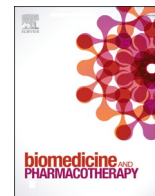




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Highly pathogenic coronaviruses and the kidney

Fang Wang^{a,b,1}, Xiao-Guo Suo^{b,1}, Cong Wang^{a,1}, Jia-Nan Wang^b, Xiao-Yan He^b, Fa-Cai Wang^a, Juan Jin^c, Jia-Gen Wen^b, Wei-Jian Ni^{b,d}, Bing-Xiang Shen^{a,*}, Xiao-Ming Meng^{b,*}

^a Department of Pharmacy, Lu'an Hospital of Anhui Medical University, Lu'an People's Hospital of Anhui Province, Lu'an 237006, China

^b Inflammation and Immune Mediated Diseases Laboratory of Anhui Province, Anhui Institute of Innovative Drugs, School of Pharmacy, Anhui Medical University, the Key Laboratory of Anti-inflammatory of Immune Medicines, Ministry of Education, Hefei 230032, China

^c School of Basic Medical Sciences, Anhui Medical University, Hefei 230032, China

^d Department of Pharmacy, Anhui Provincial Hospital, the First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei 230001, China

ARTICLE INFO

Keywords:

Highly pathogenic coronavirus
Kidney injury
SARS-CoV-2
SARS-CoV
MERS-CoV
COVID-19

ABSTRACT

Since the end of 2019, the outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has triggered a pneumonia epidemic, posing a significant public health challenge in 236 countries, territories, and regions worldwide. Clinically, in addition to the symptoms of pulmonary infection, many patients with SARS-CoV-2 infections, especially those with a critical illness, eventually develop multiple organ failure in which damage to the kidney function is common, ultimately leading to severe consequences such as increased mortality and morbidity. To date, three coronaviruses have set off major global public health security incidents: Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and SARS-CoV-2. Among the diseases caused by the coronaviruses, the coronavirus disease 2019 (COVID-19) has been the most impactful and harmful. Similar to with SARS-CoV-2 infections, previous studies have shown that kidney injury is also common and prominent in patients with the two other highly pathogenic coronaviruses. Therefore, in this review, we aimed to comprehensively summarize the epidemiological and clinical characteristics of these three pandemic-level infections, provide a deep analysis of the potential mechanism of COVID-19 in various types of kidney diseases, and explore the causes of secondary kidney diseases of SARS-CoV-2, so as to provide a reference for further research and the clinical prevention of kidney damage caused by coronaviruses.

1. Introduction

Coronavirus is an enveloped virus of the coronavirus subfamily with a single-stranded, positive-sense RNA genome. According to the serotypes and genome characteristics, coronaviruses can be divided into α , β , γ , and δ genera. It is called a "coronavirus" because its upstream envelope has a corona of protuberances [1]. In 2003, a highly pathogenic coronavirus, Severe Acute Respiratory Syndrome (SARS), caused a pandemic. As of July 5, 2003, SARS had killed 774 people worldwide [2]. Clinical data from studies of the disease outbreak revealed that the mortality rate of SARS patients with acute kidney injury (AKI) was much higher than that of SARS patients without AKI [3]. While this public health problem has made a profound impression, more outbreaks occurred thereafter. Middle East Respiratory Syndrome (MERS) was first

reported in 2012 [4]. In several case studies in the Middle East, the highest mortality rate was 35%, and MERS complications also led to renal failure [5,6]. After each outbreak, society slowly returned to calm. However, in 2019, when a novel coronavirus was isolated from patients with pneumonia of an unknown cause, the peace was broken again. The World Health Organization (WHO) named the newly discovered virus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The disease caused by SARS-CoV-2, coronavirus disease 2019 (COVID-19), was a new type of coronary pneumonia [7], which mainly manifested as a fever, dyspnea, a dry cough, and diarrhea and could develop into respiratory failure, organ failure, and death [8]. A study found that patients with kidney disease and COVID-19 had a higher mortality rate [9]. At present, COVID-19 has become a global epidemic affecting worldwide health and development. Therefore, there is an urgent need

* Corresponding authors.

E-mail addresses: sbx38545@163.com (B.-X. Shen), mengxiaoming@ahmu.edu.cn (X.-M. Meng).

¹ Fang Wang, Xiao-Guo Suo, Cong Wang contributed equally to this work.

to explore the characteristics, pathogenesis, and treatment of COVID-19.

Based on the present situation, studying how viruses work is an urgent concern, especially with respect to their epidemiology, clinical features, and pathogenic mechanisms. More attention should be paid to organ failure caused by viral infection, of which kidney damage is one of the most critical complications. Therefore, we aimed to review the characteristics, mechanisms, effects on the kidney, as well as preventive measures against kidney damage, to provide possible options for the treatment of novel coronaviruses and related renal diseases.

2. SARS-CoV-2 and kidney disease

The most recent coronavirus outbreak, COVID-19, has now reached a global pandemic status. The issue of coronavirus infection combined with kidney injury has also received a large amount of attention. Kidney disease is a risk factor for severe COVID-19 and mortality. Therefore, this review summarizes the epidemiology of SARS-CoV-2 infections, the potential pathogenesis, and the relationship with various types of kidney diseases (diabetic, hypertensive, and immunoglobulin A nephropathies [IgAN]) and proposes possible treatment methods to address this global problem.

2.1. Epidemiology of new coronavirus infections

From the end of 2019, SARS-CoV-2 infections have posed a huge global public health threat. The WHO reported that data last update 5:39 pm CEST, 23 September 2022, there have been 611,421,786 confirmed COVID-19 cases, including 6,512,438 deaths, globally (<https://covid19.who.int/>).

Basic information on SARS-CoV-2, SARS-CoV, and MERS-CoV, such as the extent of spread, number of confirmed cases and deaths, and symptoms, are listed in Table 1. The main manifestations of the illness are a fever and a dry cough. Serious cases can involve tissue damage in the lung and kidney, as well as respiratory failure, organ failure, and even death [10].

Table 1
Basic information of SARS-CoV, MERS-CoV and SARS-CoV-2.

Name of coronavirus	Number of cases	The number of deaths	Infection in organs	Common symptoms
SARS-CoV	8096	774	Lung, intestine, liver, kidney, lymph node, skeletal muscle, spleen, etc.	Fever, myalgia, discomfort, chills, cough, and later, shortness of breath, pleurisy, diarrhea, multi-organ failure and death
MERS-CoV	2468	851	Lung, kidney, liver, skeletal muscles, heart, etc.	Fever, myalgia, nausea, diarrhea, malaise, drowsy, dyspnea, cough, etc, acute respiratory distress, septic shock, multi-organ failure and death
SARS-CoV-2	611,421,786	6,512,438	Esophagus, lungs, heart, kidney, liver, ileum, bladder, etc.	Fever, myalgia, cough, sore throat, chest pain, diarrhea, etc., severe pneumonia, acute respiratory distress, death from multiple organ failure

The six known coronaviruses that can infect humans are SARS-CoV, HCoV-229E (229E), HCoV-OC43 (OC43), HCoV-NL63 (NL63), HCoV-HKU1 (HKU1), and MERS-CoV, four of which cause symptoms similar to those of the common cold. The other two, SARS-CoV and MERS-CoV, are zoonotic coronaviruses that have caused two deadly pandemics [11, 12]. However, the newly discovered coronavirus has a less than 80% genetic homology with SARS-CoV and an even lower homology with MERS-CoV [13]. Furthermore, after extracting RNA from patients with SARS-CoV-2 as a template and cloning and sequencing the genome, more than 85% of the virus fragments were shown to come from the genus coronavirus. Therefore, SARS-CoV-2 is an independent branch of the genus coronavirus and the seventh identified virus that can infect humans [7,14]. The new coronavirus not only causes respiratory and gastrointestinal symptoms but also damages the kidney. This review discusses the kidney damage caused by SARS-CoV-2 and the possible mechanisms.

Renal disease has been related to mortality in hospitalized COVID-19 patients [15]. AKI is one of the crucial complications of COVID-19; more than 40% of hospitalized patients have renal dysfunction, and 5.1% of patients have acute kidney injury [16,17]. According to the autopsy results of 26 COVID-19 patients in China, clinical symptoms of kidney injury, including elevated serum creatinine levels, increased urea nitrogen values, and diffuse proximal tubule injuries, were reported in 9 cases [18]. Another study showed that the incidence of COVID-19 that develops with AKI exceeded 0.5% [19]. Moreover, in the examination of hospitalized patients, serum creatinine and urea nitrogen levels were significantly increased, accompanied by a decrease in glomerular filtration rates and the presence of proteinuria; patients with abnormal kidney function were often severely ill [16,20].

2.2. The potential mechanism of novel coronavirus infection

The mechanism of novel coronavirus-induced kidney injury is complicated and has not been fully elucidated. The fusion of the virus envelope to the host cellular membrane is vital for the viral entrance into renal cells. A specific proteolytic cleavage of the S protein, called the priming step, generates fusion-activated SARS-CoV-2 peptides. The expressions of angiotensin converting enzyme 2 (ACE2) as well as the activity of certain proteases results in cell infection. Except ACE2, other surface receptors including transmembrane protease serine-2 (TMPRSS2) and CD147 (basigin or extracellular matrix metalloproteinase inducer) may be involved in the entry of SARS-CoV-2. TMPRSS2 initiates the SARS-CoV-2 S protein, allowing the S2 unit to undergo a conformational rearrangement, leading to cell membrane fusion. Subsequently, the virus enters the cell, releases its components, replicates, and finally infects cells [21–23], SARS-CoV-2 enters the renal cells mainly through ACE2 receptor binding, thereby causing kidney damage (Fig. 1).

Clinical samples have shown that the levels of inflammatory factors IL-2, IL-7, IL-10, and tumor necrosis factor alpha (TNF- α) were higher in patients with COVID-19 [24,25], and the number of T cells, B cells, and natural killer (NK) cells decreased sharply, along with a reduced percentage of monocytes. Increases in the neutrophil to lymphocyte ratio usually indicate a higher disease severity and poor clinical outcome. More importantly, biopsies have shown that the level of highly pro-inflammatory factors in CD4-T cells increased, confirming either immunity decline or injury [26]. Therefore, the increased incidence of COVID-19 combined with kidney injury may be due to an immune function impairment mediated by the inflammatory disease induced by SARS-CoV-2. Transforming growth factor beta (TGF- β)/Smads plays an important role in both acute and chronic kidney diseases. Recently, a study found the pathogenicity of the SARS-CoV-2 (nucleocapsid) N protein in acute kidney injury. The SARS-CoV-2 N protein can interact with Smad3, a downstream signaling molecule of TGF- β ₁, resulting in G1 cell cycle arrest and tubular epithelial cell necrosis, which directly leads to AKI (Fig. 2). However, Smad3 gene knockout mice or specific Smad3

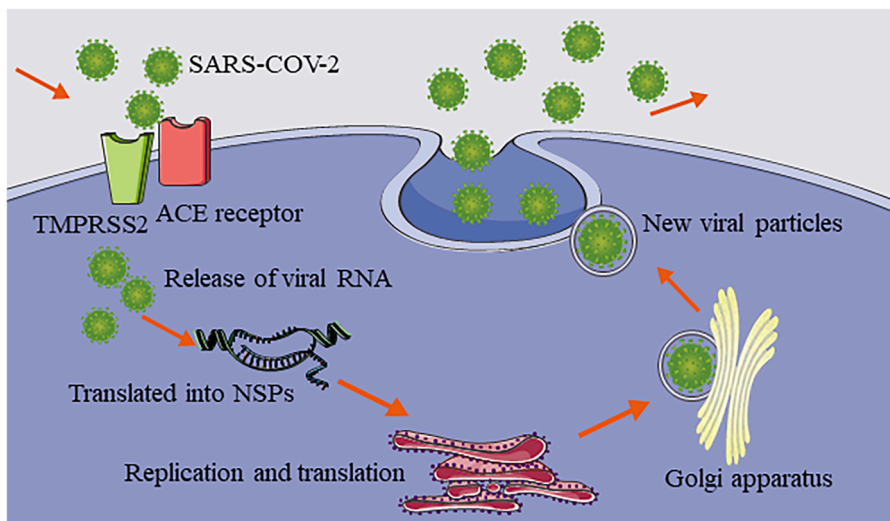


Fig. 1. Life cycle of SARS-CoV-2 in renal cells. SARS-CoV-2 enters renal cells by binding to ACE2 receptor and splicing S protein by host cell molecule TMPRSS2. The virus is then released and translated into non-structural proteins (NSPs). Next translated on the endoplasmic reticulum, and finally reassembled into new virus particles with the help of Golgi apparatus, leaving the cells to infect other renal cells, thus infecting the whole kidney and causing damage.

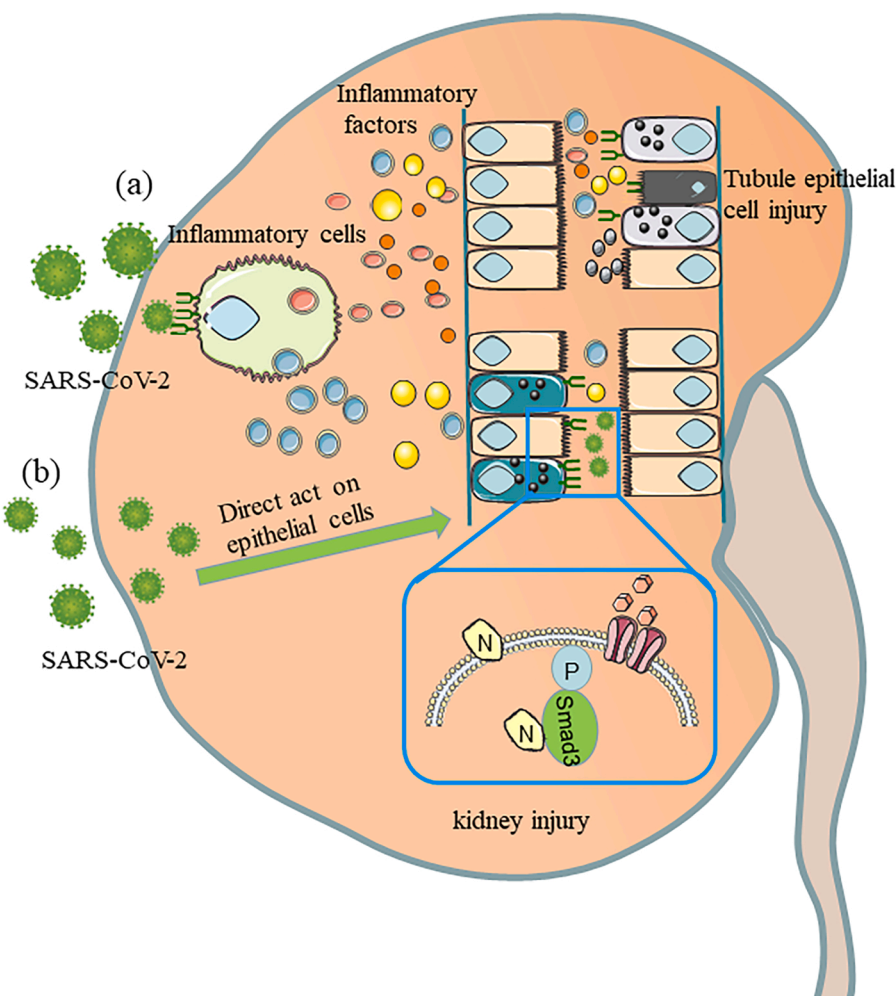


Fig. 2. Schematic diagram of kidney injury caused by SARS-CoV-2. SARS-CoV-2 enters the body through the respiratory tract, then binds to the angiotensin-converting enzyme receptor on the surface of inflammatory cells in the kidney and promotes the cells to secrete inflammatory factors (IL-6, IL-1, CXCL-1, etc.), aggravating acute kidney injury. (b) On the other hand, SARS-CoV-2 N protein can interact with Smad3 in renal tubular epithelial cells, which is a downstream signal molecule of TGF- β 1, leading to G1 cell cycle arrest, resulting in renal tubular epithelial cell necrosis, thus directly causing kidney injury.

inhibitors can significantly reduce cell death and AKI induced by the SARS-CoV-2 N protein [27]. Thus, Smad3 may be used as a target to treat AKI caused by COVID-19 infections. Next, the relationship between

various types of kidney diseases and the novel coronavirus is analyzed.

2.3. COVID-19 and diabetic nephropathy

The pathogenesis of diabetic nephropathy, the most common complication of diabetic patients, is nephron loss with a decreased estimated glomerular filtration rate (eGFR). During the COVID-19 epidemic, diabetic nephropathy was a risk factor for predicting an adverse outcome after SARS-CoV2 infection. Compared with patients with COVID-19 pneumonia alone, patients with COVID-19 pneumonia and diabetic nephropathy had a probability of fatality rate of 14.5%, while the probability of fatality rate due to COVID-19 pneumonia was 5.7%; thus, diabetes is thought to increase COVID-19 pneumonia mortality [28,29]. Currently, many studies have reported that COVID-19 infects the body through the combination of spike S protein and ACE2 [30–32]. In addition, ACE2 is highly expressed in the proximal tubules of diabetic nephropathy. The high expression of ACE2 increases the COVID-19 entry into the kidney and aggravates kidney injury [33]. Diabetic patients are more likely to be infected with COVID-19 virus, mainly because angiotensin converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker are the first-line drugs for diabetes, and taking these two drugs can increase the expression of ACE2 receptor [34–36]. So we have reason to believe that patients with diabetic nephropathy are more likely to be infected with COVID-19 under the same conditions. However, some studies have found that the overexpression of ACE2 can significantly inhibit renal fibrosis and improve renal function in diabetic nephropathy. Therefore, treating the COVID-19 disease simply by inhibiting ACE2 is still controversial [37], affecting the important life activities of the body. Because ACE2 can antagonize the effect of ACE and regulate the balance of signal peptides in tissues. ACE can catalyze the hydrolysis of AngI to produce AngII, which is one of the strongest vasoconstrictive substances found in current research [38]. At the same time, ACE can stimulate aldosterone secretion, promote the reabsorption of Na^+ and K^+ by human kidney, and lead to the increase of sodium storage and blood volume, thus leading to the increase of blood pressure [39]. It has positive inotropic and chronotropic effects on the heart. ACE gene polymorphism is also closely related to many cardiovascular diseases, left ventricular hypertrophy, myocardial infarction, diabetic nephropathy, etc.

ACE2 can antagonize the pressor effect of ACE, and has positive significance in lowering blood pressure, protecting myocardial ischemia, inhibiting thrombosis and atherosclerosis and other heart diseases. Other studies have shown that ACE2 can also inhibit tumor cell growth and angiogenesis, improve hyperglycemia, inhibit inflammatory factors, reduce fiber proliferation, etc., and has complex physiological functions [40]. Therefore, inhibiting ACE2 will cause serious damage.

Most researchers have begun to focus on other potential factors, such as neuropilin-1, mitochondrial glutathione, vitamin D, and dipeptidyl peptidase-4 (DPP-4). In particular, neuropilin-1 seems to play an important role in the underlying mechanism of COVID-19 and diabetic nephropathy [34]. The upregulation of neuropilin-1 in the diabetic kidney promotes viral entry into tissues, and the involvement of these two processes leads to the exhaustion of neuropilin-1, which is closely related to the pathogenesis of diabetic nephropathy.

In addition to targeting important signals through ACE2 and neuropilin-1, COVID-19 infection is also related to higher mechanisms mediated by DPP-4 and the inhibition of AMP-activated protein kinase (AMPK) activation in renal cells. Lowering DPP-4 and restoring AMPK levels are organ protective, indicating the pathogenic effect of DPP-4 and the protective effect of AMPK in diabetic COVID-19 patients [35, 41]. Besides providing standard treatment for COVID-19 patients, we urgently need new drug therapies to support the stability and function of diabetic organs and cell types.

2.4. COVID-19 and IgA nephropathy

IgAN is the most common form of primary glomerulonephritis worldwide, resulting in renal failure in 20–40% of patients within 20

years of diagnosis. IgAN is mainly induced by upper respiratory tract infections [42,43]. Its clinical manifestations are mainly recurrent hematuria and proteinuria after infection. However, treatment strategies are limited, and it has been mainly treated with renin-angiotensin-aldosterone system (RAAS) inhibitors and immunosuppressants. COVID-19 entering the human body through the respiratory tract can affect glomerular diseases and aggravate IgAN [44]. Several case reports have shown that the results of renal biopsies of patients with IgAN who were infected with COVID-19 were consistent with IgAN with cellular glomerulopathy and moderate-to-severe tubulointerstitial scarring, suggesting that COVID-19 aggravated the IgAN [45]. The potential mechanism of COVID-19-aggravated IgAN may involve the virus directly influencing the damage and the activation of the ACE2 pathway, hindering complement regulation. In addition, COVID-19 may act as a superantigen, driving the development of multisystem inflammatory syndrome as well as cytokine storms in patients affected by COVID-19. This effect reaches the glomerulus, leading to the development of this novel IgAN, in addition to genetic component-triggering glomerular diseases, mainly collapsing focal segmental glomerulosclerosis, tubulointerstitial, and even vascular diseases.

Vaccination is one of the most effective ways to prevent COVID-19 infection, but some patients have new autoimmune phenomena, such as immune thrombotic thrombocytopenia, autoimmune liver disease, IgA nephropathy, rheumatoid arthritis, and systemic lupus erythematosus, after vaccine administration. At present, kidney damage from vaccines appears mainly as IgAN and minimal variant nephropathy (MCD). A large number of studies have confirmed that administering the COVID-19 vaccine can also aggravate kidney damage, which is mainly manifested by increased hematuria, proteinuria, and serum creatinine levels [46,47]. Renal biopsies of IgAN samples revealed fibrocytes and fibromuscular layers. The mechanism may be due to the excessive increase of IgA in vivo while the vaccine activates the immune system, which aggravates the IgAN damage. In contrast, the development of MCD after vaccination takes longer, indicating that it plays a role in cellular immunity. The center of the MCD pathogenesis is the development of podocyte damage due to dysregulated T-cell activation. The COVID-19 mRNA vaccine has been shown to trigger an enhanced T follicular helper (T_{fh}) response, which peaked at seven days after immunization [48,49].

2.5. COVID-19 and end-stage renal disease

In this section, we mainly discuss the susceptibility of patients with end-stage renal disease to COVID-19, as well as their higher mortality. Patients with end-stage kidney disease require regular dialysis, making hemodialysis wards gathering places, owing to frequent visits and long hospital stays [50]. One study showed that among the 230 hemodialysis patients, 37 patients had concomitant COVID-19, during the SARS-CoV-2 epidemic, six of seven dialysis patient deaths were caused by COVID-19 [51]. Compared with non-hemodialysis patients, patients with COVID-19 who are undergoing hemodialysis have a decreased number of peripheral blood T cells, auxiliary T cells, and NK cells, as well as significantly decreased levels of serum inflammatory cytokines [52]. In conclusion, patients with COVID-19 who are undergoing hemodialysis have a higher mortality risk.

The reasons COVID-19 infections occur in hemodialysis patients are as follows: First, patients with kidney disease often take ACE inhibitors and angiotensin 2 receptor blockers, which increase ACE2 receptor levels. However, as the ACE2 receptor is also the receptor of SARS-CoV-2, its increased expression further increases the risk of SARS-CoV-2 entering the host cells [53,54]. Second, B- and T-cell dysfunction in hemodialysis patients can cause a decreased lymphocyte count and a long-term elevation in calcitonin levels, which are also common in patients with COVID-19 [55]. Decreased lymphoid numbers may be a factor in the disease severity of general patients. Finally, the diagnosis of

COVID-19 in hemodialysis patients depends on imaging and viral nucleic acid detection. Considering the possible immunosuppression and epidemic situation, hemodialysis patients are more likely to be infected with COVID-19 than the general population [56].

Furthermore, the mortality of patients with end-stage renal disease and COVID-19 increased significantly. The reason may be that all patients with end-stage renal disease need to take ACE2 inhibitors, and the treatment strategy for COVID-19 also targets the ACE2 enzyme. Inhibition leads to an angiotensin disorder in the body and affects important life functions, such as blood pressure regulation. In addition, patients with end-stage renal disease have low immunity. After COVID-19 enters the body, it further aggravates inflammatory reactions. The imbalance of anti- and pro-inflammatory cells leads to excessive inflammation, which can lead to high mortality.

Patients with end-stage renal disease are more prone to infection with the novel coronavirus virus, which is extremely harmful. A special treatment plan these patients is necessary. The current measures are as follows: (1) A certain distance needs to be maintained when communicating with others, and contact with patients infected with SARS-CoV-2 should be avoided [57]; (2) To break the transmission chain through the dialysis unit, a special person should be dedicated to thoroughly disinfecting the dialyzers, to ensure the safety of patients [58]; and (3) SARS-CoV-2-infected individuals should be identified to avoid the occurrence of combined diseases and reduce the death rate [57]. The Chinese Society of Nephrology has developed more detailed guidelines for the management of COVID-19 in dialysis wards [59], and has indicated that hemodialysis patients need special treatment for COVID-19. We fully agree with the proposed management guidelines.

2.6. Therapeutic drugs

There is an urgent need to develop effective therapeutic drugs to control the current occurrence of COVID-19 caused by SARS-CoV-2. Currently, the drugs used in clinical treatment include the IL-6 receptor-targeted monoclonal antibody tocilizumab, RNA polymerase inhibitors such as remdesivir and favipiravir [60,61], and protease inhibitors such as lopinavir/ritonavir [62], which reduce viral infection by affecting the assembly of virions in the cells. Chloroquine and hydroxychloroquine upregulate anti-inflammatory molecules to interfere with downstream inflammatory pathways and reduce the inflammatory response and damage to vital organs in SARS-CoV-2 patients [63, 64]. In one study, ivermectin inhibited the importin (IMP) α/β 1-mediated nuclear import of viral proteins, which disrupted the immune escape mechanism of the virus [65]. Oseltamivir specifically inhibits neuraminidase, which can inhibit the separation of the mature virus from host cells, thereby improving the disease situation; it is more effective in combination with other antiviral drugs [66]. However, some drugs used in the antiviral process can cause kidney damage. Therefore, drugs for the treatment of COVID-19 should be cautiously introduced and monitored for their effects on the kidney. As one of the main organs involved in COVID-19 pneumonia, it is important to explore whether drugs used for the treatment of COVID-19 cause kidney damage. For this reason, this review summarizes the drugs commonly used in COVID-19 pneumonia and their effects on the kidney, providing a basis for more reasonable clinical drug choices (Table 2).

3. Patients with COVID-19 and secondary nephropathy

As SARS-CoV-2 rapidly evolves and expands, the full spectrum of effects is becoming evident, from self-limiting respiratory tract illness to severe acute respiratory distress syndrome (ARDS), multiple organ failure, and death. As an important excretory organ, the kidney plays a vital role in the body. The kidney is frequently involved in COVID-19, and > 40% of cases have abnormal proteinuria at hospital admission. AKI is common among critically ill patients with COVID-19, affecting approximately 20–40% patients admitted to intensive care, according to

Table 2
Mechanism of action of therapeutic drugs against coronaviruses.

Name	Action mechanism	Effect on kidney	Reference
Oseltamivir	Inhibition of neuraminidase	The incidences of AKI in influenza-A H1N1 treated with antiviral and antibiotic combination was less as compared to patients who were given antiviral alone for treatment of influenza infection. When renal function decreases, the serum concentration of oseltamivir, a renal excretion drug, increases its efficacy, which may increase the risk and frequency of adverse reactions.	[127]
Remdesivir	Inhibition of RNA-dependent RNA polymerase	There is no significant impact for the time being.	[128]
Ivermectin	Inhibition of nuclear transport of viral proteins	P2X4 purinergic receptor agonist ivermectin can exacerbates ischemic AKI and promotes NLRP3 inflammasome signaling. Ivermectin can cause mitochondrial dysfunction, oxidative stress and damage in renal cancer cells.	[129,130]
Hydroxychloroquine	Block virus-cell membrane fusion	In addition to optimizing the inhibition of renin-angiotensin-aldosterone system, hydroxychloroquine significantly reduced proteinuria in IgA nephropathy with no adverse events for more than 6 months. Compared with patients who did not use hydroxychloroquine, the use of hydroxychloroquine in patients with newly diagnosed rheumatoid arthritis was significantly associated with a significantly lower risk of CKD. Hydroxychloroquine can reduce renal ischemia reperfusion injury and improve atherosclerosis and angiosclerosis in patients with CKD.	[131–134]

the experiences in Europe and the USA, which impacts their survival [67].

The data of a large-scale clinical study in China showed that 701 patients with COVID-19 had abnormal renal indicators, with significantly increased levels of creatinine and urea nitrogen and the presence of proteinuria and hematuria. Approximately 5% of COVID-19 patients are diagnosed with AKI during hospitalization [23]. Compared with patients with normal renal function, patients with COVID-19 and AKI are more prone to various complications. Therefore, AKI is considered a negative prognostic factor and an indicator of COVID-19 severity [68]. What causes such a high incidence of kidney injury? Next, we will

analyze the reasons why COVID-19 patients are more likely to have secondary kidney diseases.

3.1. Inflammation and immune responses

The virus multiplies and affects tissues in response to ineffective immune responses. T-cell necrosis or apoptosis is promoted by the release of a cytokine storm, leading to a reduction in T cells, especially in severe cases, reducing the number of circulating CD4 and CD8 T cells and resulting in high levels of IL-10 and TNF- α . Consequently, inflammation disrupts the viral clearance by promoting T-cell exhaustion. Almost all patients with COVID-19 develop lymphocytopenia, an important marker of immune system disorders [69]. Kidney macrophages play a critical immune defense role because they are the primary cells that communicate with viral targets and can activate phagocytic and chemokine signaling [70,71]. Moreover, the cytopathic effects of SARS-CoV-2 can directly damage renal tubular cells and propagate complex immune responses during infection and replication. In addition, chemokine networks, complement cascade activation, and coagulation play potential roles in the development of AKI in COVID-19 patients [23].

3.2. Hemodynamics and hypercoagulability

Of note, patients with COVID-19 may develop myocarditis about half a month after the onset of symptoms, and myocarditis may lead to AKI because of changes in systemic hemodynamics. ACE2, found in intestinal cells, is closely related to gastrointestinal function [72]. The mutual interaction between SARS-CoV-2 and ACE2 might disrupt the function of ACE2 and result in diarrhea [73]. However, since the main target of SARS-CoV-2 is ACE2, patients with COVID-19 may experience severe diarrhea or even dehydration, thus affecting the renal function.

COVID-19 infection has been accompanied by a surge of clotting, disseminated intravascular coagulation, pulmonary infarction, and thrombosis [74]. Moreover, a poor prognosis was found in cases with lower platelet and enhanced D-dimer levels. Evidence of microangiopathy in other organs, such as the spleen and kidney, has also been reported, leading to infarction of these important tissues [75]. Increased circulating clotting levels have been widely reported in COVID-19 patients undergoing dialysis. In addition, elevated myocardial damage, similar to myocardial infarction, is a possible outcome of myocardial tissue microangiopathy and myocarditis in patients with COVID-19 [76]. Therefore, hypercoagulation might spread acute tubular necrosis to cortical necrosis and thus, induce irreversible kidney damage in severe COVID-19 cases. Also, microthrombi and microangiopathy states can elevate the risk of micro-infarctions in different organs, such as the heart, liver, and kidney, further leading to impairments in multiple tissues.

3.3. Viral septicemia

Sepsis is caused by the imbalanced inflammatory response caused by the host infection. Data of hospitalized patients show that patients with severe COVID-19 infections have high serum levels of cytokines and chemokines, similar to sepsis [77].

SARS-CoV-2 may cause sepsis if a secondary bacterial or fungal infection occurs. Patil et al. [78] suggested that the virus itself may contribute to the sepsis syndrome through mechanisms such as immune dysregulation, respiratory dysfunction leading to hypoxemia, and circulatory dysfunction leading to metabolic acidosis. The multiple organ failure seen in COVID-19 due to hypoxia and circulatory disorders due to microvascular dysfunction can also be interpreted as secondary effects. Others have suggested that microvascular dysfunction may also interrupt the blood flow to the lungs through disseminated intravascular coagulation and micro-embolism, leading to hypoxia and subsequent organ failure. Lin [79] emphasized that various degrees of damage to the

heart, liver, kidney, and other organs in severe infection, together with laboratory abnormalities such as decreased lymphocyte and platelet counts, increased D-dimer, C-reactive protein (CRP), and liver and myocardial enzyme levels, and the high cytokine levels are similar to those seen in sepsis caused by bacterial infections. Furthermore, severe COVID-19 has all the hallmarks of sepsis, including a specific pathogen, and COVID-19 could be considered sepsis caused by a viral infection. Other studies have reinforced this view, noting that all infectious agents, including viruses, could cause sepsis. Various viral respiratory pathogens, including influenza, avian and swine flus, SARS, and MERS, have been associated with sepsis. Compared to bacterial sepsis, viral sepsis has some similarities but also some differences, including a relatively late onset and progression. The appropriate use of systemic steroids modulates immune responses and improves survival in patients with COVID-19 [80]. Considering severe COVID-19 disease as a sepsis syndrome has relevance and may assist in terms of determining treatments that will modulate the immune response, limit the intrinsic damage to tissue and organs, and potentially improve outcomes.

3.4. Rhabdomyolysis

The clinical manifestations of COVID-19 include rhabdomyolysis, which causes AKI [81]. Autopsy results of patients with COVID-19 show acute proximal tubular injury and rhabdomyolysis, as determined by the presence of pigment casting and inflammation. In particular, some patients may also have potential renal injuries without AKI symptoms. The following hypotheses are proposed for the different molecular mechanisms of virus-induced rhabdomyolysis: (1) Direct viral invasion, (2) the occurrence of a cytokine storm and the resulting damage, and (3) the direct destruction of muscle cell membranes caused by circulating viral toxins [82]. Although the exact mechanism by which COVID-19 causes rhabdomyolysis has not been determined, excessive cytokine production may be the driving factor.

3.5. Oxygen supply and demand imbalance

After a COVID-19 infection, the body's metabolism becomes more active, which increases the burden on the heart and leads to an insufficient oxygen supply. The resulting imbalance of the oxygen supply and demand in COVID-19 patients, especially in severe and critical cases, can become complicated by sepsis or septic shock [83], resulting in the occurrence or aggravation of sepsis-related AKI [84]. At the same time, hypoxia can easily cause rhabdomyolysis. Some patients infected with H1N1 in 2009 demonstrated significantly elevated creatine kinase levels [85]. An analysis showed rising creatine kinase levels in inpatients with COVID-19 in the intensive care unit (ICU). Thus, some factors may lead to kidney damage after the metabolic acceleration following a COVID-19 infection [86].

3.6. Nephrotoxicity of antiviral drugs

At present, there is insufficient evidence to show that any existing antiviral drugs can effectively treat COVID-19 pneumonia. To slow the viral spread as quickly as possible, several potentially useful drugs are being used; however, some studies have shown that they are useful but ultimately ineffective. Hydroxychloroquine, lopinavir/ritonavir, and ribavirin are examples of therapeutic agents whose efficacy against COVID-19 was later disproved. Furthermore, we found that ribavirin, atazanavir/ritonavir, and tenofovir may cause renal damage during antiviral therapy [87–89]. The kidney participates in the metabolism of antiviral drugs, which in turn affects or aggravates kidney damage. Therefore, we speculated that anti-SARS-CoV-2 treatment might also cause renal damage [90,91]. Pfizer's new drug, PAXLOVID™ (PF-07321332), has significantly reduced hospital stays and mortality in double-blind trials. Although patients could benefit greatly from PAXLOVID™, they may be at significant risk for drug interactions and harm

owing to the ritonavir component, a particularly potent inhibitor of cytochrome P450 system CYP3A enzymes. The interaction between ritonavir and CYP3A-dependent drugs can result in 1.8- to 20-fold increases in the area under the curve blood concentrations of these latter drugs. Because cyclosporine, tacrolimus, and the mTOR inhibitors sirolimus and everolimus are highly dependent on CYP3A metabolism, their plasma levels increase substantially and rapidly on exposure to ritonavir. Organ transplant recipients receive immunosuppressive drugs, such as tacrolimus. Tacrolimus is metabolized by the cytochrome P450 3A4 enzyme system, and many drugs can induce or inhibit this enzyme, affecting its levels. It can cause serious side effects such as AKI and is a hazard that deserves our attention, although there hasn't been much research [92]. Interestingly, some glucocorticoid drugs may cause kidney damage in the anti-inflammatory treatment of COVID-19 and in the rescue of critically ill patients [93,94]. As one of the main organs involved in COVID-19 pneumonia, it is important to explore whether the drugs used for the treatment of COVID-19 cause kidney damage.

4. When the kidney meets the SARS-CoV

SARS is an airborne virus. Studies have shown that SARS-CoV rapidly invades the lungs and exists in respiratory secretions, feces, and urine. As of July 5, 2003, SARS has killed 774 people worldwide [2,95]. During the epidemic, 32 countries and regions reported cases to the WHO that were mainly distributed in Asia, especially in China, Singapore, and Vietnam. However, there were also a small number of cases in Europe and America [96,97]. The major clinical manifestations of SARS are a fever, muscle soreness, a dry cough, diarrhea, and dyspnea. Severe cases can rapidly progress to respiratory failure. Laboratory tests of typical cases are characterized by a decreased lymphocyte count and low T lymphocyte function. Radiological examinations revealed that almost all patients had unilateral or bilateral lung infiltration changes [98,99]. Some researchers have found that in addition to its effects on the lungs, SARS can also cause kidney damage [100,101]. Therefore, studying the relationship between SARS and kidney injury is particularly important. Autopsy cases also have shown that coronavirus infection exists not only in the lungs but also in the kidneys of 38% (6/16) of patients [102].

During the SARS outbreak in 2003, an analysis of clinical parameters of 536 patients with SARS-CoV infection found that 36 (6.7%) patients developed AKI, and increased serum creatinine levels were found in some patients with SARS-CoV, which further confirmed the relationship between SARS and kidney injury [103]. Other studies showed that the expressions of inflammatory factors such as interleukin (IL)-6 and IL-8 were increased in patients with SARS-CoV. The patients eventually died of multiple organ failure, which suggests that inflammation may also cause AKI [102,104,105]. At present, there are two main conjectures about the mechanism of SARS-induced inflammation: virus replication/proliferation and neutralizing antibodies. In the first proposed mechanism, apoptosis and pyrolysis caused by virus replication are important factors that cause inflammation. Studies have shown that SARS-CoV can activate macrophage nucleotide-binding and oligomerization domain (NOD)-like receptor protein 3 inflammatory bodies through viroporin 3a to cause pyrolysis, which leads to the production of many inflammatory factor precursors [106]. In addition, ACE2 may also play a vital role in inflammation. Studies found that SARS-CoV can induce the downregulation of ACE2 expression on the surface and cause the extracellular region of ACE2 to fall off [107]. The imbalance of ACE2 prevents the effective decomposition of angiotensin 2. Accumulated angiotensin 2 induces an inflammatory response and further increases the vascular permeability, causing disease progression [108]. In the second proposed mechanism, neutralizing antibodies may also induce inflammation. When foreign antigens such as viruses invade the body, B lymphocytes in the immune system are stimulated by antigens to differentiate into effector B cells, namely plasma cells, which produce and release neutralizing antibodies that can bind to the virus. Destroying the virus before entering the cell is a vital part of the immune system.

Studies have shown that anti-coronavirus neutralizing antibodies may induce inflammatory reactions, which can lead to acute lung injury in severe cases [109,110]. Thus, the mechanism by which anti-coronavirus neutralizing antibodies induce inflammation and lung injury is still unclear. Some researchers have speculated that the coronavirus antibody complex binding to Fc receptors promotes lung inflammation and sustained viral replication in some patients [111–113].

The relationship between SARS and chronic kidney disease (CKD) is also noteworthy. Four SARS patients in Hong Kong were treated with high doses of ribavirin and corticosteroids during dialysis; however, all eventually died. Based on this small case series, patients undergoing dialysis may experience more serious consequences after SARS-CoV infection [114]. The use of immunosuppressive agents should be reduced to avoid excessive infection in patients with SARS and nephropathy [115]. Emerging evidence suggests that SARS is more invasive in people with kidney disease than in those without kidney disease [103]. Therefore, enhanced vigilance against SARS should be used in patients with low immunities, such as those with CKD.

5. When the kidney meets MERS-CoV

MERS is caused by infection with MERS-CoV, a β -coronavirus. MERS-CoV caused respiratory diseases in the Middle East and then spread to Europe, Africa, and Asia [116,117]. The WHO reported 2468 MERS-CoV cases globally, including 851 deaths, from April 2012 to September 2019 (<https://www.who.int/zh/>). The MERS mortality rate is high (35%), and complications caused by infection can lead to severe respiratory and renal failure [118,119]. Moreover, MERS-CoV infection manifestations range from respiratory diseases to severe diseases with septic shock and multiple organ failure [120,121].

Unlike SARS-CoV, MERS-CoV uses DPP-4 as its functional receptor for intracellular infection [122]. DPP-4, a serine peptidase, exists in various cells that highly express mRNA and proteins in the kidney [123]. DPP-4 is one of the main membrane proteins in the kidney, suggesting that the kidney is a potential target organ for MERS-CoV [124]. The pathological features of kidney injury in patients with MERS are tubular epithelial cell degeneration and regeneration, glomerular ischemia, and an increased number of sclerosing glomeruli [125]. Zhao et al. [126] found inflammatory cell infiltration in mice infected with MERS coronavirus. However, with an extended infection time, more renal tubular epithelial cells were damaged and there was evidence of focal hemorrhage in the renal interstitium. On the basis of these findings, we speculated that MERS first produces an inflammatory response to kidney damage. Thereafter, the renal tubular epithelial cells become damaged, accompanied by bleeding. A recent study using high-throughput analysis demonstrated that MERS-CoV induces renal cell apoptosis via upregulating the expression of Smad7 and fibroblast growth factor-2 (FGF2) [6]. It has also been confirmed in non-human primate models; common marmosets infected with MERS-CoV developed ARDS, and the infection spread to the kidneys and other organs, with a detectable increased expression of Smad7 and FGF2 in the kidneys [6]. These results support the view that Smad7 and FGF2 may play a vital role in the pathogenesis of MERS-CoV-induced kidney damage. However, further experimental verification is required.

6. When the kidney meets SARS-CoV-2

COVID-19 is a global health problem. Currently, SARS-CoV-2 infection is mainly reduced through vaccination and prevention. When infections occur, there are still no effective treatments. The renal effects of SARS-CoV-2 were the focus of this paper, including the kidney damage after infection with SARS-CoV-2 and the renal effects before and after COVID-19 treatment. We hoped to address the adverse consequences caused by SARS-CoV-2 and contribute to the knowledge of this issue.

7. Conclusion

In this review, we summarized the kidney damage caused by SARS-CoV, MERS-CoV, and SARS-CoV-2 infections. We also discussed the detailed situation of COVID-19 patients undergoing hemodialysis as well as current therapeutic drugs that cause renal damage. We concluded that highly pathogenic coronaviruses might cause cytopathic changes, such as to the ACE2 receptor, or excessive inflammation leading to kidney damage. Patients with CKD and kidney transplants are more susceptible to infection because of their weakened immune systems, which makes them more susceptible to the virus. These conclusions lay an important foundation for the control of COVID-19 and provide possibilities for future treatments of coronavirus infections. Clinically, in addition to actively treating primary diseases induced by SARS-CoV-2, the renal injury and other complications caused by the infection should be considered. Therefore, to treat pneumonia caused by coronaviruses, the renal function of infected patients should be monitored, and drugs without adverse renal effects should be used to accelerate the patient's recovery. Our analysis included not only the kidney damage caused by the coronavirus infections, including the renal damage from therapeutic drugs, but also explored the impact to patients with pre-existing renal damage. Our findings provide guidance for primary coronavirus disease treatment, and strategies for monitoring and treating patients to prevent renal damage and other secondary complications.

Funding

This work was supported by the project of collaborative innovation for colleges of Anhui province (NO. GXXT-2021-070).

Ethical statement

There are no ethical issues with this review.

CRediT authorship contribution statement

Xiao-ming Meng and Bing-Xiang Shen: Conceptualization, Roles/Writing - original draft, Writing - review & editing. **Fang Wang, Xiao-guo Suo and Cong Wang:** Conceptualization, Roles/Writing - original draft, Writing - review & editing. **Jia-nan Wang, Xiao-yan He, Fa-cai Wang, Juan Jin, Jia-gen Wen, Wei-jian Ni:** Conceptualization, Writing - review & editing, Supervision. All the authors have read and approved the final draft of the manuscript. Juan Jin and Jia-gen Wen put forward valuable suggestions in the revision, and Wei-jian Ni helped us solve some problems in the revision. All authors agreed to the author list change in the manuscript.

Declaration of conflicting interests

The authors report no conflict of interest.

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