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NEPHROLOGY - REVIEW

COVID-19 and the kidney: time to take a closer look

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Abstract

Although coronavirus disease (COVID-19) is primarily a respiratory disease, the kidney may be among the target organs of infection with severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Independently of baseline kidney function, acute kidney injury (AKI) is a common complication of COVID-19, associated with increased mortality and morbidity. Most frequently, COVID-19 causes acute tubular necrosis; however, in some cases, collapsing focal segmental glomerulosclerosis and direct viral tropism of the kidneys have also been documented. AKI secondary to COVID-19 has a multi-factorial origin. Even mild impairment of renal function is an independent risk factor for COVID-19 infection, hospitalisation and mortality. Dialysis patients also carry an increased risk of other severe COVID-related complications, including arrhythmias, shock, acute respiratory distress syndrome and acute heart failure. In such patients, COVID-19 may even present with atypical clinical symptoms, including gastrointestinal disorders and deterioration of mental status. More research is needed on the exact effects of SARS-CoV-2 on the kidneys. Finally, it remains to be proven whether the outcome of patients with kidney disease may be improved with anticipated vaccination programmes.

Keywords Acute kidney injury · Chronic kidney disease · COVID-19 · End-stage kidney disease · Hemodialysis · SARS-COV-2

Although coronavirus infectious disease (COVID-19) is primarily a respiratory disease, the kidney may be among the target organs of infection with severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Data on the kidney involvement of COVID-19 patients are still very scarce. However, as more patients are infected worldwide, our understanding of the disease is rapidly evolving.

Independently of baseline kidney function, acute kidney injury (AKI) is a common complication of COVID-19 [1]. Several pathogenic mechanisms have been implicated, including critical hypoxia, inflammation and sepsis, haemodynamic changes, acute cardiorenal syndrome, rhabdomyolysis, mitochondrial injury, endothelial dysfunction, microembolism, kidney infarction and use of nephrotoxic drugs (Table 1) [1]. The frequency of AKI reaches 9% in hospitalised patients with COVID-19, but it has been reported to be as high as 68% [2] among critically ill patients admitted to the intensive care unit. In the majority of cases, COVID-19 associated AKI is mild to moderate and is manifested as an increase in serum creatinine, haematuria and/or proteinuria [3, 4], while electrolyte abnormalities such as hyperkalemia may be also be seen [5]. Among in-patients, the most common cause of AKI is acute tubular necrosis, which is associated with a nearly sixfold mortality [6]. Of note, recent data suggest a significant reduction in the frequency of AKI from spring to autumn [7]. This may possibly be attributed to the rising proportion of younger patients with fewer comorbidities managed with non-invasive positive pressure ventilation rather than intubation during this second pandemic [7].

However, data from post-mortem kidney autopsies showed that COVID-19 may, in addition to acute tubular injury, also cause glomerulonephritis, including collapsing focal segmental glomerulosclerosis and direct viral tropism of the kidneys [8]. Collapsing focal segmental glomerulosclerosis is rare, typically presents with nephrotic-range proteinuria, and is associated with phenotypic changes in the podocytes and the Apolipoprotein

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Table 1 Acute kidney injury in COVID-19 infection

Mechanisms	Kidney injury	Clinical manifestations
Hypoxia	Acute tubular necrosis	Increase in serum creatinine
Inflammation	Collapsing focal segmental glomerulosclerosis	Haematuria
Sepsis	Direct viral tropism of the kidney	Albuminuria (ranging from micro- to macroalbuminuria)
Hemodynamic changes	Endothelitis	Electrolyte disorders
Rhabdomyolysis		
Acute cardiorenal syndrome		
Mitochondrial injury		
Endothelial dysfunction		
Microembolism		
Kidney infraction		
Nephrotoxic drugs		

L1 (APOL1) genotype [4]. The presence of virus-like particles in autopsy samples from COVID-19 patients with AKI has led to the hypothesis that the virus may enter kidney tubule epithelial cells and podocytes via angiotensin-converting enzyme 2 (ACE2) receptors and cause direct nephrotoxicity [9].

AKI is associated with high mortality and morbidity. A recent meta-analysis of 58 studies including 13,452 patients has shown that AKI requiring kidney replacement therapy (KRT) is common among hospitalised, critically ill patients (about 5–9%) and increases the overall hospital mortality rate (Odds Ratio 3.43, 95% Confidence Interval 2.02–5.85) [3, 10]. Of note, nearly all of the patients who required KRT were mechanically ventilated. Although the majority of patients who recover from AKI due to COVID-19 regain their kidney function, one-third of them run the risk of remaining on dialysis at discharge [11]. Several conditions have been recognised as risk factors for AKI requiring KRT [11, 12]. These include pre-existing chronic kidney disease (CKD), diabetes mellitus, hypertension, male gender, high body-mass index, increased severity of hypoxia on admission, need for mechanical ventilation, and high interleukin-6 levels [11, 12]. In turn, AKI increases mortality and contributes to long-term complications such as CKD, leading to prolonged hospitalisation and high healthcare costs [1]. Given that there is no specific therapy, prevention and treatment strategies of AKI are mainly supportive [11, 12]. Individualised management of volume status and correction of volume depletion is of the utmost importance. Furthermore, lung-protective ventilation and cytokine removal strategies may decrease the risk of AKI and prevent its complications by limiting the cytokine storm and the ventilator-derived hemodynamic effects on the kidney [11, 12]. Due to the hypercoagulation state of the infection, continuous KRT should be carried out with regional citrate anticoagulation [13].

CKD patients at various stages (both pre-dialysis and dialysis) have an increased risk of COVID-19 infection. The true prevalence and implications of COVID-19 in CKD patients remain under investigation, but a recent meta-analysis reported a pooled prevalence of 5.2% of pre-existing CKD in a cohort of 17,391 COVID-19 patients [5]. Among patients infected with COVID-19, CKD and hypertension were associated with a threefold increase in infection severity and a twofold increase in mortality [10, 14]. The prevalence of prior CKD was 9 times higher in hospitalised patients with severe infection, compared with those having mild infection [14]. CKD patients presenting with symptoms suggestive of virus infection should be closely monitored and early admitted to the hospital if needed.

Kidney transplant recipients might be extremely vulnerable to COVID-19 infection as they are immunosuppressed and commonly characterised by increased comorbidity. The Spanish Registry prospectively included 1011 kidney transplant recipients with COVID-19, followed until death or recovery and reported that advanced age, pneumonia and kidney transplant performed in the last six months before SARS-CoV-2 infection were independent predictors of mortality, whereas gastrointestinal symptoms were associated with low mortality rates [15]. Compared to the first (March–June 2020), in the second pandemic wave (July–December 2020), kidney transplant recipients infected with COVID-19 were significantly younger with reduced overall mortality rates. A careful and tailored therapeutic approach regarding immunosuppressive drugs is needed in kidney transplant recipients with COVID-19. It should consider both severity of the infection and potential interactions between antiviral and immunosuppressive treatment, to balance the risks of graft rejection/loss vs, the complications of the infection [16].

Angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) are anti-hypertensive

agents frequently prescribed in CKD patients. Granted that ACE2 is a receptor used by the SARS COV-2 virus to enter host cells, there was an initial concern that infected patients receiving these drugs might be at increased risk for disease severity and mortality [17]. However, since this hypothesis remained unproven in large cohort studies and systematic reviews, joint guideline panels suggest that the use of these agents should not be discontinued in stable CKD patients and only stopped in the event of hypotension or severe hyperkalaemia [18, 19].

Although at the beginning of the COVID-19 pandemic, non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen were widely used, shortly thereafter, it was hypothesised that ibuprofen might facilitate COVID-19 infection and increase the risk of transmission, through upregulation of ACE2 expression [20]. An additional concern raised by several researchers was that short-term treatment with NSAIDs in lung infections might amplify the risk of bacterial complications [21, 22] and it has been suggested that the use of these drugs might lead to super-infection during SARS-CoV2 infection and thus should be avoided. However, Vaja et al. performed a systematic review of 8 studies and 44,140 patients treated with NSAIDs during acute lower respiratory tract infections and found a non-significant trend towards a decrease in mortality and increase in pleuro-pulmonary complications. Since available data were highly heterogeneous and of poor quality and all studies had a severe risk of bias, the authors concluded that these results should be interpreted with caution [23]. In agreement with this finding, another multicentre, observational study with a small sample size also failed to show any association between NSAIDs and mortality risk [24], whereas a recent meta-analysis including three studies and 2414 patients with SARS-CoV2 infection failed to show any difference in mortality among patients treated with NSAIDs and those that did not use NSAIDs [25].

A further major concern regarding the use of these drugs in COVID-19 patients is that both selective and non-selective NSAIDs have been repeatedly associated with increased risk for developing AKI [26] and venous thromboembolism [27], conditions that might affect the clinical course of COVID-19 infection. There is a controversy regarding the use of NSAIDs and the worsening of respiratory complications in COVID-19 infected patients; however, there is strong evidence linking NSAIDs with AKI. Since there is a much safer therapeutic alternative with paracetamol at recommended doses, NSAIDs should be avoided in these patients.

Importantly, during this pandemic, patients with end-stage kidney disease (ESKD) who are referred for initiation of KRT should undergo all necessary selective procedures (arteriovenous fistulae or graft, or peritoneal dialysis (PD) catheter or central venous catheter) as scheduled without delays [28]. Conversely, it is recommended that regular monitoring of CKD patients should be preferably done via remote and not by in-person visits [28]. Compared to pre-dialysis CKD, dialysis patients have an increased risk for infection and in-hospital mortality [29]. The frequency of COVID-19 infection in ESKD patients undergoing haemodialysis (HD) varies from 1 to 22% [10, 30, 31], but it typically reflects the overall frequency among the corresponding general population.

Compared to PD patients, those undergoing HD have a fourfold increased incidence rate of COVID-19 infection [32]. This could be attributed to the fact that PD is a home-dialysis modality, whereas HD is conducted in dialysis outpatient centres, where viral transmission is commoner [32]. ESKD patients are extremely vulnerable to severe virus infection, due not only to kidney impairment but also due to advanced age and high prevalence of comorbidities such as hypertension and diabetes mellitus [33]. The overall mortality rate of hospitalised HD patients varies among studies from 20 to 50% [10, 29]. When compared with propensity-score matched controls, HD patients have a 20-fold increased risk for 28-day mortality risk, male gender and old age being the strongest risk factors associated with death [34]. This risk difference among genders could be attributed to genetic, hormonal and behavioural factors. In HD patients hospitalised for COVID-19, C-reactive protein was the strongest laboratory predictor of mortality with an area under the curve of 0.90 and outperformed procalcitonin [35].

In addition to mortality, HD patients carry an increased risk of other severe COVID-related complications, including arrhythmias, shock, acute respiratory distress syndrome and acute heart failure [33]. Compared with patients having normal kidney function, HD patients may present different clinical manifestations, including gastrointestinal disorders and deterioration of mental status, rather than fever or respiratory symptoms [29]. During the first wave of the pandemic, no more than 9% of in the United States and about 20% in the United Kingdom of adult HD patients formed antibodies for SARS-COV-2 [30], while 90% were asymptomatic [36]. Several international societies and organisations, including the International Society of Nephrology [37], the American Society of Nephrology [38] and the European Renal Association-European Dialysis and Transplant Association [39] have published information, resources and interim recommendations on CKD, AKI and HD in the new era. A further emerging issue is the potential renoprotective action of sodium glucose cotransporter-2 inhibitors in subjects with mild to moderate COVID-19 [40], which, however, is still under investigation.

In conclusion, we are beginning to learn that the kidney is one of the target organs for COVID-19 [1]. AKI is a frequent complication of the infection, associated with worse clinical outcomes [3, 10]. Patients with any degree of renal

impairment are at increased risk for COVID-19 infection, hospitalisation and mortality [5, 10, 14]. Whether these outlooks may be improved with expected vaccination programmes is clearly interesting but needs to be investigated.

Declarations

Conflict of interest None.

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