COVID-19 and Kidney: a narrative review

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Abstract

COVID-19 is a pandemic associated with systemic clinical manifestations. In this study, we aimed to present a narrative review on kidney involvement in COVID-19. Kidney involvement could be derived from direct cytopathic effects, immunological mechanisms, indirect effects on renal tissue through other mediators, and dysfunction or injury of other organs. The evolution of COVID-19 may be complicated with acute kidney injury (AKI) in a significant percentage of patients, and renal dysfunction seems to be associated with worse prognosis. Patients with chronic kidney disease (CKD) seem to be more susceptible to the severe forms of COVID-19. Patients with renal replacement therapy (RRT) are also a vulnerable population as consequence of their advanced age, underlying comorbidities, impaired immune response, and clustering in hemodialysis centers, with requirements for frequent contact with healthcare services. Kidney transplant patients may be at high-risk due to long-term immunosuppression and comorbidities, hence, managing immunosuppression is imperative. Lastly, renal replacement therapy may be required during COVID-19, and different modalities are discussed based on clinical findings and laboratorial aspects. Therefore, COVID-19 seems to affect kidney by different mechanisms, which contributes for AKI development and increases the severity of the disease. Also, patients with CKD and kidney transplant recipients are at higher risk for COVID-19 and mortality.

Key words SARS-CoV-2, COVID-19, Acute kidney injury, Chronic kidney disease, Kidney transplantation, Renal replacement therapy

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Introduction

In December 2019, an increased number of patients with unknown origin of pneumonia was linked to a seafood market in Wuhan, China.1 A new β-coronavirus was identified as a pathogen and temporarily named 2019 novel coronavirus (2019-nCoV). Later, the World Health Organization (WHO) named this as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease it causes as coronavirus disease 2019 (COVID-19).2

On March 11, 2020, WHO declared the COVID-19 pandemic, which is probably by now the worse pandemic in the XXI century.3 As of September 22, 2020, there have been more than 31 million confirmed cases of COVID-19, and more than 962 thousand deaths globally, reported by the WHO.4 SARS-CoV-2 is a β-coronavirus, member of the Coronaviridae family, which is comprised by enveloped positive-sense RNA viruses.2 Besides the newly discovered coronavirus, there are other six known pathogens of the Coronaviridae family that infect humans: HCoVs-NL63, HCoVs-229E, HCoVs-OC43, HCoVs-HKU1, SARS-CoV and MERS-CoV.2,5,6 The first four present low pathogenicity, causing mild respiratory symptoms.2 The other two lead to severe respiratory infections and are known as the causative agents of causing important outbreaks in the twenty-first century.2

Transmission occurs mainly by respiratory droplets, and asymptomatic patients also have a relevant role on the transmission of the disease.7,8 The median time from symptom onset to hospital admission is 7 days.7,8 Evidence suggests that SARS-CoV-2 infected patients were predominantly male, with the median age of hospitalized patients varied between 47 and 73 years.7,8

Also, COVID-19 has a heterogeneity of symptoms, and many patients with confirmed infection presented more than one symptom, such as fever (90%), cough (60%-86%), myalgia (38%) and gastrointestinal symptoms (15%-39%) being the most prevalent.7,8,10 Anosmia or ageusia have also been reported in a substantial percentage of patients (64-80%).7 COVID-19 complications include acute respiratory distress syndrome (ARDS), bleeding and coagulation dysfunction, liver dysfunction, acute kidney injury (AKI) and septic shock.7,9,10 Severity and mortality are associated with the increased age (>70 years) and the presence of any comorbidity.9,12 Moreover, the disease tended to have a faster progression in elderly.12

Unfortunately, knowledge about the epidemiology, clinical manifestations, laboratory characteristics, and treatment for COVID-19 is still limited, given the magnitude and accelerated pace of this pandemic. Nevertheless, given the wide spectrum of this disease, it is imperative to understand the potential impact of SARS-CoV-2 infection on the kidneys.7,8,10

Thus, in this study, we aimed to present a comprehensive narrative review on the current understanding of the COVID-19 impact on the kidneys, including possible mechanisms related to kidney involvement during COVID-19 pathogenesis, AKI, chronic kidney disease (CKD), renal transplantation, and renal replacement therapy (RRT).

Results

Pathogenesis of SARS-CoV-2 infection: Renal involvement

COVID-19 is associated with clinical manifestations not restricted to the respiratory system.2,8-10,13-16 These findings and the isolation of SARS-CoV-2 from an infected patient’s urine implied the kidney as a possible target.17,18

Kidney involvement in COVID-19 may occur due to direct cytopathic effects of the virus, deposition of immune complexes or by specific immunological mechanisms and, in more severely affected patients, systemic inflammatory response syndrome (SIRS) and shock, which may lead to death.19-21 There may also be other mediators, which might exert indirect effects on renal tissue.19

Mohamed et al.22 suggested that ischemic acute tubular injury (ATI) is the main cause of AKI in COVID-19, accounting for 66% of cases, mainly as consequence of hypotension (53%) and prolonged volume depletion. Toxic ATI was accounted for 7% of AKI cases, due to rhabdomyolysis (4%) or exposure to a nephrotoxic agent (2.5%). In 13%, no obvious cause of AKI was identified aside from COVID-19 diagnosis, and in 2.5%, de novo (new-onset) glomerulopathy was verified, including collapsing glomerulopathy and proliferative glomerulonephritis.22

Possible mechanisms of AKI could also be explained by acute tubular necrosis (ATN) as consequence of volume depletion due to the decreased fluid intake and high fever, multiple organ dysfunction syndrome (MODS) and shock.20 Nephrotoxicity and radiographic contrast exposure can also contribute to the pathogenesis of AKI.20

Rhabdomyolysis, metabolic acidosis and hyperkalemia can also occur in patients with COVID-19, and might exert indirect effects on renal tissue, which is frequently associated with hemodynamic

Reference
SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor to invade the host cells. This ACE2 is a key counterregulatory enzyme that degrades angiotensin II to angiotensin-(1-7), attenuating its effects on vasoconstriction, sodium retention, and fibrosis, and is expressed in urinary organs nearly 100-fold than that in respiratory organs. Transmembrane serine proteases (TMPRSSs) are also determinant key for SARS-CoV-2 entry into the host cells. High co-expression of ACE2 and TMPRSSs in podocytes and proximal straight tubule cells was demonstrated by Pan et al., putting those cells as possible hosts and contributing to the direct cytopathic hypothesis. In this context, podocyte injury could be responsible for the levels of proteinuria described in other studies.

Histopathological examination of kidney specimens from autopsy of six COVID-19 patients with renal dysfunction evidenced different degrees of ATN, luminal brush border sloughing, vacuolar degeneration and absence of glomerular injury; lymphocyte infiltration in five patients and viral infection associated to syncytia in three cases. Immunohistochemistry studies have shown nucleocapsid (NP) protein expression in kidney tubules, viral inclusion bodies and CD68+ macrophages in the tubulointerstitial compartment in all biopsies. The expression of CD8+ T cells was moderately seen in two cases; in contrast, CD4+ T cells and CD56+ NK cells were seldomly found. Strong C5b-9 deposition on tubules was observed in all these six cases.

Another series of 26 renal biopsies of patients with severe COVID-19 demonstrated proximal tubular injury, with brush border sloughing and vacuolar degeneration. Glomerular and peritubular capillary erythrocyte stagnation was frequently noted, indicating a systemic hypercoagulable state. Occasional hemosiderin granules, in patients with hematuria, and pigmented casts, in patients with elevated levels of creatinine phosphate, were also observed. In addition, immunostaining demonstrated NP antibody positivity in tubules, and electron microscopy identified coronavirus-like particles in the cytoplasm of podocytes, proximal tubules and in distal tubules. However, it has not been proven that coronavirus-like particles visualized by electron microscopy were of SARS-CoV-2 origin, so the presence of SARS-CoV-2 on kidney tissue remains unproven and need to be replicated before being generalized.

Thus, these histopathological findings suggest direct cell injury given the presence of NP expression and coronavirus-like particles on renal parenchyma and support the role of specific immunological mechanisms, including infiltration of inflammatory cells and complement deposition and, also a prothrombotic state.

It is known that the lung-kidney interaction (i.e., inflammatory reactions derived from lung injury damaging the kidney, and renal tubular cell injury damaging the lung through large amounts of pro-inflammatory substances) could lead to an irreversible self-amplifying cytokine release syndrome (CRS), also termed “cytokine storm”, that rapidly induces MODS and, ultimately, contributes to the increase of deaths. On this basis, a retrospective cohort with 357 patients admitted to the intensive care unit (ICU) with ARDS who did not develop AKI or CKD before ARDS reported that 68.3% of the patients developed AKI after ARDS. Additionally, worsening of pulmonary diseases by kidney damage is supported by the fact that patients with AKI had twice the chance to develop respiratory failure requiring mechanical ventilation than patients without AKI.

Moreover, patients with AKI and respiratory failure, when compared with AKI-associated non-respiratory organ failure, present a worse prognosis (OR = 10.3 vs 1.7), illustrating the relevance of lung-kidney interaction among critically ill patients. Recently, a retrospective study with 333 COVID-19 patients concluded that severity of pneumonia was an independent negative prognostic indicator for renal complications, including proteinuria and hematuria, and the most important factor in the development of AKI, defined by Yang et al., expanded criteria; also supporting the importance of lung-kidney interaction in the pathogenesis of COVID-19.

The dysregulated immune response, especially in the late stages of the disease, may have a decisive role in endothelial dysfunction and microcirculation impairment. Cytokine overproduction is involved in lung-kidney bidirectional damage as formerly discussed. Interleukin (IL)-6, IL-8, tumor necrosis factor (TNF), tumor necrosis factor receptor 1 (TNFR1), caspase-3, nuclear factor-kB (NFkB), high mobility group box 1 protein (HMGB1) and T cells promote lung injury after AKI via neutrophil and T cell chemotaxis, lung tissue injury and lung endothelial apoptosis, mediating non-cardiogenic pulmonary edema, due to proinflammatory mediators which induce SIRS.

Wu et al. indicated that patients with COVID-19 who developed ARDS had increased systemic IL-6 [difference, 0.93 pg/L (CI95% = 0.07-1.98 pg/L),...
p=0.03) which was significantly associated with the progression from ARDS to death [HR, 1.03 (CI95%= 1.01-1.05), p=0.01]. Huang et al. indicated that serum levels of the anti-inflammatory cytokine IL-10 were higher in patients admitted to ICU than in those not admitted to ICU.

Kidney involvement in patients with COVID-19 (represented by proteinuria, hematuria, and AKI) carries a worse prognosis. However, it is not clear whether this worse prognosis is due to direct cytopathic effects of the virus on renal parenchyma or due to the pulmonary dysregulated inflammatory response produced. Moreover, it could also be derived from severe pulmonary and systemic involvement that consequently have a greater secondary kidney involvement and a worse general prognosis or even from prior renal involvement (e.g., elderly populations with a previous cardiovascular risk).

Furthermore, the heart-kidney interaction could also be implicated in the pathogenesis of AKI in patients with COVID-19. In this scenario, hypotension, renal hypoperfusion and renal vein congestion, precipitating a decrease in glomerular filtration rate (GFR), can result from cardiomypathy, acute myocardial infarction, arrhythmia, exacerbation of heart failure, cardiovascular instability, endothelial injury and an associated prothrombotic state.

### Acute kidney injury and SARS-CoV-2 infection

A retrospective cohort of 536 severe acute respiratory syndrome (SARS) patients demonstrated an AKI incidence of 6.7%, with a 4-fold higher adjusted mortality rate in patients with AKI compared with patients without renal impairment [RR 4.06 (CI95%= 1.46-11.27, p<0.001)]. A retrospective analysis of 30 patients with Middle East respiratory syndrome (MERS) showed that 26.7% developed AKI, which was also a risk factor for mortality in the univariate analysis [HR 12.74 (CI95%= 1.42-114.57)]. Given the fact that SARS-CoV-2 has 79% nucleotide identity to SARS-CoV and 51.8% identity to MERS-CoV, we may estimate epidemiological, clinical and prognostic characteristics to be similar to those presented by SARS patients. 

Early studies suggested a lower AKI incidence (3%-9%) in those with COVID-19 infection. In Wuhan, Cheng et al. analyzed a prospective cohort of 701 patients with COVID-19 with median age of 63 years (IQR= 50-71) and found that, at admission, 43.9% of patients had proteinuria, 26.7% had hematuria, 14.4% and 13.1% had elevated baseline serum creatinine (SCr) and blood urea nitrogen (BUN), respectively.

![Figure 1](attachment:image.png)

**Flowchart for renal involvement on the pathogenesis of SARS-CoV-2 infection.**

ACE2: angiotensin-converting enzyme 2, TMPRSSs: transmembrane serine proteases.
respectively, and 13.1% had estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m². During hospitalization, AKI occurred in 5.1% of patients. Comparing patients admitted with elevated Scr with those with normal Scr, patients with high Scr were predominantly older [73 (IQR= 62-79) vs 61 years (IQR= 49-69), p<0.001] and male (72.2% vs 49.0%, p<0.001), were more severely ill (52.5% vs 40.7%, p=0.026), had any comorbidity (60.0% vs 39.6%, p<0.001), had CKD (9.0% vs 8.8%, p=0.001), had a higher leukocyte count (9.5 vs 7.2 x10⁹/L, p=0.005), lower lymphocyte (0.8 vs 0.9 x10⁹/L, p=0.015) and platelet counts (191 vs 216 x10⁹/L, p=0.014), prolonged activated partial thromboplastin time (54.2% vs 40.4%, p=0.029), higher D-dimer (89.8% vs 75.3%, p=0.002), increased procalcitonin (29.3% vs 6.9%, p<0.001), and lactate dehydrogenase (458 vs 364 U/L, p=0.001). Those with an elevated Scr at admission were more likely to undergo mechanical ventilation (21.8% vs 12.5%, p=0.012), had a higher incidence of AKI (11.9% vs 4.0%, p=0.001) and had significantly higher intra-hospital mortality (33.7% vs. 13.2%, p<0.001). After the adjustment for confounding factors, proteinuria [1+ (HR 2.47), 2+ ~ 3+ (HR 6.8)], hematuria [1+ (HR 3.05), 2+ ~ 3+ (HR 8.89)], elevated baseline Scr (HR 2.04), elevated baseline BUN (HR 4.20), peak serum creatinine >133 µmol/l (HR 3.09), and AKI over stage 2 [stage 2 (HR 3.53) and stage 3 (HR 4.72)] were all associated with in-hospital mortality.19

In New York City, United States, Hirsch et al.37 analyzed a retrospective cohort involving 5,449 patients with COVID-19 with median age of 64 years (IQR= 52-75) and reported an incidence of AKI of 36.6% during hospitalization, being the peak stages 1 in 46.5%, 2 in 22.4% and 3 in 31.1%. Most cases developed AKI early, with 37.3% either arriving with AKI or developing it within 24 hours at hospital admission. In this study, urinalysis results obtained 24 hours before up to 48 hours after the development of AKI, exhibited proteinuria and hematuria in 74% and 63.8% of patients, respectively. There was also noted a close temporal proximity between the development of respiratory failure with need for mechanical ventilation and the occurrence of AKI. Of those patients who required mechanical ventilation and developed AKI, 52.2% of patients had onset of AKI within 24 hours of intubation, supporting the role of the lung-kidney interaction in COVID-19 pathogenesis. After the adjustment for age, sex and race, older age (OR= 1.03, p<0.001), black race (OR= 1.23, p=0.04), diabetes (OR= 1.76, p<0.001), hypertension (OR= 1.25, p=0.02), cardiovascular disease (OR= 1.48, p<0.001), need for mechanical ventilation (OR= 10.7, p<0.001) and use of vasoactive medications (OR= 4.53, p<0.001) were all independent predictors of the development of AKI.37

Hansrivijit et al.,36 in a meta-analysis including 5,497 patients with COVID-19, found a pooled incidence of AKI of 8.4% (CI95%= 6-11.7) overall, with a significantly higher incidence in critically ill patients compared with hospitalized patients (19.9% vs 7.3%, p=0.002). After the adjustment for sex and CKD, older age (p=0.02), diabetes (p=0.01), hypertension (p=0.02) and elevated baseline Scr (p<0.01) were all associated with AKI incidence. AKI development was associated with an increased mortality by 13-fold [OR 13.33 (CI95%= 4.05-43.91)].36

Therefore, AKI may be uncommon in patients with COVID-19 overall, but it is frequent in critically ill patients with COVID-19. Thus, as renal function abnormalities, even without characterizing AKI, have a significant negative impact on the prognosis of patients with COVID-19, early recognition of renal dysfunction, close monitoring, and adequate management could attenuate severity and mortality rates remarkably.

**Chronic kidney disease and SARS-CoV-2 infection**

Patients with CKD have a proinflammatory state with functional defects in innate and adaptive immune cell populations and are known to have a higher risk for upper respiratory tract infection and both inpatient and outpatient pneumonia.19,41 In CKD patients, the pneumonia-related mortality rate seems to be 14 to 16-fold higher in comparison with the general population.41

Chronic kidney disease is found in 0.7% to 3% of patients with COVID-19, being 12-fold more frequent in ICU than in non-hospitalized patients with COVID-19, a higher ratio than that for diabetes or cardiovascular disease.8,9,21,42,43 Henry et al.,41 in a meta-analysis including 1,389 patients with COVID-19, found a significant association of CKD with severe COVID-19 [OR= 3.03 (CI95%= 1.09–8.47)]. Therefore, preventive measures should be adopted by this group of patients, and special consideration must be taken by the medical staff.

Patients undergoing maintenance hemodialysis (MHD) constitute a susceptible population as they tend to be older and have multiple comorbidities, often including hypertension, cardiovascular disease, and diabetes, and suppressed immune systems, because of the uremic state.44,45 Moreover, the need for frequent trafficking and patient clustering during dialysis increases the risk for SARS-CoV-2 infec-
Hypertension and diabetes, which are highly prevalent in this population, are the most prevalent comorbidities and significantly associated with ARDS development in patients with COVID-19.48-51

Kidney transplant recipients may be at high-risk for infection and mortality due to long-term immunosuppression, with particularly T cell immune response suppression; residual to CKD and other comorbidities.48-51 Hypertension and diabetes, which are highly prevalent in this population, are the most prevalent comorbidities and significantly associated with ARDS development in patients with COVID-19.34,52,53

Trujillo et al.55 reported a case series of 51 patients with a mean age of 64 years (SD, 15), including 25 MHD patients, and 26 kidney transplant recipients. Clinical manifestations of COVID-19 were similar in both groups, and only 55% presented fever. In particular, kidney transplant recipients seem to present less fever (46%) and more gastrointestinal symptoms (38%) compared with the general population. In this series, immunosuppression management included partial reduction of antimetabolites and/or mammalian target of rapamycin (mTOR) inhibitors, reducing tacrolimus and continuing low-dose prednisone. The mortality rate in kidney transplant recipients was 23%.55

Therapeutic decisions regarding to immunosuppression management while protecting graft function is challenging and should be taken according to age, baseline graft function, time since transplantation, presence of donor-specific antibodies, prior history of rejection, time since transplantation, associated comorbidities, and COVID-19 severity.51,52

For now, immunosuppression reduction, or even detention, is not a global recommendation for all kidney transplant recipients with COVID-19. Thus, it would be recommended to use due diligence and individualize therapeutic decisions regarding to immunosuppression management while protecting graft function based on patient’s age, baseline graft function, time since transplantation, presence of donor-specific antibodies, prior history of rejection, time since transplantation, associated comorbidities, and COVID-19 severity.51,52

Renal replacement therapy and SARS-CoV-2 infection

Continuous renal replacement therapy (CRRT) has been successfully applied in the treatment for SARS, MERS, and sepsis; consequently, this approach may also be useful in patients with COVID-19 and sepsis syndrome.17 In fact, 1.5% to 9.0% of patients with COVID-19 required CRRT, and among critically ill patients admitted to the ICU 5.6% to 23% required CRRT.55

Indications for RRT in patients with COVID-19 are the same as for other patients with AKI.20 In order to prevent CRS-induced organ damage, direct hemoperfusion using a neuro-macroporous sorbent for ≥2 hours for 3 consecutive days, associated with anticoagulation with heparin or citrate and blood flow >120 ml/min; and CRRT, the preferred dialysis modality, with special membranes (acrylonitrile and sodium methallyl sulfonate plus polyethyleneimine) promote cytokine removal.20,23 If the patient surge overwhelms CRRT capacity, consideration should be taken for prolonged intermittent treatments with higher flow rates and then, after terminal cleaning, use the machine for another patient.20

In patients with rhabdomyolysis, metabolic
acidosis and hyperkalemia, the use of medium cut-off membranes is preferred over high cut-off membranes given its effectiveness in myoglobin, IL-6 and IL-10 removal. Extracorporeal membrane oxygenation (ECMO) directly connected to the CRRT circuit is also known to provide heart and lung support and could be of great value owing to ARDS and the previously discussed organ interactions.

Another concern in patients during a long ICU stay is superimposed infections. Yang et al. reported the occurrence of hospital-acquired infections in seven (13.46%) critically ill patients with COVID-19 admitted to ICU. In patients with suspected or confirmed Gram-negative bacterial infections and an endotoxin activity assay result of 0.6-0.9, direct hemoperfusion for 2 hours for 2 subsequent days and a blood flow of around 100-120 ml/min with cartridge containing polystyrene fibers functionalized with polymyxin-B provides effective endotoxin adsorption. CRRT filters with acrylonitrile and sodium methallyl sulfonate plus polyethyleneimine also have adsorptive capacity for endotoxins.

Therefore, in the absence of definitive treatment for COVID-19, different RRT approaches could be useful in SARS-CoV-2 infected patients based on clinical findings and laboratorial aspects. Renal replacement therapy should be discontinued once the patient is non-oliguric, euvolemic and improved ventilation requirements, being supported by the improvement of laboratorial findings and the absence of relevant electrolyte and acid-base disorders.

Limitations

This review has limitations as data regarding COVID-19 is still limited. Also, information provided here is based on the current evidence, which may be modified as new data become available. Despite these limitations, our study provides early findings about the potential impact of SARS-CoV-2 infection in kidneys in the context of a rapidly evolving pandemic.

Conclusion

At this moment, the rapidly evolving COVID-19 pandemic still presents many uncertainties regarding pathogenesis, epidemiology, demographic, clinical manifestations, laboratorial findings and treatment.

On the basis of the available evidence, COVID-19 seems to affect the kidney through different mechanisms, which includes direct cytopathic effects, immunological mechanisms, indirect effects on renal tissue through other mediators, and dysfunction or injury of other organs. These mechanisms appear to contribute for renal dysfunction and AKI incidence in patients with COVID-19, which are associated with the severity of the disease and intra-hospital mortality. Also, CKD patients are related to COVID-19 severity and death. Patients undergoing MHD constitute a susceptible population due to advanced age, high prevalence of comorbidities and impaired immune response and seem to present distinct clinical and laboratorial findings and a worse prognosis compared to the general population. Moreover, kidney transplant recipients may present higher risk for infection and mortality owing to long-term immunosuppression and concurrent comorbidities. Then, managing immunosuppression is crucial for graft function protection and viral elimination. Distinct RRT modalities could be applied in patients with COVID-19 according to clinical and laboratorial findings.

Given the limited level of evidence, more studies are required to investigate the association between ACE2 and TMPRSSs expression and direct cytopathic effects of the virus on renal parenchyma as well as establish the value of kidney injury biomarkers and lung-kidney biomarkers in patients with COVID-19. Prospective cohort studies are also necessary to clarify the impact of AKI on the prognosis of patients with COVID-19 and to define clinical models to predict AKI development in those patients. Finally, clinical trials should evaluate the impact of different therapeutic strategies on the prognosis of patients with COVID-19.

Authors’ contribution

Chagas GCL contributed to the main idea and aided in the data collection, data analysis, and preparation of the manuscript. Rangel AR and Noronha LM aided in the data collection and preparation of the manuscript. Silva Júnior GB, Meneses GC, Martins AMC, and Daher EF contributed to data analysis and preparation of the manuscript. All authors approved the final version of the article.
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