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CKJ REVIEW

Coronavirus disease 2019 in chronic kidney disease

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ABSTRACT

The clinical spectrum of coronavirus disease 2019 (COVID-19) infection ranges from asymptomatic infection to severe pneumonia with respiratory failure and even death. More severe cases with higher mortality have been reported in older patients and in those with chronic illness such as hypertension, diabetes or cardiovascular diseases. In this regard, patients with chronic kidney disease (CKD) have a higher rate of all-type infections and cardiovascular disease than the general population. A markedly altered immune system and immunosuppressed state may predispose CKD patients to infectious complications. Likewise, they have a state of chronic systemic inflammation that may increase their morbidity and mortality. In this review we discuss the chronic immunologic changes observed in CKD patients, the risk of COVID-19 infections and the clinical implications for and specific COVID-19 therapy in CKD patients. Indeed, the risk for severe COVID-19 is 3-fold higher in CKD than in non-CKD patients; CKD is 12-fold more frequent in intensive care unit than in non-hospitalized COVID-19 patients, and this ratio is higher than for diabetes or cardiovascular disease; and acute COVID-19 mortality is 15–25% for haemodialysis patients even when not developing pneumonia.

Keywords: cardiovascular disease, chronic kidney disease, COVID-19, immunity, SARS-CoV-2, therapy

INTRODUCTION

Since the first reports of some cases of atypical pneumonia in China in December 2019 and the extreme measures adopted by the Chinese government in closing the city of Wuhan (the focus of the problem), everything rapidly changed. The causative agent of this respiratory disease was identified as a novel coronavirus [1], called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease was termed coronavirus disease 2019 (COVID-19) by the World Health Organization [2].

Coronaviruses were described for the first time in 1966 by Tyrell and Bynoe, who cultivated the viruses from patients with common colds [3]. They are enveloped, positive, single-stranded large RNA viruses that not only infect humans, but also a wide range of animals (bats, pangolins, cats, pigs and birds, among others). The genome size varies between 26 and 32 kb. Based on their morphology as spherical virions with a core shell and

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Table 1. COVID-19 in the CKD population

Key points: the COVID-19 pandemic and the CKD population
Decreased kidney function causes marked alterations in the immune system.
CKD patients are prone to develop all-cause infections.
CKD represents a risk factor for COVID-19 complications.
Causal conditions for CKD (hypertension, DM and CVD) are risk factors for COVID-19 mortality.
Special measures must be taken in CKD Stage 5 on dialysis and renal transplant patients.

surface projections resembling a solar corona, they were termed coronaviruses. At present, four subfamilies are recognized: α-, β-, γ- and δ-coronaviruses [4]. SARS-CoV-2 belongs to the B lineage of β-coronaviruses and is closely related to the SARS-CoV. The major four structural genes encode the nucleocapsid protein (N), the spike protein (S), a small membrane protein (SM) and the membrane glycoprotein (M), with an additional membrane glycoprotein (HE) occurring in the HCoV-OC43 and HKU1 β-coronaviruses [5].

The clinical spectrum of COVID-19 infection is very variable, ranging from asymptomatic infection, anosmia, ageusia or minor upper respiratory tract illness to severe pneumonia with respiratory failure and even death [6]. Diarrhoea and cutaneous and thrombotic manifestations were recently described [7, 8]. More severe cases with higher rates of mortality have been reported in older patients and in those with chronic illness such as cardiovascular disease, hypertension or diabetes. However, deaths have also occurred in previously healthy young patients. Patients with chronic kidney disease (CKD) are expected to be at higher risk of severe disease since their rate of all-type infections and the prevalence of cardiovascular disease are higher than in the general population. Marked alterations in the immune system have been reported in CKD patients, leading to an immunosuppressed state and frequent infectious complications. Likewise, chronic systemic inflammation may also contribute to higher morbidity and mortality in CKD patients [9]. In this review we discuss the pathogenesis of COVID-19, the chronic immunologic changes observed in CKD patients and the risk of COVID-19 and the clinical implications for CKD patients (Table 1).

COVID-19 PATHOGENESIS

For most patients, COVID-19 will affect mainly the upper and lower respiratory tract. The primary mode of infection is human-to-human transmission through close contact, which occurs via spraying droplets from an infected individual through coughing or sneezing. Additionally, surfaces are thought to retain the virus for variable periods of time, depending on their nature [10]. COVID-19 has an asymptomatic incubation period of 2–14 days during which the virus can be transmitted [11].

After entering the lungs, COVID-19 infects cells expressing certain cell surface receptors such as angiotensin-converting enzyme 2 (ACE2; e.g. alveolar type 2 cells) or CD147 [also known as basigin, extracellular matrix metalloproteinase inducer (EMMPRIN) and leukocyte activation antigen M6], which besides lung cells, is also expressed in kidney tubular cells, among others [11, 12] (https://www.proteinatlas.org/ENSG00000172270-BSG/tissue). In healthy individuals, the innate immune response against viral infection relies heavily on interferon (IFN) type I responses and its downstream cascade that culminates in controlling viral replication and induction of effective adaptive immune response [13]. Coronaviruses may dampen the antiviral IFN type I effect, resulting in uncontrolled viral replication, with the consequent influx of neutrophils and monocytes/macrophages and hyperproduction of pro-inflammatory cytokines, the so-called cytokine storm. Thus oxidative stress and inflammation are crucial for defence against COVID-19 infection, but they may be deleterious if not properly regulated [14]. Specific lymphocyte T helper (Th1/Th17) activation may intensify inflammatory responses. Severe COVID-19 is characterized by severe lymphopaenia that is associated with an increased risk of death [15]. The high mortality of patients with severe lymphopaenia may reflect resistance to currently available experimental therapies. Lymphocyte depletion is thought to impair antiviral defences and there have been attempts, discussed below, at boosting these defences. Natural killer (NK) cells are essential for defence against virus infections in general, and as discussed below, some cell-based therapeutic approaches aim at increasing their efficacy. They are thought to be activated in COVID-19 and may contribute to both viral clearance and tissue injury. Indeed, there is profound depletion of NK cells [16]. There is little information on T regulatory cells (Tregs) and COVID-19. In one report, patients with COVID-19 had lower numbers of Tregs, and this was more obvious in severe cases [15]. Regarding a potential role of Tregs in disease pathogenesis, there is information from other coronavirus infections. Thus, in murine models of central nervous system infection, Tregs limited T cell–mediated tissue damage without impairing viral clearance [17]. Meanwhile, B and plasma cells produce specific antibodies that may help neutralize SARS-CoV-2. Both uncontrolled viral replication and the cytokine storm are thought to contribute to disease pathogenesis, as illustrated by therapeutic trials of both antiviral drugs and tocilizumab [neutralizing anti-interleukin-6 (IL-6) antibody; NCT04317092].

Additionally, the findings of endothelial cell injury and thrombotic microangiopathy have raised the spectrum of complement involvement and triggered the use of anticomplement strategies [18, 19]. In case reports, both the anticomplement C5 antibody eculizumab [20] and the complement C3 inhibitor AMY-101 (Amyndas Pharmaceuticals, Philadelphia, PA, USA) [21] were apparently effective in COVID-19 and an eculizumab clinical trial is ongoing (NCT04288713).

At present, the mortality rate of COVID-19 worldwide is ∼2.4% of diagnosed cases. SARS-CoV-2 infection causes both pulmonary and systemic severe inflammation, leading to multi-organ dysfunction. Acute respiratory distress syndrome and respiratory failure, sepsis and heart failure and thrombotic complications have been reported as the most common causes of death [22]. Mortality is higher in elderly people and those with underlying health conditions such as hypertension, cardiovascular disease and diabetes [23]. The case fatality rate during the first week of the epidemic was 0.15% [95% confidence interval (CI) 0.12–0.18)] in mainland China, excluding the city of Wuhan, in which this estimation was 5.25% (95% CI 4.98–5.51) [24]. Outside China, the USA, Italy and Spain have the highest mortality rates. The mortality rate will depend on testing

policies (it will be higher when just severely ill patients that are hospitalized are tested) as well as on the overwhelming of healthcare facilities [mortality shoots up once hospitals run out of ventilators or intensive care unit (ICU) beds].

In a retrospective, multicentre Chinese cohort study, older age, D-dimer levels >1 μg/mL and higher Sequential Organ Failure Assessment scores on admission were associated with higher odds of in-hospital death [6]. Furthermore, elevated serum levels of IL-6, high-sensitivity cardiac troponin I, lactate dehydrogenase and lymphopaenia were more commonly seen in severe COVID-19-affected patients. The age-dependent defects in T and B cell function and the excess production of type 2 cytokines could lead to a deficiency in the control of viral replication and/or more prolonged and intense pro-inflammatory responses, potentially leading to poor outcome [6]. In another small study of 68 hospitalized patients, the risk of death was higher in patients with cardiovascular disease. Older age, the presence of underlying diseases, secondary infections and elevated serum inflammatory cytokines were associated with increased mortality. They suggested that COVID-19 mortality might be due to virus-activated 'cytokine storm syndrome' or fulminant myocarditis [25]. Further reports have linked cardiovascular disease with a higher risk of mortality [26]. Higher body mass index is more often seen in critical patients and non-survivors. Aggravating factors include fulminant inflammation, lactic acid accumulation and thrombotic events [26]. High ferritin has recently emerged as a severe disease indicator [27].

CKD AND COVID-19

At present, the literature regarding CKD and COVID-19 is scarce. A PubMed search for '(CKD OR chronic kidney disease) and (COVID-19 OR SARS-CoV-2)' performed on 10 April 2020 disclosed only one relevant citation, corresponding to a letter to the editor meta-analysis that recorded a higher risk of severe COVID-19 disease in CKD patients [odds ratio 3.03 (95% CI 1.09–8.47), $I^2 = 0.0\%$, Cochran's Q, $P = 0.84$] after analysing four studies including 1389 COVID-19 patients, among which 273 (19.7%) had severe disease [28]. An analysis of 7162 laboratory-confirmed COVID-19 cases in the USA confirmed that CKD was 12-fold more frequent in those with ICU admission and 9-fold more frequent in hospitalized, non-ICU COVID-19 patients than in those not hospitalized. The increased prevalence of CKD in ICU admission was higher than the prevalence of other pre-existing conditions (ratio of prevalence in ICU versus not hospitalized patients ranged from 2- to 6.7-fold; Figure 1A and B), although these data were not adjusted for covariates [29]. In an 'in press' report, evidence of kidney disease at admission in 701 patients hospitalized for COVID-19 was associated with a significantly higher risk for in-hospital death in an adjusted analysis. This ranged from 1.8-fold for proteinuria to 2.1-fold for elevated serum creatinine and 3-fold for haematuria. The risk associated with acute kidney injury (AKI) ranged from 1.9- to 4.4-fold higher depending on AKI severity [30]. However, the study design could not distinguish between pre-existent CKD and COVID-19-associated kidney injury. Hence CKD patients should be included in the COVID-19 high-risk groups. Additionally, the main causes of CKD are cardiovascular, hypertension and/or diabetes related. In this regard, a preprint report, not yet peer-reviewed, of a small study of 37 COVID-19 haemodialysis (HD) patients from Wuhan observed lower peripheral blood T cells, Th cells, killer T cells and NK cells than in the infected general population as well as remarkably lower serum levels of inflammatory cytokines than other COVID-19 patients [31]. Of note, 72% of these patients presented with no obvious symptoms. This could mask the suspicion of active disease and transform them into carriers and transmitters of the virus. During a short follow-up (<2 months), 6/37 (16%) COVID-19 HD patients and 1/193 (0.5%) COVID-19-free HD patents died. The high mortality was not related to respiratory causes, which would be in line with the current understanding of the pathogenesis of lung injury (mainly inflammation mediated) and the low evidence of inflammation observed. How to explain the high mortality then? This is not surprising either, given that viral (e.g. influenza) or severe infection is associated with an increased risk of cardiovascular events both in the general population and in CKD patients [32, 33]. The Wuhan report is in line with preliminary data from the national registry of COVID-19 from the Spanish Society of Nephrology that includes 637 patients to date (409 patients on HD, 203 transplanted patients and 25 patients on peritoneal dialysis) and shows a mortality rate of 21% (https://mailchi.mp/senefro/registro-epidemiolgico-vhc-vhb-vih-1314521; date last accessed 8 April 2020).

KIDNEY INVOLVEMENT IN COVID-19

Beyond respiratory cells, other organs might be affected by SARS-CoV-2, including the kidneys, ileum and heart, especially in the presence of viraemia. Thus cultured renal proximal tubular epithelial cells, glomerular mesangial cells and podocytes express ACE2 on their surface and may represent another target for COVID-19 [34]. Additionally, CD147 is expressed in the basolateral membrane of proximal and distal tubular cells (https://www.proteinatlas.org/ENSG00000172270-BSG/tissue; Figure 2A).

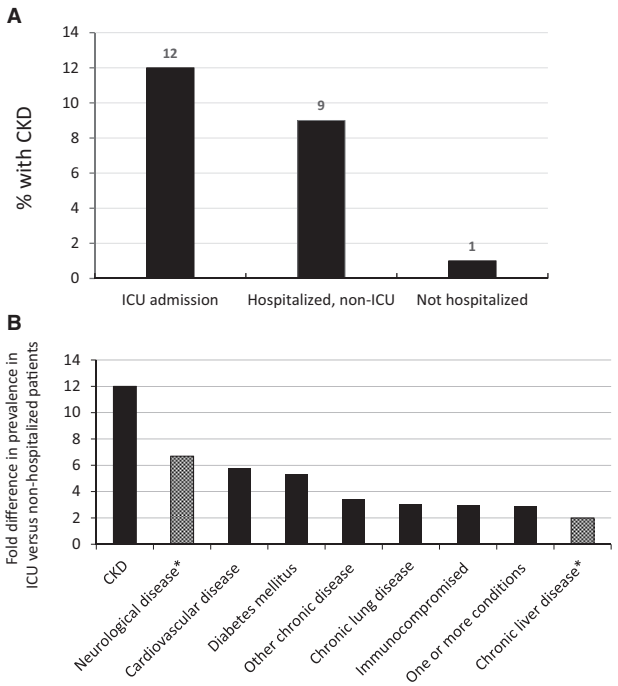

FIGURE 1: (**A**) Prevalence of CKD according to severity of COVID-19. There is a gradient in CKD prevalence from the more severe (ICU patients) to the less severe patients (not hospitalized). (**B**) Prevalence of CKD and additional pre-existing conditions according to COVID-19 severity. The ratio of the prevalence in ICU patients versus the prevalence in non-hospitalized patients is presented. *Conditions in which <100 patients were analysed. Data were obtained from CDC COVID-19 Response Team [29].

As the main site of ACE2 expression is the brush border of proximal tubular cells (https://www.proteinatlas.org/ENSG00000130234-ACE2/tissue/kidney; Figure 2B), it is likely that in the absence of viruria (and the few reports that addressed this issue did not find it) or glomerular filtration of the virus (unlikely given its 70–90 nm size), CD147 may represent the key receptorfor kidney involvement of the virus. In culture, SARS-CoV, the cause of SARS, leads to productive infection in immortalized proximal tubular cells but not glomerular mesangial cell or podocytes [35]. Although the kidneys have higher ACE2 activity than the lungs, heart and pancreas [36], heart and arterial smooth muscle cells also express ACE2 and may theoretically become infected.

Circulating and local renin–angiotensin–aldosterone system (RAAS; including ACE2) are activated in kidney disease [37]. In this regard, in different models of experimental diabetic nephropathy, local kidney ACE2 is increased, reflecting largely tubular cells that account for ~90% of kidney mass [38]. One may speculate that increased tubular cell ACE2 as a consequence of pre-existent pathological conditions may facilitate SARS-CoV-2 infection of tubular cells. However, as data regarding the ACE2/SARS-CoV-2 interaction in kidney disease are scarce, it would be premature to speculate about intrarenal RAAS modulation of SARS-CoV-2 infection at this point.

AKI, proteinuria and haematuria have been reported in COVID-19-positive patients. AKI is usually observed in the context of systemic organ failure [39]. Among 701 patients with COVID-19 admitted in a Wuhan hospital, at admission 44% had proteinuria, 27% had haematuria and the prevalence of elevated serum creatinine, elevated urea and estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 was 14, 13 and 13%, respectively. Additionally, 5% of patients developed AKI [39]. However, as discussed above, the study design could not distinguish between pre-existent CKD and COVID-19-associated kidney injury and there is evidence that CKD patients are at higher risk of severe disease requiring hospitalization.

It is currently unclear to what extent the virus directly damages renal cells or whether kidney injury is mainly secondary to the cytokine storm syndrome [40]. Understanding the key mechanisms of kidney injury in COVID-19 will have therapeutic implications. The cytokine storm has the potential to directly cause AKI, as supported by research in sepsis, endotoxemia, the direct parenteral administration of inflammatory cytokines and interventional studies [41]. It may be speculated that the interaction of both processes may be most damaging: previously injured infected cells may be more sensitive to a deleterious cytokine environment. Thus there is morphological and immunohistochemical evidence of SARS-CoV-2 infection of tubular cells and podocytes. Potentially the contribution to kidney injury may differ at different stages of the natural history, with viral-induced tissue injury more prominent in early stages, when lymphopaenia may contribute to viral expansion, and a more

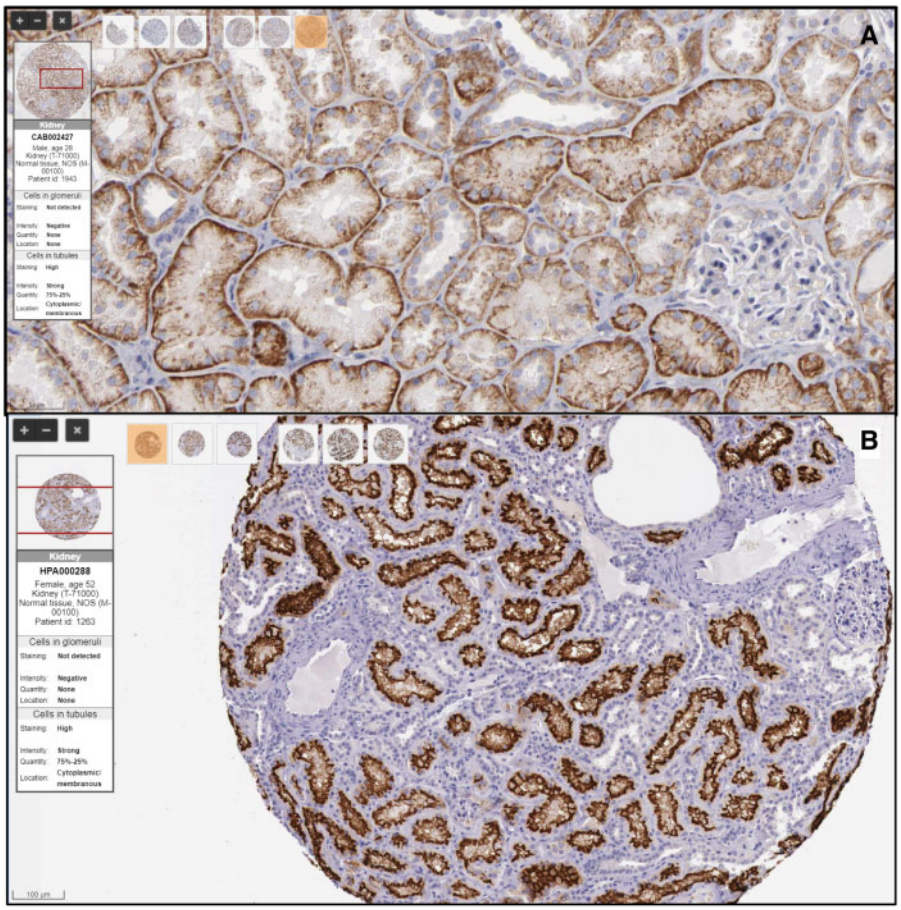

FIGURE 2: Kidney expression of cell receptors for SARS-CoV-2 according to the Protein Atlas. (**A**) CD147 immunostaining in normal human kidney (https://www.proteinatlas.org/ENSG00000172270-BSG/tissue/kidney#img). (**B**) ACE2 immunostaining in normal human kidney (https://www.proteinatlas.org/ENSG00000130234-ACE2/tissue/kidney). Note than CD147 is mainly expressed in the basolateral membrane of proximal and distal tubular cells while the main site of ACE2 expression is the brush border in the luminal side of proximal tubular cells.

prominent role of inflammation in more advanced stages. A post-mortem report in COVID-19 patients who developed kidney failure suggests that coronaviruses directly infect kidney tubular cells, inducing acute tubular damage [35]. Moreover, there was $CD68^{+}$ macrophage infiltration and complement C5b-9 deposition. Data are available for 26 autopsies of patients with COVID-19 dying from respiratory failure associated with multiple organ dysfunction syndrome, of whom 9 had developed increased serum creatinine and/or new-onset proteinuria. There was diffuse proximal tubule injury and red blood cell casts. Electron microscopy showed clusters of coronavirus particles in the tubular epithelium and podocyte anti-SARS-CoV nucleoprotein-stained tubules [42]. Of note, no viral load of SARS-CoV-2 in urine samples was found in the few studies that searched for it in a small number of patients [43–45].

There is evidence for several potential mechanisms of kidney injury, potentially depending on the severity of infection, magnitude of the inflammatory response and even genetic background. The most common mechanism based on both clinical characteristics and histological studies is an acute tubular necrosis form of AKI [42]. However, complement-mediated microvascular injury, rhabdomyolysis-associated kidney injury and collapsing glomerulopathy associated with apolipoprotein L1 risk variants have been described, among others [19, 46].

CKD, IMMUNE DYSFUNCTION AND COVID-19

CKD causes marked alterations in the immune system, including persistent systemic inflammation and acquired immunosuppression [47] (Figure 3). The most common alterations in the immune system in CKD patients are characterized by B and T cell phagocytic dysfunction and increased concentrations of pro-inflammatory cytokines and inflammatory monocytes [5, 48]. These alterations progress as renal function declines. Regarding immune dysfunction in CKD, neutrophil function is decreased in pre-dialysis and dialysis patients [49]. Likewise, B lymphocytes of advanced CKD patients have an increased rate of apoptosis that may contribute to B lymphopaenia [50]. T cells from CKD patients have an aberrant state of early activation. Activated T cells may be driven to apoptosis, thereby contributing to T lymphopaenia, progressive immunodeficiency and the increased risk of infection observed in these patients [51]. Persistent inflammation, *per se*, is a risk factor for progression of CKD and cardiovascular disease [52]. Multiple actors contribute to chronic inflammation in CKD, including patient-related factors, oxidative stress, infections and HD-related factors such as biocompatibility and dialysate quality [53]. Thus there was a correlation between the presence of microorganism DNA/RNA in the dialysate and oxidative stress and serum C-reactive protein and IL-6 [53].

PREVENTION AND TREATMENT OF COVID-19 IN CKD

At present, there is no vaccine against COVID-19, although multiple human trials are ongoing (e.g. NCT04299724, NCT04276896, NCT04334980 and NCT04283461, among others). Moreover, there is no approved therapy for COVID-19 and all current therapies should be considered experimental. Thus, although clinical trials of chemoprophylaxis are also ongoing (e.g. NCT04328285, NCT04330495, NCT04304053, NCT04318015), prevention relies mainly on social isolation and preventive hygienic measures as recommended by nephrological societies for HD and transplanted patients [39, 54, 55].

There was some initial controversy regarding the need to stop RAS blockade, which is widely prescribed to CKD patients. ACE2 expression is increased in diabetes and treatment with ACE inhibitors and angiotensin II receptor blockers(ARBs) increases ACE2 expression [56, 57]. It was thus hypothesized that RAS blockade–induced ACE2 expression may facilitate COVID-19 infection [56]. Conversely, since ACE2 protects from experimental lung injury and recombinant ACE2 is undergoing clinical trials for acute respiratory distress syndrome (28877748, NCT00886353), it has been hypothesized that RAS blockade should be part of the therapeutic regimen for COVID-19 in order to increase ACE2 expression and its potential lung-protective function [58]. There are no data regarding which of these medications (ACE inhibitors or ARBs) are better in COVID-19 patients. In a multicentre retrospective evaluation of 511 patients with COVID-19, in elderly (age >65 years) patients with hypertension, the risk of severe disease was significantly lower in patients receiving ARBs. However, in this older group of patients, only 10 were on ARBs [59]. In any case, there is an ongoing clinical trial of valsartan for prevention of acute respiratory distress syndrome in hospitalized patients with COVID-19 (NCT04335786). In the absence of definitive evidence, some centres have opted for stopping RAS blockade in COVID-19 patients, while others follow clinical guidelines. In this regard, position statements from major societies have emphasized the lack of clinical evidence that RAS blockade is deleterious for COVID-19 patients and the overwhelming evidence that stopping RAS blockade may increase mortality acutely in cardiovascular disease patients (https://www.eshonline.org/spotlights/esh-statbtement-on-covid-19, https://professional.heart.org/professional/ScienceNews/UCM_505836_HFSAACCAHA-statement-addresses-concerns-re-using-RAAS-antagonists-in-COVID-19.jsp). Recent data support the safety of RAS blockade in COVID-19 [60, 61]. When RAS blockade is prescribed for CKD from hypertension only and the patient is anxious because of social media reports, RAS blockade may be more safely changed than in cardiovascular disease patients.

Once CKD patients become infected, they should be quarantined and, if on HD, dialyzed by fully protected personnel and separated from non-COVID-19 patients, including transport to the HD facility, while in the facitlity and back home. Criteria for hospital admission are very variable, depending on whether hospitals are overloaded by COVID-19. In general, patients with low oxygen saturation or bilateral pneumonia on chest X-ray should be hospitalized. There is general agreement on supportive therapy. Thus adequate oxygenation, euvolemic state surveillance, haemodynamic support and all those measures destined to prevent AKI or rapid progression of CKD should be considered in renal disease patients [39]. However, there is wide variability of therapeutic approaches for COVID-19-positive patients (Table 2). This is related to the lack of approved therapies. This variability includes decisions about treatment of individuals that are not hospitalized. In this regard, in Spain, all inpatients receive some therapy, but this is not always the case for outpatients, even those with pneumonia. Potential components of the therapeutic cocktail in milder disease include antiviral drugs, non-antiviral drugs that may decrease viral replication and low molecular weight heparin. Hospitalized patients usually have hyperinflammation and may receive different combinations of anti-inflammatory agents such as steroids or anti-interleukin agents on top of the medication for milder cases. Thus Table 1 presents potential alternatives for

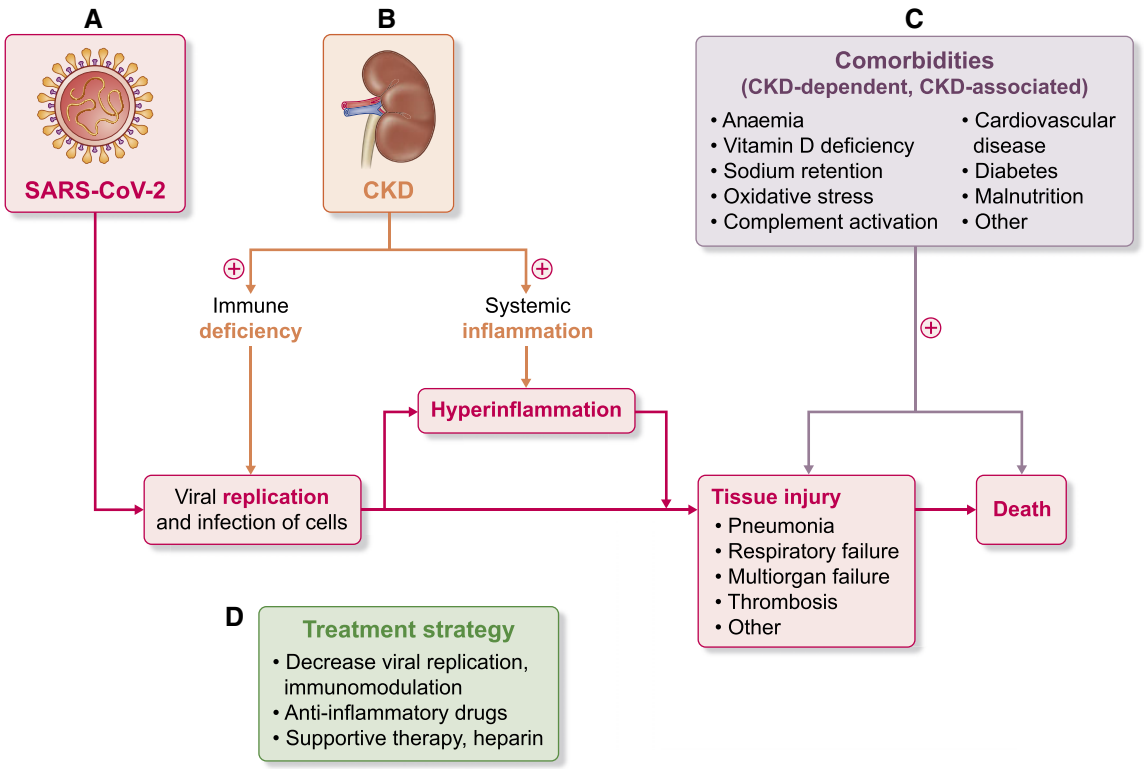

FIGURE 3: Interaction between SARS-CoV-2 and CKD. (**A**) Infection by SARS-CoV-2 results in viral entry into cells and viral replication, causing tissue injury. Tissue injury is aggravated by a severe inflammatory response, eventually leading to death in some patients. (**B**) CKD is characterized by both evidence of immune deficiency, which may facilitate viral replication and expansion, and systemic inflammation, which may aggravate the hyperinflammation observed in more severe COVID-19 patients. (**C**) CKD is frequently associated with comorbidities that are dependent (e.g. anaemia, malnutrition and vitamin D deficiency) or associated (e.g. cardiovascular disease and diabetes) with CKD. These comorbidities may also contribute to more severe disease, leading to death. Thus there is a biological plausibility supporting the empirical evidence of a higher mortality of COVID-19 in CKD patients. (**D**) Current therapy is aimed at decreasing viral replication and boosting antiviral defences, limiting hyperinflammation and supporting measures and thrombosis prevention. Currently these measures are similar for CKD and non-CKD patients. Research is needed for optimization and individualization of the therapeutic approach to the CKD state.

therapy, but not all drugs are prescribed to the same individual. Generally speaking, therapy for COVID-19-positive patients with CKD is the same as in the general population.

Drugs targeting the virus

Aerosolized IFN-α and lopinavir/ritonavir showed some benefit in a Chinese trial (ChiCTR2000029308) but no benefit beyond the standard care treatments in another report [65]. Similarly, the efficacy of chloroquine phosphate and remdesivir against COVID-19 has been tested in human cells and showed inhibitory properties for the virus [66]. Remdesivir was recently (1 May 2020) authorized for emergency use in COVID-19 by the US Food and Drug Administration based on preliminary clinical trial results [67]. Moreover, hydroxychloroquine plus azithromycin decreased SARS-CoV-2 viral load in COVID-19 patients [68]. However, this combination may increase the risk of long QT–associated arrhythmia.

Drugs targeting inflammation

Immunosuppressive treatment with short-term systemic corticosteroids or monoclonal antibodies may decrease severe inflammation [63]. Ongoing trials with convalescent plasma have shown that early application in patients with COVID-19 could accelerate clinical recovery [69]. Arguments for the use of cyclosporine A include *in vitro* data showing inhibition of coronavirus replication, as this requires peptidyl-prolyl cis-trans isomerase activity of cyclophilin [70, 71], as well as evidence of its efficacy in haemophagocytic lymphohistiocytosis, which may be a complication of COVID-19 [72]. However, it remains an immunosuppressive and nephrotoxic agent and protocols for haemophagocytic lymphohistiocytosis suggest a delayed initiation of cyclosporine A not compatible with the time course of COVID-19.

Drugs targeting complications

Prophylactic low molecular weight heparin is the latest addition to the standard therapeutic package for COVID-19. Thus, beyond venous thrombosis due to inactivity, large vessel arterial thrombi and small vessel thrombi have been observed. Recently, anti-phospholipid antibodies were described [73].

Future therapeutic approaches

As discussed above, another interesting approach in COVID-19 is to block the early stages of SARS-CoV-2 infection using human recombinant soluble ACE2, and clinical trials are ongoing [74, 75]. Very recently, investigators from Sweden, Canada, Spain and Austria described this new approach to the infection [76]. Infection of human blood vessels and kidney organoids by

Table 2. General approach of some therapeutic approaches that have been used to treat COVID-19

Drug	Mechanism of action	Dose	Administration	CKD adjustment need
Drugs targeting the virus				
IFN-α	Stimulate innate antiviral responses	5 million U or equivalent dose, 2 times/day	Inhalation	ESKD not recommended
Lopinavir/ritonavir	Inhibit the 3-chymotrypsin-like protease of SARS	200 mg/50 mg capsule, 2 capsules each time, 2 times/day	Oral	Low renal clearance, no significant clearance in HD
Remdesivir [62]	Incorporates into nascent viral RNA chains and causes their pre-mature termination	200 mg once time, following by 100 mg/day	IV	No data
Ribavirin	Nucleoside analogues target the RNA-dependent RNA polymerase and block viral RNA synthesis	500 mg, 2–3 times/day in combination with IFN-α or lopinavir/ritonavir	IV	GFR 30–50 mL/min: 400 mg daily; GFR <30 mL/min: 200 mg daily. HD: 200 mg daily
Darunavir/cobicistat	Inhibitor of cytochrome P450 (CYP) 3A enzymes	800/150 mg day	Oral	No data
Chloroquine phosphate or hydroxychloroquine[a]	Immune modulator with inhibitory effects against COVID-19	500 mg (300 mg for chloroquine), 2 times/day 200 mg 2 times/day	Oral	Monitoring in GFR <15 mL/min: same doses but every 48 h Not dialyzable
Azithromycin[a]	Prevents viral production and virus-mediated cell death	500 mg/24 h or 500 mg/12 h	Oral or IV	No adjustment needed
Drugs targeting inflammation				
Tocilizumab	Recombinant humanized monoclonal IgG1 against human IL-6 receptor	8 mg/kg every 2–4 weeks; in COVID-19, frequently used as a single dose	IV	No adjustment needed
Sarilumab	IL-6 receptor antagonist	200 or 400 mg day	IV	No data
Anakinra	Blocks activity of IL-1 α and β by competitively inhibiting IL-1 binding to the (IL-1RI)	100–200 mg every 12–24 h	IV	Monitoring in GFR <15 mL/min: every 48 h
Cyclosporine A	Inhibition of cytokines involved in the regulation of T-cell activation	2.5 mg/kg day divided into two doses (1.25 mg/kg per dose). Maximum dosage: 4 mg/kg day	Oral	Monitoring serum levels
Drugs targeting complications				
Low molecular weight heparin	Prevent large and small vessel thrombosis	Prophylactic dosing	SC	No adjustment needed

Different centres use different combinations of the drugs indicated above. Some are more widely used while others are only used at specific centres. There is currently no approved drug for COVID-19. Thus, informed consent should be obtained for the experimental use of these drugs. Adapted from Dong *et al.* [63] and Francisco Alm and Canga [64].

[a]Beware of increased risk of long QT–associated arrhythmia, especially if both are associated. In this regard, the dose of chloroquine should be adjusted if azithromycin is prescribed.

IV, intravenous; ESKD, end-stage kidney disease; IL-1RI, interleukin-1 type I receptor; SC, subcutaneous.

SARS-CoV-2 was significantly inhibited by recombinant soluble ACE2 (rACE2) at the early stages of infection. Soluble rACE2 competes with cell membrane ACE2 for virus binding. Currently a Phase 2 trial has started in 200 COVID-19 patients in Germany and Austria (NCT04287686). Additionally, a Chinese trial is evaluating NKG2D-ACE2 chimeric antigen receptor–NK cells (NCT04324996). NKG2D is an activating receptor of NK cells, which can recognize and thus clear virus-infected cells.

Vitamin D has important functions beyond those of bone and mineral homeostasis that include modulation of the innate and adaptive immune responses. Vitamin D has pleiotropic effects in the immune system and documented benefits in chronic inflammatory states such as those observed in CKD patients [77]. To date, the benefit of vitamin D supplementation in COVID-19 patients has not been demonstrated; nevertheless, a clinical trial has been designed in Spain (NCT04334005).

It was recently postulated that extracorporeal membrane oxygenation may help patients through non-specific removal of circulating pro-inflammatory cytokines that cause the cytokine storm [78]. Therefore, continuous renal replacement therapies may play an important role in patients with COVID-19 and sepsis syndrome.

CONCLUSIONS

In conclusion, CKD patients are at an increased risk of developing severe COVID-19. Moreover, the mortality rate appears to be higher than in the general population and not always directly related to the severity of pulmonary compromise. This is not surprising, given that viral (e.g. influenza) or severe infection is associated with an increased risk of cardiovascular events both in the general population and in CKD patients [32, 33]. Additionally, CKD patients frequently have cardiovascular and diabetes comorbidities that may independently predispose to severe COVID-19. Given the absence of vaccine or approved therapy, nephrologists should advise CKD patients to follow social isolation recommendations directed at high-risk patients. These should be extended to dialysis units, where a high index of suspicion and testing for COVID-19 should be implemented. Additionally, if healthcare systems are overwhelmed by the pandemic, nephrologists should fight so that, despite the higher risk, CKD is not considered a comorbidity that weighs down the patient's chances to access ICU care or a respirator.

CONFLICT OF INTEREST STATEMENT

None declared.

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