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Kidney injury in COVID-19 patients, drug development and their renal complications: Review study

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ABSTRACT

Since December 2019, the world was encountered a new disease called coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although SARS-CoV-2 initially causes lung damage, it also affects many other organs, including the kidneys, and on average, 5–23% of people with COVID-19 develop the symptoms of acute kidney injury (AKI), including elevated blood creatinine and urea, hematuria, proteinuria, and histopathological damages. The exact mechanism is unknown, but the researchers believe that SARS-CoV-2 directly and indirectly affects the kidneys. The direct pathway is by binding the virus to ACE2 receptor in the kidney, damage to cells, the renin-angiotensin system disturbances, activating coagulation pathways, and damaging the renal vascular endothelium. The initial evidence from studying the kidney tissue in postmortem patients is more in favor of the direct pathway. The indirect pathway is created by increased cytokines and cytokine storm, sepsis, circulatory disturbances, hypoxemia, as well as using the nephrotoxic drugs. Using renal tissue biopsy and autopsy in the patients with COVID-19, recent studies found evidence for a predominant indirect pathway in AKI induction by SARS-CoV-2. Besides, some studies showed that the degree of acute tubular injury (ATI) in autopsies from COVID-19 victims is milder compared to AKI degree. We review the mechanism of AKI induction and the renal side effects of the most common drugs used to treat COVID-19 after the overview of the latest findings on SARS-CoV-2 pathogenicity.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a virus of coronaviridae family which has single-stranded RNA and causes coronavirus disease-2019 (COVID-19) [1]. Seven coronaviruses were identified which cause the disease in humans [2,3]; four of them are endemic worldwide and cause a mild seasonal respiratory illness. These four viruses infect upper respiratory tract and are low pathogenic coronaviruses. Highly pathogenic coronaviruses infect the lower respiratory tract and include severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV caused an epidemic in the humans in 2002 for one year which had a fatality rate of about 10% [4]. MERS-CoV caused an epidemic in the humans in 2012. Although MERS-CoV incidence was lower than that of SARS-CoV, the case fatality ratio (CFR) was reported to be higher at about 35% [2]. The new member of this family is SARS-CoV-2 which caused an epidemic in late 2019, and the resulting

disease was named coronavirus disease-2019 (COVID-19). The disease rapidly spread worldwide which became a global problem, being recognized as a pandemic disease by World Health Organization (WHO) on March 11, 2020 [5]. At the time of writing this review (June 2021), the virus has infected more than 180 million people in 223 countries, killed more than 4000,000, and more than 3 billion vaccine doses were administered [6]. Preliminary reports indicate that about 81% of people infected with SARS-CoV-2 have only mild symptoms, and only 5% show severe symptoms. The mortality rate in COVID-19 is reported to be about 2–4% [2]. The disease initially damages the lungs but also affects many other organs including the kidneys, and causes renal malfunction [7]. Hence, up to 25% of people with severe COVID-19 develop the acute kidney injury (AKI) symptoms [8]. After the overview of latest findings on COVID-19 pathophysiology, we focus SARS-CoV-2 induced renal impairment etiology and the most commonly used drugs for COVID-19 treatment, along with renal side effects of these drugs. Then, the most important new variants are mentioned.

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2. Pathogenesis of COVID-19

SARS-CoV-2 genome encodes structural and non-structural proteins. Structural proteins include spike (S), membrane (M), nucleocapsid (N), and envelope (E) proteins. Several nonstructural proteins play a key role in virus entering and replication in the host cells [9]. The first step in SARS-CoV-2 pathogenesis is the binding of S protein to angiotensin-converting enzyme-2 (ACE2) receptor [10]. The binding affinity of S protein to ACE2 in SARS-CoV-2 is 10–20 times higher than that of SARS-CoV [11]. Moreover, transmembrane serine protease 2 (TMPRSS2) is required for coronavirus to enter host cells [3]. Spike protein was shown to bind to ACE2 on alveolar epithelial type II cells using TMPRSS2, and the virus enters the cell via endocytosis (Fig. 1). Then, the virus releases its RNA into the host cell, and after translation,

the viral proteins are produced in the endoplasmic reticulum and Golgi apparatus. Furthermore, viral RNA replicates using cell's transcription machine. Finally, after the synthesis of structural and non-structural proteins, viral RNA and synthesized proteins are assembled and a new virus is released from the cell by exocytosis [12–14].

Following the replication and enhancement of SARS-CoV-2, the molecular patterns of virus (including proteins, nucleic acids, and pathogen components) are detected by innate immune system components including pattern recognition receptors. These receptors then stimulate the expression of inflammatory mediators which lead to cytokine storms through activating NF-κB and MAPK [3,15]. It was shown that the cytokine storm is associated with disease severity [14].

Moreover, SARS-CoV-2 was shown to increase blood coagulation factors and blood clotting ability in patients [16]. The main mediators of

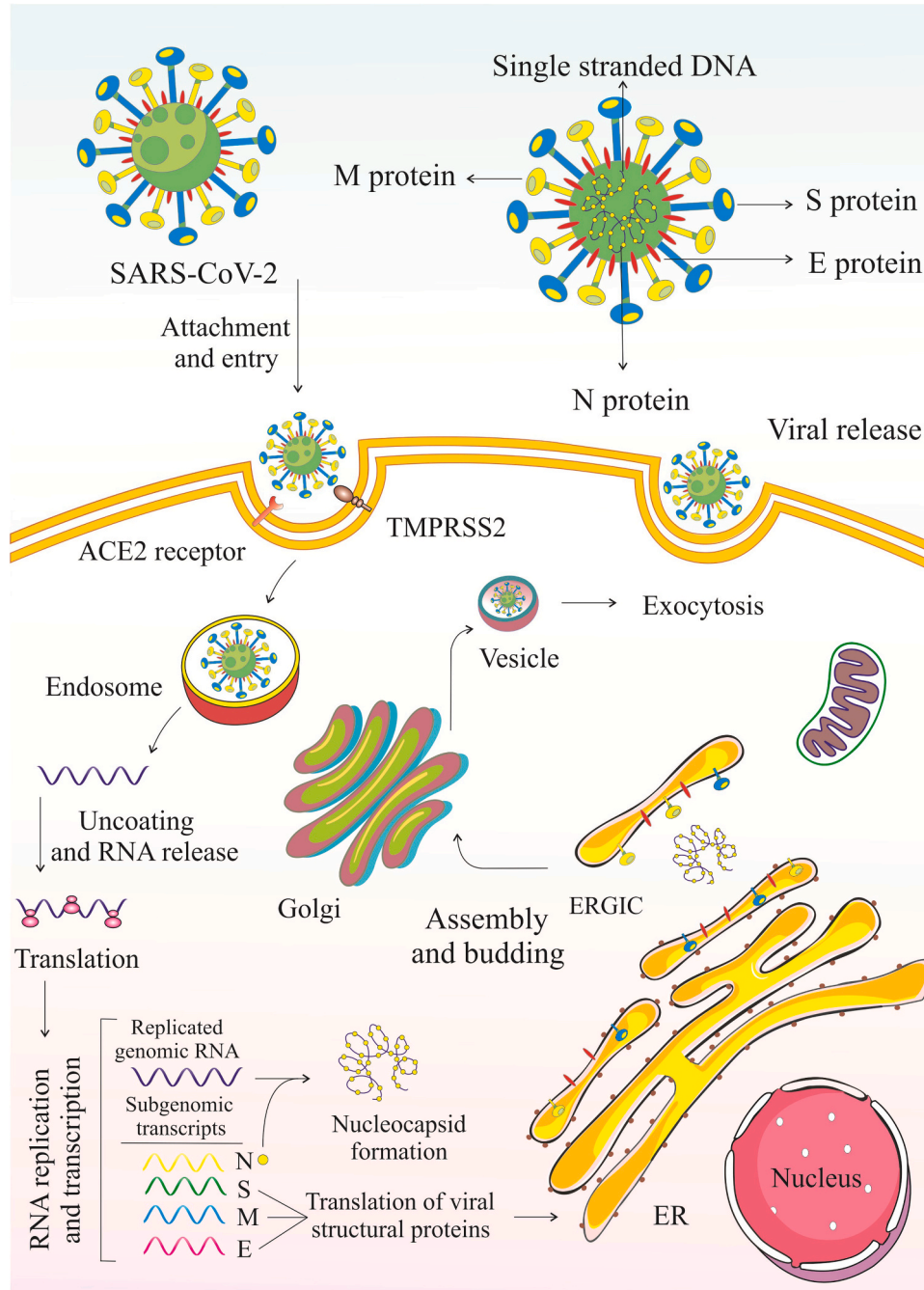


Fig. 1. Schematic representation of SARS-CoV-2 binding to host cells and using host machinery for replication. ERGIC: Endoplasmic reticulum-Golgi intermediate compartment.

blood clotting (including fibrinogen, tissue factor, and thrombin) act as proinflammatory factors. SARS-CoV-2 increases fibrinogen expression and fibrinogen causes platelet aggregation and immune system activation [17]. On the other hand, hypoxia due to COVID-19 also accelerates thrombosis formation by increasing blood viscosity [18]. Finally, vascular endothelial function is impaired by COVID-19 infection, which in turn increases thrombin production and inhibits fibrinolysis, thereby increasing blood clotting ability [16]. Therefore, clot formation in the blood vessels of people with COVID-19 is a risk factor that increases mortality rate and causes anticoagulants to be prescribed in these patients [19].

3. Epidemiology and pathophysiology of COVID-19 induced acute kidney injury

Although coronavirus primarily appears as an acute respiratory disease, it can affect other organs, including the kidneys, heart, gastrointestinal tract, blood, and central nervous system [20,21]. Coronavirus penetrates central nervous system through nerve cells, and it causes damage to the respiratory center, confusion, lethargy, disorientation, loss of senses of smell and taste in most patients, and other symptoms related to brain dysfunction [22]. Coronavirus in the kidney can cause AKI and other disturbances in kidney function [23,24]. Acute kidney injury is a condition which blood urea and creatinine concentrations increase via the retention of nitrogenous wastes, decrease GFR, as well as extracellular fluid volume and electrolyte homeostasis derangement [25–27]. Although AKI is an uncommon feature of SARS-CoV-2, it is known to be a fatal complication with early reports indicating 3–9% prevalence of AKI in the patients with COVID-19 [28]. However, subsequent studies reported that AKI incidence in hospitalized patients with COVID-19 is from 5% to 23% [8,29–31], and recent cohort studies have even reported an incidence of up to 46% which has reached 68% in ICU patients [32,33]. Risk factors for AKI in COVID-19 include the need for mechanical ventilation, intubation, old age, diabetes mellitus, hypertension, severe illness, obesity, male gender, and chronic renal failure [33,34]. However, some studies showed that the patients with COVID-19, in addition to AKI, also develop the glomerular disease because hematuria and proteinuria have also been detected in them [31].

The exact COVID-19 mechanism on kidney is not yet known, but researchers believe that SARS-CoV-2 directly and indirectly affects the kidney. Because SARS-CoV-2 is found in the urine, kidney damage pattern caused by the virus is limited to areas with ACE2 receptor, and the time course in which the virus appears in the urine coincides with the onset of AKI, so it was suggested that the virus directly affects the kidneys [35–37]. The virus is claimed to enter the kidney cell by binding to membrane-bound ACE2 receptors in the glomerular podocyte cells and the apical membrane of proximal tubule cells, and in addition to damaging the kidney epithelial cells, it disarranges the balance of renin-angiotensin system [38]. The angiotensinogen is primarily converted to angiotensin-I by renin and then to angiotensin-II under the influence of angiotensin-converting enzyme (ACE). Moreover, angiotensin-II is converted to angiotensin 1–7 by the ACE2 which dilates blood vessels. If SARS-CoV-2 occupies ACE2, angiotensin-II levels increase, leading to vasoconstriction, glomerular dysfunction, inflammation, and fibrosis [38,39]. Recently Wang et al. and Chiu et al. found that SARS-CoV-2 also invades host cells via CD 147-spike protein pathway and this glycoprotein is highly expressed in proximal tubule [40,41]. Moreover, SARS-CoV-2 causes kidney damage by activating inflammatory pathways and cytokine storm, activating coagulation pathways, damage to renal vascular endothelium, sepsis, hemodynamic instability as well as hypoxemia [38,42,43]. Viral infection of endothelium via immune cell recruitment causes defective endothelial function and reduces the production of vasodilators, including the nitric oxide. Decreased vasodilators increase the response to vasoconstrictors and, together with ischemia-induced oxidative stress lead to AKI

development [44].

Furthermore, there are different opinions about the timing of the onset of AKI symptoms in different studies. In a study conducted by Na et al. out of 66 patients with COVID-19, three cases showed AKI symptoms, all of which became apparent in the severe patients after the first week of hospitalization [20]. Other studies have also reported the onset of AKI symptoms from days 5–9 after the hospitalization [24,45,46]. However, in one case report, symptoms started on the second day of hospitalization [47], and in four other studies, there were symptoms at the time of admission [48–51].

4. Pathological findings in COVID-19-induced acute kidney injury

Preliminary pathological findings regarding renal injury in the people with COVID-19 are mainly the result of studies performed on post-mortem tissues (Autopsy). Due to a study by Su et al. on autopsy specimens using a light microscope, renal damages included acute tubular damage in proximal tubule, brush border loss, lumen dilation, vacuolar degeneration, and sometimes necrosis, and tubular epithelial detachment [52]. The tubular casts, sometimes cell swelling and interstitial edema without inflammation in the distal tubule and collecting ducts, accumulation of erythrocytes and obstruction of glomerular and peritubular capillaries, segmental thrombus in glomerular capillaries with glomerular ischemia along with endothelial damage and swelling were observed. In the electron microscopic study, virus particles were observed in the cytoplasm of proximal tubule cells and podocytes which this evidence is in favor of the fact that SARS-CoV-2 directly causes kidney damage. Furthermore, indirect fluorescence expressed the SARS-CoV-2-related nucleoprotein in the tubular epithelium. Other studies have also reported evidence of SARS-CoV-2 virus in the autopsy specimens of COVID-19 patients [53,54].

The second category of findings comes from the research on the tissues obtained from kidney biopsy and autopsy in COVID-19 patients. These findings include immune-mediated glomerular disease and glomerulosclerosis, and no viral particles were found in the cytoplasm of cells [55]. In a recent study by Kudose et al. on 17 patients with COVID-19, they reported that collapsing glomerulopathy with acute tubular injury (ATI), tubuloreticular inclusions, minimal change disease, endothelial damage, pigment casts, and immune-mediated glomerular disease were observed in biopsy specimens using a light microscope [56]. Electron microscopy also showed glomerular endothelial tubuloreticular inclusion and the absence of viral particles in kidney cells. Immunohistochemical staining and automatic in situ hybridization indicated the absence of spike and nucleocapsid proteins and RNA of SARS-CoV-2 virus in renal cells. However, in manual in situ hybridization, the presence of RNA in tubular cells was slightly positive in two patients.

In line with above-mentioned results, it was shown that SARS-CoV-2 RNA is not found in the urine of all patients with COVID-19 induced AKI according to plasma creatinine concentration [57]. This finding indicates that urinary secretion of virus is not common in the patients with AKI following COVID-19. Therefore, the virus does not directly cause kidney damage, because in this case, the virus was secreted into the urine. Furthermore, Tampe et al. showed that urinary levels of SARS-CoV-2 nucleocapsid protein in the patients were directly related to the risk of AKI, but urinary ACE2 and TMPRSS2 protein levels were not associated with AKI [58]. The researchers concluded that since urinary levels of ACE2 and TMPRSS2 proteins are not associated with AKI, SARS-CoV-2 affects the kidneys via systemic inflammation rather than directly.

Besides, Santoriello et al. examined the kidneys of 42 patients who had died of COVID-19 [59]. They studied all autopsies with light microscopy, electron microscopy, immunofluorescence, and in situ hybridization. This study's results showed that ATI degree in these autopsies is milder compared to AKI degree. They suggested that several

factors, including ischemia, hypoxia, toxins, and other factors, may play a role in the development of AKI following COVID-19.

Therefore, it seems that the findings of some studies on postmortem tissues further confirm the direct damage to the kidney by SARS-CoV-2. However, in the studies with biopsy specimens, the presence of virus in kidney cells is negligible, and it is suspected that such a small amount of virus is sufficient to cause pathological changes and agrees with the predominant role of cytokines and other systemic effects.

5. Drugs used to treat COVID-19 and their renal complications

There are several potential approaches for COVID-19 treatment including drugs, monoclonal antibodies, peptides, interferon, and so on; hence, we review drugs which have side effects on the kidneys (Table 1).

5.1. Lopinavir/ritonavir

Lopinavir/ritonavir (KALETRA) was approved for HIV patients, and its mechanism of action is protease inhibition. In humans, lopinavir is used with ritonavir because ritonavir increases the plasma half-life of lopinavir by inhibiting cytochrome P450 [60]. In a study, Alvarez et al. estimated that 50% effective concentration of lopinavir against the SARS-CoV-2 virus is 16.7 mg/L. Their model indicated that with a dose of 400 mg (b.i.d) about 40% of patients remain below the minimum effective concentration. But with 1200 mg, this proportion reduces to 22% [61].

Lopinavir was shown to have the inhibitory activity in vitro against SARS-CoV, SARS-CoV-2, and MERS-CoV [62–65]. Although COVID-19 treatment with lopinavir/ritonavir was recommended in many studies, the results of one study showed that lopinavir/ritonavir could not be an effective treatment for the hospitalized patients with COVID-19 [66]. This study's results showed that using the lopinavir/ritonavir for the treatment of 199 patients with COVID-19 did not significantly reduce mortality and ICU admission.

In a study using World Health Organization Drug Base (VigiBase) performed by Binois et al., all patients with COVID-19 who were taking lopinavir/ritonavir and had acute kidney injuries were extracted from the database. They showed that there were 8 COVID-19 patients who developed type 2 or 3 acute kidney injury on the second or third day of hospitalization in the ICU after receiving lopinavir/ritonavir [67]. Due to these studies, lopinavir/ritonavir may also have synergistic effects with COVID-19 in developing the acute kidney injury which requires

further study.

5.2. Vancomycin

Vancomycin is an antibiotic used to treat pneumonia against gram-positive bacteria, especially *Staphylococcus aureus* [68]. This drug penetrates into most spaces of body, and its concentration depends on the degree of inflammation [69]. In some studies, vancomycin has also been used to treat pneumonia caused by COVID-9 [20,70]. A 33-year-old pregnant woman with COVID-19 increased her blood urea and creatinine after taking vancomycin in a case report. In this patient, the vancomycin was discontinued due to renal function deterioration after a few days, and creatinine and urea were severely reduced on the sixth day after hemodialysis [45]. In another study of 3 patients with acute kidney injury following COVID-19, blood creatinine and urea concentrations increased after starting vancomycin, indicating acute kidney injury, and discontinuation of vancomycin caused a return of blood creatinine and urea concentrations in some of them [20]. Furthermore, it is difficult to determine whether acute kidney injury was caused by SARS-CoV-2 infection alone or treatment with vancomycin has also helped. Since in both studies, acute kidney injury started after using vancomycin, so the possibility of nephrotoxicity of this drug and its synergistic effects with the adverse effects of SARS-CoV-2 on the kidney is raised.

5.3. Remdesivir

Remdesivir is a modern nucleotide analogue that is effective against coronaviruses such as SARS-CoV and MERS-CoV in vitro and in animal studies, as well as in SARS-CoV-2 in vitro [71,72]. It was reported that remdesivir inhibits RNA synthesis in SARS-CoV, MERS CoV, and SARS-CoV-2 [73]. Although US Food and Drug Administration (FDA) have not approved any definitive drug to treat the COVID-19, it has authorized the emergency use of remdesivir to treat hospitalized adults [74]. Humeniuk et al. in their study found that single-dose i.v. administration of remdesivir as a solution or lyophilized formulation at doses ranging from 3 to 225 mg and multiple-dose i.v. administration of 150 mg once daily for 7 or 14 days is generally well-tolerated. No subject had a graded ALT or AST elevation in a single-dose study, but mild elevations in ALT and AST were observed in the multiple-dose study [75]. Recent studies showed that remdesivir prevents SARS-CoV-2 infection by inhibiting virus replication in human respiratory tract epithelial cells which is, therefore, a potential therapeutic drug against

Table 1

The most common drugs used in the treatment of SARS-CoV-2, mechanism of action and their side effects on various organs, including the kidneys.

Drug	Mechanism of action	Side effects	References
Lopinavir/Ritonavir	Protease inhibitor	Development of AKI in some COVID-19 patients	[66,67]
Vancomycin	It is bactericidal through inhibiting the biosynthesis of peptidoglycan in bacterial cell wall	Interstitial nephritis and acute renal failure, ototoxicity, decreasing neutrophil and platelet count	[20,45]
Remdesivir	Inhibition of RNA synthesis	Diarrhea, skin rash, elevated liver enzymes, renal failure, hypotension, increasing creatinine, septic shock, multiple organ dysfunction syndrome	[45,78]
Favipiravir	Inhibition of RNA-dependent RNA polymerase (RdRp)	Gastrointestinal side effects, increasing uric acid, SGOT, SGPT, and triglyceride, decreasing neutrophil count	[82]
Chloroquine/ Hydroxychloroquine	Inhibiting heme polymerase	Gastrointestinal side effects, cardiac toxicity	[85]
Azithromycin	Inhibiting mRNA translation	CNS and gastrointestinal side effects, hepatitis and hepatic failure, thrombocytopenia and hemolytic anemia, interstitial nephritis and acute kidney injury	[99]
Doxycycline	Inhibiting metalloproteases and expression of CD 147 and has anti-inflammatory property	Gastrointestinal side effects such as nausea, vomiting and abdominal pain	[100,101, 103]
Baricitinib	Janus kinase (JAK) inhibitor	Upper respiratory tract infection, headache, nasopharyngitis, decreases in neutrophil and lymphocyte counts, decreases in hemoglobin, small increases in creatinine, increases in lipid parameters, elevations in liver enzymes and bilirubin and increases in creatine phosphokinase	[110,111]
Arbidol	Inhibition of virus-mediated fusion to the host cell membrane	Nausea and vomiting	[117]
Tocilizumab	humanized anti-IL-6 receptor antibody	The risk of secondary infection, hepatotoxicity, decreased neutrophils and platelets, hypercholesterolemia, anaphylaxis, skin/soft tissue infections, and intestinal perforation	[133,134]

SARS-CoV-2 [76]. Besides, in an experiment performed on 12 SARS-CoV-2-infected monkeys, the administration of remdesivir 12 h after virus injection reduced respiratory symptoms and lung damage, and at autopsy, reduced viral load on the lungs [77]. In a study by Grein et al. on using remdesivir in 61 patients with COVID-19, common adverse drug reactions reported were diarrhea, skin rash, elevated liver enzymes, renal failure, and hypotension. Besides, 12 patients developed severe complications, including septic shock, multiple organ dysfunction syndromes, and acute kidney injury [78]. In a case report, three days after using the remdesivir, they had to stop taking the remdesivir due to an increase in blood creatinine. In this patient, when receiving the remdesivir was stopped, and hemodialysis was performed, creatinine level decreased on the 16th day and the patient was transferred from ICU to the ward [45]. Since Remdesivir is excreted via the kidneys and contains compounds which accumulate in the kidneys (sulfobutylether- β -cyclodextrin), these compounds may cause kidney damage, which requires further study.

5.4. Favipiravir

Favipiravir is approved to treat the severe cases of influenza which is an inhibitor of RNA-dependent RNA polymerase (RdRp) [79]. Favipiravir prodrug is phosphoribosylated after entering the cells. In this form, it is considered a substrate for RNA polymerase and enters nascent viral RNA which leads to the chain's termination and mutation in viral RNA [80]. Therefore, favipiravir inhibits transcription and replication of the virus. This drug has a wide safety margin and therefore can be prescribed in high doses. It was shown that plasma concentration of favipiravir reaches maximum of two hours after oral administration and then rapidly decreases with a half-life of 2–5.5 h [81]. Favipiravir is metabolized by the hepatic enzyme aldehyde oxidase and excreted by the kidneys. It can booster its concentration by self-inhibition of aldehyde oxidase [79]. Side effects of favipiravir include gastrointestinal side effects, elevated uric acid, aspartate aminotransferase (SGOT), alanine transaminase (SGPT), and triglyceride and decreased Neutrophil count and should not be used in people with hepatic or renal insufficiency [82]. Various studies were performed on the efficacy of favipiravir for the treatment in patients with COVID-19. There was no significant difference in recovery from the disease among favipiravir receiving patients compared with arbidol receiving group in one study. The symptoms improved earlier in the patients receiving favipiravir [83]. In another study, patients receiving favipiravir had shorter viral clearance time and faster recovery of chest CT symptoms than patients receiving lopinavir/ritonavir [84]. Based on the results of above-mentioned studies and others, it can be concluded that if favipiravir is used in the early stages of disease, this drug can increase the speed of the recovery of symptoms in the patients with COVID-19. Not yet, the renal side effects were reported for favipiravir.

5.5. Chloroquine and hydroxychloroquine

Chloroquine is an antimalarial drug that acts by inhibiting heme polymerase [79]. In hydroxychloroquine, one of the ethyl groups of alkyl side chain is hydroxylated which has slightly fewer side effects and toxicity than chloroquine [85]. The antiviral mechanism of both drugs is inhibiting host receptors glycosylation, endosomal acidification, and proteolytic processing [86,87]. SARS-CoV-2 requires endosomal acidic pH for entering the cell and beginning of proliferation process, and if acidification is inhibited, this process does not begin [36]. There are three groups of drugs used to inhibit endosomal acidification, one of which is weak bases such as chloroquine and ammonium chloride. Chloroquine inhibits virus binding to the endosome by increasing endosomal pH [19]. It was reported that the bioavailability of chloroquine from the oral tablet is about 89%. Chloroquine and hydroxychloroquine are metabolized by Cytochrome P450 enzymes, primarily eliminated via the kidneys, and the elimination half-life is much longer

for chloroquine [88].

Studies on the effect of these two drugs on COVID-19 showed that in the chloroquine or hydroxychloroquine receiving group, clinical symptoms improve earlier than in the control group, and hydroxychloroquine is more effective [89,90]. In another study, it was shown that taking hydroxychloroquine did not reduce the risk of intubation or death in patients with COVID-19 [91]. Moreover, the recent update of international randomized controlled trials for COVID-19 treatments stated that hydroxychloroquine had little or no effect on overall mortality, the onset of mechanical ventilation, and duration of hospitalization, but in the early stages of disease, it is effective [92]. Therefore, the efficacy of chloroquine and hydroxychloroquine in the care of COVID-19 cannot be confirmed at this time, and further studies are needed.

Chloroquine and hydroxychloroquine are usually well-tolerated, and their most important side effects are gastrointestinal side effects and cardiac toxicity; and concomitant use of chloroquine with azithromycin increases its cardiac toxicity [85]. There are no reports of adverse effects for chloroquine and hydroxychloroquine on the kidneys, but in people with underlying heart or kidney diseases, should be used with caution [93].

5.6. Azithromycin

Azithromycin, a broad-spectrum antibiotic and as a weak base, has anti-inflammatory properties which is used to treat the various infections including respiratory infections. Azithromycin interferes with protein synthesis in bacteria by inhibiting mRNA translation [94]. Azithromycin bioavailability is about 37% and has a rapid and extensive distribution of plasma into the intracellular compartments so that its tissue concentration increases to more than 100 times the plasma concentration. Its peak plasma concentration is 0.4 mg/L, renal clearance is 100–189 mL/min, and its elimination half-life is 14 to less than 40 h. Hepatic demethylation is the primary route for azithromycin metabolism and is excreted through the bile and kidneys [95].

Some studies showed that it is useful along with hydroxychloroquine for treatment of COVID-19 [96]. In another study, pretreatment with azithromycin reduced proinflammatory cytokines and NF- κ B translocation in the patients with COVID-19 [97]. Although this antibiotic does not directly affect SARS-CoV-2, some researchers believe that it is useful to treat the severe acute respiratory syndrome that occurs in these patients [98].

There are several side effects of azithromycin, some of which are more likely to occur. These side effects are listed by Bakheit et al. and include anorexia, dyspepsia, flatulence, dizziness, headache, drowsiness, convulsions, arthralgia, and disturbances in taste and smell; rarely constipation, hepatitis, hepatic failure, syncope, insomnia, agitation, anxiety, asthenia, paraesthesia, hyperactivity, thrombocytopenia, hemolytic anemia, interstitial nephritis, acute renal failure, photosensitivity, tooth and tongue discoloration [99].

5.7. Doxycycline

Doxycycline is an antibiotic of tetracycline compounds which has bacteriostatic properties by inhibiting bacterial protein synthesis as well as inhibiting metalloproteases. Furthermore, it was shown to have an anti-inflammatory property and modulate proinflammatory cytokines [100,101]. The absorption of doxycycline is higher than 80% after orally administration of the usual single dose from 100 to 200 mg which is well distributed in tissues due to its lipophilic nature. Doxycycline's peak plasma concentration is 1.9–5.4 mg/L, total body clearance is about 3 L/h, its elimination half-life is 13–14 h, and is excreted through the kidneys (30–40%), and the digestive tract [102].

Doxycycline can inhibit CD 147 expression, and as mentioned earlier, CD 147 is one of the pathways of entry of SARS-CoV-2 into cells, especially T lymphocytes [40,103]. As previously noted, although using the azithromycin with hydroxychloroquine increases its effectiveness in

COVID-19, it increases its side effects on the heart [104,105], and doxycycline appears to be a more useful alternative for azithromycin [101]. Yates et al., in their study on four high-risk, symptomatic, COVID-19 positive patients with known pulmonary disease, showed that the administration of doxycycline accelerates the recovery of patients [103]. However, there is still insufficient evidence which doxycycline is useful in the COVID-19 and requires more clinical trials.

The most common side effects of doxycycline include gastrointestinal side effects such as nausea, vomiting and abdominal pain and so far no kidney complication was reported for it [100,101,103].

5.8. Baricitinib

Baricitinib or olumiant was approved in 2018 by US FDA for the treatment of patients with rheumatoid arthritis as an oral Janus kinase (JAK) inhibitor [106]. JAK is an intracellular enzyme which transmits signals from cytokine receptors to induce signal transducers and activators of transcription (STAT) phosphorylation. Activated STAT regulates intracellular activities including gene expression. Thus, baricitinib inhibits cytokine gene expression; therefore, it has anti-inflammatory properties [19,106]. Baricitinib is usually safe and well tolerated, and no serious treatment-related adverse events (AEs) were reported. After oral administration, its plasma concentration attains its peak value within 1.5 h. The mean renal clearance of baricitinib was determined to be 12 L/h, and its elimination half-life was about 8 h [107].

In an in vitro study, Stebbing et al. showed that baricitinib inhibited the signaling of cytokines involved in COVID-19 (including IL-2, IL-6, and IFN- γ) which had antiviral activity by inhibiting host viral propagation [108]. In a case series of 4 patients with COVID-19, the team showed that taking baricitinib improved the symptoms faster, reduced IL-6, and reduced the SARS-CoV-2 RNA viral load. Other studies have also shown that baricitinib could be a potential treatment for COVID-19 [86,109]. However, baricitinib is not an effective drug to treat COVID-19 because it has adverse reactions [110]. These adverse reactions include upper respiratory tract infections, anemia, nausea, thrombosis, and reactivation of viruses. The most common side effects with baricitinib are upper respiratory tract infection, headache, nasopharyngitis, as well as decreases in neutrophil and lymphocyte counts, decreases in hemoglobin, small increases in creatinine (<0.1 mg/dL), increases in lipid parameters, elevations in liver enzymes and bilirubin and increases in creatine phosphokinase [111].

5.9. Arbidol

Arbidol (umifenovir) is a broad-spectrum antiviral drug approved in Russia and China to treat viral diseases including influenza and hepatitis C [112,113]. The mechanism of the action of arbidol is the inhibition of virus-mediated fusion to the host cell membrane [19]. After a single oral administration of 200 mg of arbidol hydrochloride, its plasma concentration attained its peak value within 1.4 h, and its elimination half-life was about 15 h. It is reported that liver and intestines were the major organs that metabolize arbidol in humans, and CYP3A4 was major isoform involved in arbidol metabolism. It is excreted unchanged as well as metabolized in the feces (32.4%) and urine [114].

Zheng et al. showed in their study that arbidol prevents SARS-CoV-2 infection by interfering with virus release from vesicles [115]. Nojomi et al. also indicated in their study that using the arbidol improved clinical symptoms, shortened the length of hospital stay, increased oxygen saturation, and reduced the requirement for ICU compared to KALETRA group in COVID-19 patients. The patients receiving KALETRA had a higher WBC count and ESR seven days after admission [116]. Two retrospective studies showed that patients receiving arbidol have lower viral load, improved viral clearance, and lesser symptoms on chest CT scan compared to KALETRA receiving patients [117,118]. Besides, Liu et al. found in a cohort study that arbidol significantly reduced mortality in COVID-19 patients [119]. On the other hand, some researchers

showed that taking arbidol does not reduce or improve the symptoms of COVID-19 [120–122], and Huang et al. in a systematic review and meta-analysis indicated that arbidol administration increases the number of negative PCR cases on day 14 compared to the control group, but has no effect on other symptoms. Hence, they concluded that there is no evidence to use the arbidol in COVID-19 patients [123]. Therefore, our information about the effectiveness of arbidol to treat the COVID-19 is still insufficient. The only side effect reported for arbidol includes nausea and vomiting [117].

5.10. Tocilizumab

As mentioned earlier, SARS-CoV-2 increases cytokines, including IL-6, and it leads to cell damage after binding to its receptor. In their study, Saito et al. showed that in IL-6 deficient mice, the rate of the infiltration of neutrophils, macrophages, and inflammatory cells, as well as fibrosis decreased in bleomycin-induced lung injury [124]. Therefore, IL-6 is involved in lung damage and fibrosis. Although IL-6 receptor is only expressed on hepatocytes and some leukocytes, this cytokine also binds to its soluble receptors (sIL-6R), and this complex can affect all cells [124].

Tocilizumab (Actemra) is a humanized anti-IL-6 receptor antibody that interferes with the binding of soluble receptor-IL-6 to the cell membrane [125]. Intravenous tocilizumab administration was generally well tolerated, and when its serum concentrations were above 1 mg/mL, more than 90% of IL-6 receptor saturation was achieved. This component indicates dose-dependent, non-linear pharmacokinetics and has a long elimination half-life [126].

Xu et al., in a clinical trial, showed that tocilizumab is an effective treatment for the COVID-19 [127]. Other researchers indicated that using the tocilizumab improves clinical and radiological symptoms, as well as reduces inflammatory markers and the need for mechanical ventilation [128–130]. Moreover, in a case report, Fontana et al. successfully treated a man with COVID-19 who had received kidney transplantation using tocilizumab [131].

On the other hand, some studies showed that tocilizumab is not effective to treat COVID-19. Tsai et al. showed that using the tocilizumab did not control cytokine storm and can not reduce mortality rate in COVID-19 patients [132]. Besides, using this drug had no significant effect on mortality rate and the need for ICU compared to the control group [125]. Therefore, due to the lack of sufficient clinical evidence for the effectiveness of tocilizumab for care in COVID-19, as well as the presence of serious side effects, the use of this drug should be done with extreme caution.

The most important side effects of tocilizumab include the risk of secondary infection, upper respiratory tract infections, nasopharyngitis, headache, hypertension, hepatotoxicity, decreased neutrophils and platelets, hypercholesterolemia, anaphylaxis, skin/soft tissue infections, and intestinal perforation [133,134].

Using natural compounds in medicinal plants which have anti-coronavirus properties and lead to the cessation or suppression of viral entry or replication in the host by inhibiting viral proteins and enzymes recently was considered, because these compounds have no side effects of synthetic compounds and are also economical. These compounds include essential oils, alkaloids, and flavonoids [135].

6. New variants of SARS-CoV-2

So far, different variants of SARS-CoV-2 were identified, four of which are better known. These four mutations are included alpha variant (B.1.1.7) in UK, beta variant (B.1.351) in South Africa, gamma variant (B.1.1.248) in Brazil, and delta variant (B.1.617.2) in India. These mutations alter the transmissibility as well as the lethality of the virus [136]. In September 2020, N501Y or B.1.1.7 variant of SARS-CoV-2 was spread in Wales. This new strain of SARS-CoV-2 has an asparagine mutation at position 501 to tyrosine (N501Y) which is one of

the amino acids at the site of contact of virus on the spike with ACE2 receptor [137]. Various studies were performed on the transmission power and individuals with the N501Y variant. A report states that the N501Y variant causes more infections in children and young people under the age of 18 than the previous type; on the other hand, this new type has increased the incidence in adults by 3 times [138]. Zhao et al. also reported that N501Y variant has a higher potential for a larger epidemic and a 52% higher transmissibility than the wild type [139]. Ali et al. showed in a study that the electrostatic reaction between the receptor binding domain (RBD) of N501Y variant and ACE2 is stronger than its preliminary type [140]. In a study on mice, Rathnasinghe et al. found that the N501Y mutation increased the risk of infection in obese and older mice, and it responds to existing vaccines similar to the wild-type SARS-CoV-2 [141].

The delta variant was first identified in India in April and May 2021. It is reported that the delta variant has about 60% higher transmissibility than alpha variant, is moderately resistant to vaccines, and its mortality rate is twice that of alpha [142]. Campbell et al. in a study showed that estimated transmissibility in these four mutations increased by 29%, 25%, 38%, and 97%, respectively, for B.1.1.7, B.1.351, B.1.1.248, and B.1.617.2 variants compared to wild type [136]. Khan et al. also reported that South African and Brazilian variants are more lethal than the others, and UK variant is comparable to the wild type [143]. Delta mutation resulted in increased virus shedding and infectivity and enhanced affinity of spike protein with TMPRSS2 protease [144]. So far, no report was published showing that the effect of these variants on the kidney is different from the wild type.

7. Conclusion

COVID-19 is an emerging disease which affects various human organs including the kidneys, and the more severe the disease, the greater the risk of kidney involvement which worsens the prognosis. The exact mechanism by which SARS-CoV-2 induces acute kidney injury is unknown, but researchers believe that it directly and indirectly affects the kidney. The direct pathway is to bind the virus to ACE2 in the kidney, enter and destroy cells, disrupt the renin-angiotensin-aldosterone system balance, activate coagulation pathways, and damage the renal vascular endothelium. However, recent studies on kidney tissue biopsy specimens in the patients with COVID-19 and some autopsy have found evidence which indicates indirect pathway has a dominant role in AKI induction by SARS-CoV-2. Moreover, It was reported that ATI degree in autopsy specimens is milder compared to the degree of AKI. So it can be suggested that several factors, including ischemia, hypoxia, toxins, and other factors, may play a role in the development of AKI following COVID-19. In confirmation of this suggestion, most of the drugs used for the treatment in COVID-19 also have adverse effects on the kidneys and may have a synergistic effect with SARS-CoV-2 itself in inducing AKI. Therefore, it is better to use drugs which have the least harmful effect on the kidneys for the treatment in COVID-19.

Recently, new variants of SARS-CoV-2 were identified; the most common are alpha, beta, gamma, and delta variants. All these variants have increased transmissibility and infectivity. It is not clear whether their effect on the kidneys is different from the wild type or not.

CRedit authorship contribution statement

HN designed and supervised the study, designed the figures, revised the final version of the manuscript, checked the clinical and immunological-associated statements of the manuscript. ZMY drafted the first version of the manuscript, performed artworks on the manuscript. All authors read and approved the final version of the manuscript.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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