm, hyperferritinemia, liberation of damage-associated molecular proteins (DAMPs) and pathogen associated molecular patterns, and the activation of coagulation factors all facilitate hypercoagulability.<sup>84</sup> The activation of blood monocytes by circulating pro-inflammatory factors occurs initially. Cytokines and viral particles activate endothelial cells, which produce adhesion molecules and monocyte chemoattractants. This leads to the recruitment of activated monocytes to endothelial cells. The virus-related endothelial damage may also expose tissue factor. The extrinsic coagulatory pathway is stimulated by the function of tissue factor on monocytes, monocyte-derived microvesicles, and endothelial cells. Furthermore, the activated endothelial cells recruit neutrophils, which release neutrophil extracellular traps and in turn stimulate the coagulation contact pathway via the activation of platelets.<sup>85</sup> Hypoxia-induced by Covid-19 enhances the blood viscosity directly and via hypoxia-inducible transcription factor-dependent signalling pathway thus stimulates thrombosis.<sup>86,87</sup> Thrombosis laboratory indexes like partial thromboplastin time, prothrombin time, and international normalized ratio are elevated D-dimer. Also, fibrinogen levels were reduced and thrombocytopenia and schistocytes were found in peripheral blood

smears. Elevated D-dimer levels in hospitalization time or during illness correlate with high mortality rate in patients.<sup>88</sup> The anti-phospholipid antibodies leading to thrombotic events are enhanced in Covid-19 patients with thrombocytopenia. Therefore, regarding the effect of Covid-19 in thrombosis, prophylaxis with heparin has been suggested for hospitalized Covid-19 patients.

Covid-19 infection has been accompanied by surged clotting, disseminated intravascular coagulation, pulmonary infarction, and thrombosis.<sup>89</sup> Moreover, poor outcomes have been detected in cases with lower platelet level and enhanced D-dimer.<sup>89</sup> The evidence of microangiopathy in other organs has also been reported such as spleen and kidney resulting in infarction in these vital tissues. In Covid-19 patients who undergo dialysis, an increased level of circuit clotting has been widely reported.<sup>90</sup> In addition, elevated myocardial damage similar to myocardial infarction is a plausible outcome of microangiopathy and myocarditis in heart tissue of Covid-19 patients.<sup>90</sup> Therefore, hypercoagulation might spread acute tubular necrosis to cortical necrosis and thus, induce irreversible kidney damage in severe Covid-19. Also, microthrombi and microangiopathy states can elevate the risk of micro-infarctions in different organs such as heart, liver and kidney, further leading to impairments in multiple tissues.

### 3.3 | Rhabdomyolysis

Several factors can induce rhabdomyolysis, a serious damage of skeletal muscle. Skeletal muscle injury and subsequent release of breakdown products into the blood could be followed by AKI.<sup>91,92</sup> Rhabdomyolysis can be a clinical manifestation of Covid-19.<sup>93,94</sup> Autopsy results from Covid-19 patients demonstrate acute proximal tubular damage, glomerular fibrin thrombi with ischaemic collapse, and peritubular erythrocyte aggregation.<sup>95</sup> Rhabdomyolysis as determined by the presence of pigment casts as well as inflammation has also been reported. Particularly, a number of patients have not shown the signs of AKI, proposing the probability of extensive sub-clinical renal damage.<sup>95</sup> Different assumptions have been proposed regarding the molecular mechanism of viral-induced rhabdomyolysis. (1) A direct virus invasion can result in rhabdomyolysis, (2) The occurrence of cytokine storm and following injuries happen in muscle tissue and (3) the direct destruction of muscle cell membrane occurs by circulating viral toxins.<sup>93,96</sup> However, the exact Covid-19 rhabdomyolysis mechanism has not yet been investigated but cytokine overproduction might be the contributing factor.

### 3.4 | Organ crosstalk

#### 3.4.1 | Lung–kidney axis

The crosstalk between the lung and kidney has been observed in ARDS.<sup>97</sup> The disease severity, the presence of diabetes, and older age are risk factors for AKI in ARDS patients. Additionally, the severity of

AKI is connected with a history of heart failure (cardio-renal syndrome [CRS]) and body mass index(BMI).<sup>98</sup> AKI is seen in ARDS patients and similar findings are detected in Wuhan Covid-19 infected cases. AKI induced by ARDS can be attributed to numerous causes such as an inflammatory/immune reaction and the release of circulating factors that can interact with kidney-resident cells and damage them.<sup>95</sup> Gas exchange impairment and acute a are also related to AKI in patients with ARDS.<sup>99</sup> A recent retrospective study involving 375 patients with ARDS without CKD and/or AKI before the onset of ARDS has attested that ARDS is a result of pneumonia in 83% of patients and about 70% of them developed AKI. Half of the patients with renal damage have shown stage 3 AKI. The development of AKI was independent of risk factors such as older age, diabetes, and greater severity of the disease.<sup>97</sup> The lung-kidney axis and the subsequent damages are linked with cytokine storm. IL-6 is up-regulated in response to renal tubular damage, and IL-6 overexpression is accompanied by lung injury during the progress of AKI.<sup>100</sup> However, the role of IL-6 in the induction of pulmonary haemorrhage and increased alveolar-capillary permeability need to be elucidated on. Renal medullary hypoxia could also be induced by ARDS.<sup>100</sup>

#### 3.4.2 | Cardiovascular–kidney crosstalk

Beyond preferentially targeting patient's lungs, dysfunction in cardiovascular system is frequently seen in early stage of Covid-19, leading to acute myocardial infarction, myocarditis, and heart failure. These effects are established by increased levels of troponin and natriuretic peptides that can be mediated by RAS imbalance. This mechanism may complicate the clinical course mediated by the hyperinflammation, microvascular damage and endothelial dysfunction.<sup>101</sup> Diffuse microangiopathy along with thrombosis can occur due to inflammation in the vascular system. Also, the inflammatory process in myocardium can lead to myocarditis, arrhythmias, heart failure, rapid deterioration, acute coronary syndrome and even sudden death.<sup>102</sup>

CRS contains a total of circumstances involving both the kidneys and heart, in which any dysfunction in one organ can manually promote an impairment in the other. The function of these two organs can be impaired by a chronic or acute systemic condition.<sup>103</sup> The crosstalk between the cardiovascular system and kidney may be also associated with AKI in Covid-19. Not only does Covid-19-induced myocarditis impair the cardiac output and compromises end-organ perfusion, but also the concomitant right-ventricular dysfunction creates diastolic dysfunction and venous congestion that transmitting backward to the kidney and further compromising its perfusion by creating kidney congestion.

Acute viral myocarditis and cytokine cardiomyopathy can both be associated with hypotension, renal vein congestion, and hypoperfusion which in turn can reduce the glomerular filtration rate (GFR).<sup>15</sup> Type 1 CRS phenotype can occur consequent to cardiomyopathy from a cytokine storm and/or myocarditis in Covid-19 patients. Also, AKI can promote the induction of cardiomyocyte



damage and lead to type 3 CRS phenotype, while type 5 CRS phenotype is characterized by dual renal and cardiac injury due to inflammatory response, vascular damage and microthrombosis.<sup>104,105</sup> Some risk factors of cardiovascular comorbidity such as hypovolaemia, sepsis and nephrotoxicity are important mediators of AKI.<sup>105</sup> Kidney congestion and AKI might occur consequent to cardiorenal syndrome, especially right ventricular failure secondary to the Covid-19-induced pneumonia. Also, left ventricular dysfunction can result in a decreased cardiac output, arterial underfilling and renal hypoperfusion along with subsequent diminution of GFR.<sup>2,105</sup>

The occurrence of the cytokine storm develops AKI as a result of the renal inflammatory response, enhanced vascular permeability and cardiomyopathy; the latter can induce CRS type 1 which also involves systemic endothelial damage and results in pleural effusion, intra-abdominal hypertension, oedema, hypotension and intravascular fluid reduction.<sup>15,45</sup> The involvement of kidney endothelium and lung tissues has been reported in autopsy results.<sup>4</sup> Moreover, the existence of viral particles in renal endothelial cell suggests that viraemia might be a plausible reason for endothelial damage in the renal tissue and a possible cause of AKI.<sup>4</sup>

### 3.5 | Other Covid-19-induced-AKI causes

Beyond the aforementioned factors, volume depletion at admission may be a common cause of the AKI, as individuals with Covid-19 usually represent themselves with fever and rarely is pre-hospital fluid resuscitation done. In patients who exhibit signs of shock, fluid expansion might result in positive fluid balance which further causes negative effects in ARDS because it augments alveolar-capillary leakage and triggers renal vein congestion in AKI and renal compartment syndrome. It is hypothesized that a similar condition occurs in Covid-19 patients as well as rhabdomyolysis, metabolic acidosis hyperkalaemia and haemodynamic instability.

Superimposed infections can occur in cases with elongated ICU stay period. The generation of endotoxins via the action of circulatory enzymes in Gram-negative microorganisms can result in septic shock. It has been reported in a cohort study that 6.4% of the 113 patients with severe Covid-19 also exhibit septic shock. It has been speculated that septic AKI might occur in these patients and synergistically trigger kidney damage.

Since Covid-19-induced organ damage is mainly mediated by cytokine storm, strategies to reduce or remove inflammatory cytokines would be effective in preventing cytokine-induced organ injury. Targeting the production of IL-1, IL-6, TNF and IFN by related-inhibitors are reported by different studies. Cytokine removal can be performed based on adsorption, diffusion and convection methods. Cytokine removal can downregulate the inflammatory response, decrease lung injury and improve survival.

Extracorporeal treatments such as hemoperfusion can be effective methods to eliminate cytokines in cases with critical COVID-19. At present, encouraging results have been stated, however, there is

limited evidence for them and their efficacy and safety need to be determined.<sup>15</sup> Like other AKI causes, life-saving haemodialysis (HD) is started for severe management of COVID-19 life-threatening complications, such as uraemic pericarditis, severe pulmonary oedema and hyperkalemia.<sup>106</sup> However, HD-induced inflammation, haemodynamic instability, complement activation and thrombosis may further harm the common course of AKI.

The implementation of medium and/or high cutoff membranes in the continuous veno-venous haemodialysis modality might be used to enhance cytokine removal and thus help the management of AKI and other complications in Covid-19.<sup>15</sup> Moreover, the use of haemoperfusion might be effective in the prohibition of cytokine-mediated kidney injuries during the early phases of cytokine storm. Since the inflammatory factors' half-life is only a few minutes in circulation and the efficacy of the cytokine removal may be limited after a cascade influence of inflammatory factors, blood purification therapies need to be performed at an early stage in severe Covid-19.<sup>107</sup> Immunodysregulation, cytokine increment and the insufficiency of the supporting therapies paves the way for possible application of these treatments. However, the lack of enough clinical trials in order to evaluate their efficiency and safety limits their use.<sup>2</sup>

Beyond targeting excessive immune responses, there is an urgent need to develop effective therapy to target SARS-CoV-2 entry and dysregulated RAS, KKS and ACE2. In all these contexts, angiotensin (1-7), recombinant ACE2 and angiotensin II blockers can be novel candidates in Covid-19 infected patients.<sup>11,52</sup> Host protease (TMPRSS2 and furin) inhibitors can also exert a high potential for the treatment of SARS-CoV-2 infections. In this regard, the efficacy of bromhexine hydrochloride, a TMPRSS2 inhibitor, in the decreasing the mortality of cases with COVID-19 disease has been reported in our recent clinical trial.<sup>108</sup>

## 4 | CONCLUSIONS

The present review highlights the possible underlying mechanisms of SARS-CoV-2-induced kidney damage. Kidney dysfunction mainly AKI, haematuria and proteinuria occur in cases with Covid-19 within 3 weeks after the onset of the symptoms; however, kidney complications are connected with higher mortality.

The pathophysiology of AKI can be associated with COVID-specific mechanisms (direct viral entry, an imbalanced RAS activation, proinflammatory cytokines provoked by the viral infection and a thrombotic state) and non-specific mechanisms (right heart failure, hypovolaemia, nosocomial sepsis, nephrotoxic drugs, high PEEP in cases demanding mechanical ventilation and haemodynamic changes). Up till now, no specific therapy is available for Covid-19-induced AKI. Therefore, further research is needed to expand our understanding of kidney involvement to identify diagnostic, prognostic and therapeutic strategies in the clinic. It is crucial to understand the molecular pathways and critical targeted molecules to design novel drugs to manage the disease. Blocking the virus entry pathways including viral receptor(s), viral priming enzymes and

controlling immune responses may be important strategies to target the virus and decrease multi-organ dysfunction.

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## CONFLICTS OF INTEREST

No conflict of interest is declared.

## AUTHOR CONTRIBUTIONS

SZV and MA designed the study and prepared the outline. SZV performed literature review research and prepared the first draft. EA and SMHK cooperated in drafting and revising the sentences. All authors contributed in revising the manuscript. All authors read and signed the paper manuscript.

## DATA AVAILABILITY STATEMENT

This is a review article; data openly available in a public repository that issues datasets with DOIs.

## ORCID

Sepideh Zununi Vahed  <https://orcid.org/0000-0003-0179-4562>

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