Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Best Practice & Research Clinical Anaesthesiology 35 (2021) 449–459

Contents lists available at ScienceDirect

Best Practice & Research Clinical Anaesthesiology

journal homepage: www.elsevier.com/locate/bean

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COVID-19 impact on the renal system: Pathophysiology and clinical outcomes

Alan D. Kaye, MD, PhD, Professor, Provost, Chief Academic Officer, and Vice Chancellor of Academic Affairs [a],
Chikezie N. Okeagu, MD, Resident Physician [b],
Gregory Tortorich, MD, Resident Physician [c],
Alex D. Pham, MD, Resident Physician [d],
Eric I. Ly, BS, Medical Student [e],
Kimberley C. Brondeel, BS, Medical Student [f],
Matthew R. Eng, MD, Associate Professor [b],
Markus M. Luedi, MD, Anesthesiology Consultant [g],
Richard D. Urman, MD, Associate Professor [h, *],
Elyse M. Cornett, PhD, Assistant Professor [i]

[a] *Departments of Anesthesiology and Pharmacology, Toxicology, and Neurosciences, LSU Health Shreveport, 1501 Kings Highway, Shreveport, LA, 71103, USA*
[b] *Department of Anesthesiology, LSU Health Sciences Center, 1542 Tulane Avenue, New Orleans, LA, 70112, USA*
[c] *LSUHSC New Orleans, New Orleans, LA, USA*
[d] *Department of Anesthesiology, LSU Health New Orleans, 1542 Tulane Ave, Room 659, New Orleans, LA, 70112, USA*
[e] *University of Tennessee Health Science Center College of Medicine, 910 Madison Avenue, Memphis, TN, 38103, USA*
[f] *School of Medicine, University of Texas Medical Branch, 301 University Blvd, Galveston, TX, 77555, USA*
[g] *Bern University Hospital Inselspital, University of Bern, Bern, Switzerland*
[h] *Department of Anesthesiology, Perioperative and Pain Medicine, Harvard Medical School, Brigham and Women's Hospital, 75 Francis St, Boston, MA, 02115, USA*
[i] *Department of Anesthesiology, LSU Health Shreveport, 1501 Kings Highway, Shreveport, LA, 71103, USA*

* Corresponding author. Department of Anesthesiology, Perioperative and Pain Medicine, Harvard Medical School/Brigham and Women's Hospital, 75 Francis St, Boston, MA, 02115, USA.
E-mail addresses: akaye@lsuhsc.edu (A.D. Kaye), cokeag@lsuhsc.edu (C.N. Okeagu), gtort1@lsuhsc.edu (G. Tortorich), apham5@lsuhsc.edu (A.D. Pham), ely@uthsc.edu (E.I. Ly), kcbronde@utmb.edu (K.C. Brondeel), meng@lsuhsc.edu (M.R. Eng), markus.luedi2@insel.ch (M.M. Luedi), rurman@bwh.harvard.edu (R.D. Urman), ecorne@lsuhsc.edu (E.M. Cornett).

https://doi.org/10.1016/j.bpa.2021.02.004

Keywords:
COVID-19
renal
injury
kidney
coronavirus
outcomes
dialysis

Coronavirus disease (COVID-19) causes many deleterious effects throughout the body. Prior studies show that the incidence of acute kidney injury in COVID-19 patients could be as high as 25%. There are also autopsy reports showing evidence of viral tropism to the renal system. In this regard, COVID-19 can damage the kidneys and increase a patient's risk of requiring dialysis. Available evidence suggests that renal involvement in COVID-19 infection is not uncommon, and there has been an increased incidence of chronic kidney disease related to the pandemic. In this literature analysis, we address COVID-19 and its effects on the renal system, including the pathophysiologic mechanisms. We also address current studies on the causes of injury to the renal system, the cause of kidney failure, its effect on mortality, the impact on dialysis patients, and the impact on renal transplant patients. COVID-19 disease may have unique features in individuals on chronic dialysis and kidney transplant recipients, requiring increased vigilance in limiting viral transmission in perioperative, in-patient, and dialysis center settings.

Introduction

Since the first case discovered in Wuhan, China, in 2019, there have been over 5 million confirmed cases of Coronavirus disease (COVID-19) and over 30,000 deaths as of May 25th, 2020, with rapid expansion into over 150 countries [1,2]. Initially, common symptoms were presented (usually 2–14 days after exposure), including fatigue, dry cough, fever, sore throat, diarrhea, and dyspnea [1,2]. Patients had shown bilateral ground-glass opacities on computerized tomography (CT) scan revealing lung pathology, which contributed to the thought that COVID-19 predominantly affected the respiratory system [1]. As investigations continued, new reports emerged that COVID-19 was not solely restricted to the respiratory system but impacted numerous others, including the nervous system, immune system, hematology, cardiac system, gastrointestinal system, and kidneys [1].

Prior studies had shown that the incidence of acute kidney injury (AKI) in COVID-19 patients was speculated to be as high as 25% [3]. There were also autopsy reports showing evidence of viral tropism to the renal system. It was also shown that 60% of 147 patients with COVID-19 had experienced proteinuria, with 48% experiencing hematuria [3]. Lab values had demonstrated that patients experienced increased BUN and creatinine [3] showing further evidence of renal insult. Understanding the impact of COVID-19 on the renal system is tantamount as AKI may be associated with increased mortality, particularly for patients who require escalating treatment such as renal replacement therapy (RRT) [3].

In this manuscript, we discuss COVID-19 and its impact on the renal system. We also describe current research on diagnosing COVID -19 related kidney dysfunction, the mechanism of injury to the renal system, its cause of kidney dysfunction and effect on mortality, the impact on dialysis patients and renal transplant patients, and current treatments.

COVID 19 impact on kidneys

The incidence of AKI in patients with COVID-19 in the hospital setting varies from 0% to 14.7%, with a pooled incidence rate of 7%. In the intensive care unit (ICU) setting, the rate varies from 8.3% to 28.8%, with a pooled incidence rate of 19%, based on a meta-analysis of 9 studies [4]. In two large cohorts from New York, incidence rates were 36.6% and 46%, with this patient population representing a heavier burden of comorbidities. Risk factors that increase AKI incidence include older age, baseline CKD, DM, HTN, cardiovascular disease, and need for ventilation and vasopressor support. The incidence of AKI

occurs most commonly within 24 h of hospital admission, with most cases seen in patients who required ventilation and vasopressor support [4].

The pathogenesis is multifactorial and varies from direct viral impact on the kidneys to immune response–mediated kidney injury. COVID-19 has an impact on the tubulointerstitial, vascular, and glomerular systems of the kidneys. Acute tubular necrosis (ATN) is most commonly seen with COVID-19. ATN findings include loss of brush border, vacuolar degeneration, luminal dilatation, and in some cases, areas of necrosis and detachment of tubular epithelium. The cause of ATN includes hypovolemia, severe inflammation, and direct viral infection. Glomerulonephritis is less commonly seen, but it is thought to be more associated with cytokine-mediated damage because of the absence of viral particles. COVID-19 has been shown to produce a hypercoagulable state, which causes renal thrombotic microangiopathy (TMA) or microvascular thrombosis, occluding vessels, and contributing to the severity of AKI [5].

COVID-19's direct impact on the kidney requires the spike (S) protein, which binds to angiotensin-converting enzyme II (ACE2). The S protein is primed by proteases in the TMPRSS family, allowing the viral protein to enter the host cell. ACE2 is highly expressed in the epithelial cells of the lung, GI tract, and kidneys. Electron microscopic examination revealed clusters of coronavirus particles with distinctive spikes in the tubular epithelial cells and podocytes. ACE2 expression was upregulated in patients with COVID-19 infection, amplifying the direct viral injury to kidneys. The proximal tubules were found to be the most severely damaged portion of the renal tubules [6].

Severe inflammation is a known trigger for AKI in many different disease states. Interestingly, COVID-19 most closely represents the inflammatory pattern of hemophagocytic lymphohistiocytosis. The complement cascade is an important component of our innate immune system that rapidly responds to pathogens. Dysregulation of this complement system can have detrimental effects, however. Overactivation of the complement system notably injures the lungs, which is a known risk factor in AKI development. There is some evidence for anti-complement C5a blocking antibodies to reduce lung damage and combat COVID-19's effects. Levels of ferritin, IL-6, CRP, platelets, and d-dimer are seen in severe COVID-19 cases and can be used to measure the severity of illness. This finding suggests the importance of inflammation in the damage and fatality driven by COVID-19 infections [6].

Vascular injury is another major driver of kidney injury in COVID-19. Widespread endothelial damage caused directly by viral particles and inflammatory molecules causes a decrease in vasodilatory agents such as nitrous oxide (NO). This causes an increased response to vasopressor support and an imbalance in constriction versus dilation. This overwhelming constriction causes decreased renal perfusion, creating a pre-renal azotemia. This endothelial damage also causes activation of the coagulation cascade. The combined effect of vasoconstriction and increased thrombus formation causes further microvascular damage, a key component to kidney damage. This overconsumption of coagulation factors can lead to diffuse intravascular coagulation (DIC), which is seen in 71% of non-survivors [6].

With all these devastating factors affecting the kidneys, management of AKI in COVID-19 is extremely difficult. The best management strategy includes early detection, appropriate volume resuscitation, avoidance of nephrotoxic agents, managing metabolic and electrolyte abnormalities, and beginning RRT when appropriate [6].

Mechanism of COVID-19-related kidney injury

Available evidence suggests that renal involvement in COVID-19 infection is common. Hallmarks of kidney injury such as proteinuria, hematuria, and elevated BUN and creatinine have been observed in up to 60% of affected patients [7–9]. Furthermore, post mortem studies of patients who died with COVID-19 have revealed elements of renal injury such as acute tubular injury and collapsing glomerulopathy, and the presence of viral particles within both the tubular epithelium and podocytes [10–15]. As is the case with many aspects of the novel coronavirus, the exact methods by which COVID-19 causes renal injury have not yet been fully elucidated. However, the pathogenesis of kidney injury in COVID-19 appears to be multifactorial, and multiple direct and indirect mechanisms have been implicated [8–10].

First, current evidence suggests that SARS-CoV-2 may directly affect the kidney via viral tropism. The virus enters cells by binding its spike protein to membrane-bound ACE2. ACE2 is highly expressed in the kidneys in renal tubular epithelial cells and podocytes. Additionally, endothelial dysfunction, coagulopathy, and complement activation are likely to play a role in renal injury in COVID-19 infection. Complement activation and thrombotic microangiopathy are known to be important mechanisms of kidney injury in other settings. As such, high D-dimer levels and microvascular damage, characteristics of endothelial dysfunction, represent important risk factors for COVID-19-associated coagulopathy.

Similarly, other inherited or acquired prothrombotic conditions such as hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) may potentially contribute to endothelial dysfunction coagulopathy in infected patients. Direct SARS-CoV-2 viral activation of complement is also thought to be possible. While complement activation and thrombotic microangiopathy are plausible mechanisms, no histological evidence has been presented to date. A third proposed mechanism of direct renal injury in COVID-19 infection implicates high circulating levels of inflammatory cytokines. The SARS-CoV-2 infection has been associated with activation of an exaggerated inflammatory response termed “cytokine storm,” which may contribute to the dysfunction observed in the kidneys and other organs [8,10].

Specific indirect pathogenic mechanisms of kidney injury have been postulated as well. For one, it is thought that the systemic effects of COVID-19 infection coupled with the resultant critical care interventions indirectly cause or exacerbate renal damage. Insensible fluid losses due to hyperpyrexia and the GI effects of COVID-19 infection can lead to volume depletion, a key risk factor for kidney injury. Furthermore, many medications used in the treatment of critically ill patients are nephrotoxic. Mechanical ventilation, a common intervention in COVID-19 infection, can contribute to kidney injury due to increased intrathoracic pressure, ultimately resulting in increased renal venous pressure and reduced filtration. Organ crosstalk, a complex phenomenon of mutual biological communication between distant organs mediated by signaling factors, is another proposed indirect mechanism of COVID-19-related renal damage. The release of damage-associated molecular patterns (DAMPs) from injured organ tissues (i.e., lung tissue) is thought to contribute to kidney injury via these signaling pathways. This method of kidney injury has previously been suggested in the setting of acute respiratory distress syndrome (ARDS) [10].

COVID-19-induced kidney dysfunction and mortality

Given the relative novelty of COVID-19, much is still unknown about its effects on different organ systems and the resultant impact on mortality. Current research suggests that renal impairment in COVID-19 is associated with increased mortality. Gasparini et al. conducted a retrospective study of 372 patients hospitalized in the ICU with COVID-19 to investigate the effects of kidney injury on patient outcomes. Kidney injury was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Patients were divided into five categories: those with no kidney injury; those who developed new-onset AKI; those with pre-existing CKD; those with ESRD; and those who had previously undergone a renal transplant. In-hospital mortality was examined as the primary outcome, while change in mean creatinine and need for RRT were examined as secondary outcomes. Of the 372 patients, 168 (45%) developed AKI during their ICU stay. Forty-eight patients (13%) had preexisting renal impairment. The authors found that COVID-19 patients with AKI or CKD exhibited greater in-hospital mortality than those with preserved renal function. Of the 216 patients, 107 with AKI and/or CKD (50%) died in hospital compared to only 32/156 (21%) in the non-AKI group. Mortality rates were comparable when comparing patients with new-onset AKI to patients with pre-existing CKD. The highest mortality was observed in patients who had previously undergone renal transplantation (6/7 patients, 86%). Worsening renal function, as indicated by increased KDIGO stage, was associated with increased mortality.

Furthermore, of those who survived, a significant proportion required RRT after discharge [16]. Though limited, these data serve to demonstrate the considerable impact of kidney injury in COVID-19 outcomes. Further investigation is warranted to refine treatment to prevent kidney dysfunction, thereby improving patient mortality.

COVID-19 in dialysis patients

Patients undergoing hemodialysis with COVID-19 require special considerations in medical management. In particular, dialysis patients often carry other comorbidities (hypertension, heart disease, diabetes, etc.) that may impact clinical outcomes for those with COVID-19 [17,18]. Therefore, careful preventative measures remain integral for hemodialysis patients in the perioperative and intensive care setting.

Patients presenting with uremia carry weaker immune systems and demonstrate greater fluctuations in infectivity and clinical symptoms [19]. For hemodialysis patients with COVID-19, in particular, Ma et al. describe their impaired immune responses with significantly lower proinflammatory cytokines and circulating CD4 and CD8 T cells than those with the virus not undergoing hemodialysis [20].

Whether the development of AKI in the setting of a COVID-19 diagnosis stems from direct COVID-19 infection or a sequela from the virus remains heavily debated. In one retrospective study involving 5449 hospitalized patients with COVID-19, nearly 40% of patients developed AKI, and 14% of those with AKI required support with hemodialysis [21]. Some postmortem kidney biopsy studies suggest nephropathy development due to COVID-19 and reported that the kidney is a target for COVID-19 through staining and histopathological methods [22,23]. In contrast, Rossi et al. observed no viral particles on ultrastructural examination in one COVID-19 patient on dialysis and refuted the COVID-19 nephropathy theory [24].

Diagnosis of COVID-19 in hemodialysis patients is integral since AKI is a primary predictor for poor outcomes during a COVID-19 infection [21]. However, the variance in clinical symptoms in this patient subset remains a challenge. In one case series of patients with COVID-19 in Zhongnan Hospital of Wuhan University, diarrhea (80%) was the most common symptom, followed by fever (60%) and fatigue (60%), and lymphopenia occurred in every patient [25]. Xiong et al. demonstrated in a study involving 65 hemodialysis centers that of the 2% of hemodialysis patients who tested positive for COVID-19, nearly 50% exhibited fever, and 20% remained asymptomatic [26].

Furthermore, the high mortality rates among hemodialysis patients with COVID-19 indicate the importance of taking special considerations for their medical management. Some studies report a mortality rate that is nearly 30% greater than the COVID-19 general population [26,27]. Other studies involving the European Dialysis and Transplant Association Registry report a mortality rate for dialysis patients with COVID-19 of approximately 25% [28,29].

Lastly, in–center hemodialysis centers raise the risk of infection transmission due to their densely populated outpatient units. At one hemodialysis center of Renmin Hospital of Wuhan University, nearly 20% of patients on hemodialysis and 15% of facility workers developed the COVID-19 infection over one month [30]. Therefore, increasing home dialysis utilization, particularly with the current challenge of obtaining operating room availability for peritoneal dialysis catheter placements, remains a crucial method to protect infection transmission [31]. Hsu et al. present guidelines for hemodialysis facilities and hemodialysis patients to reduce the COVID-19 spread [32]. In summary, the management of these at-risk patients must follow stringent guidelines to reduce the transmission risk to other patients and healthcare workers.

COVID-19 in renal transplant patients

Until more data become available, managing kidney transplant patients with COVID-19 remains not well understood in the transplant community. In particular, balancing the chronic immunosuppression, a well-recognized risk factor for viral infection, of these patients in the setting of COVID-19 and preventing transplant graft rejection makes the challenge of managing these patients even more crucial. Therefore, taking strict precautions and detecting early signs of the viral infections in these patients remain integral.

Like the general population of COVID-19 patients, kidney transplant patients with the viral infection present with a variety of nonspecific symptoms (fever, cough, sore throat, diarrhea, myalgias, etc.) [33] and atypical presentations [34] that make diagnosis of COVID-19 in this patient population challenging. In one report involving 36 subjects, Akalin et al. reveal that transplant patients with COVID-19 exhibit a fever at a significantly lower rate than the general population of COVID-19 patients. Nearly 80% of these

patients demonstrated lymphopenia, approximately 70% exhibited low CD3 and CD4 cell counts, and about 20% showed low CD8 cell counts [35]. Therefore, that considerable number of patients suggests the increased requirement to lower immunosuppression doses.

The medical decision to withdraw immunosuppression in kidney transplant patients with COVID-19 remains heavily debated in the transplant community. Cravedi et al. demonstrated no significant association with calcineurin inhibitor, mycophenolate, or everolimus withdrawal and mortality [36]. In contrast, total withdrawal from immunosuppression in kidney transplant patients with COVID-19 and minimal symptoms is not recommended in guidelines issued by the European Renal Association—European Dialysis and Transplant Association [37].

Instead, providers should, on a case-by-case basis, carefully reduce dosages of immunosuppressants, such as azathioprine, mycophenolate, and calcineurin inhibitors, while avoiding drug-to-drug interactions with medications specifically utilized against COVID-19 [37], and consider using low-dose methylprednisolone for immunosuppression [38]. In cases where kidney transplant patients with COVID-19 pneumonia require critical care, however; Gandolfini et al. suggest the withdrawal of immunosuppressive therapy, utilizing only steroids for immunosuppression, to support the patient in developing an adequate viral immune response [39].

Besides immunosuppression concerns, reports of AKI in kidney transplant patients with COVID-19 is another potential challenge for providers. Banerjee et al. describe a case series of COVID-19 kidney transplant patients in which 57% of patients developed an AKI [40]. Though the study reports a low sample size, early indications demonstrate a higher risk for AKI when kidney transplant patients become infected with COVID-19 compared to the lower AKI rates in the COVID-19 general population [21].

Just as in dialysis patients, mortality rates among kidney transplant patients are high. In one study assessing 28-day mortality after a COVID-19 diagnosis, kidney transplant recipients carried a 1.28 times higher mortality as dialysis patients with COVID-19 [29]. In another study involving 305 subjects from the European Renal Association COVID-19 Database, kidney transplant patients with COVID-19 carried a 21% probability of death over 28 days [28].

Treatment of COVID-19-related kidney injury

Kidney involvement in COVID-19 is frequent and clinical presentation can range from mild proteinuria to progressive AKI, necessitating RRT [41]. Given the substantial kidney involvement in the disease manifestation of COVID-19 and evidence linking kidney function decline to mortality, treatment of COVID-19-related kidney injury is a vital area that needs to be explored further. In a multicenter, retrospective, observational study, Li et al. cautioned through a univariate Cox regression of 193 COVID-19 patients that proteinuria, hematuria, and elevated blood urea nitrogen levels, serum creatinine, uric acid as well as D-dimer were significantly associated with the death of COVID-19 patients. Their data also suggested that COVID-19 patients who developed AKI had a ~5.3 times mortality risk than patients without AKI. The fatality in these conditions should prompt clinicians to employ a high degree of caution in monitoring kidney functions of patients with severe COVID-19 affliction, regardless of their disease history. Additionally, clinicians should consider any potential interventions to protect kidney functions at the early stage of the disease and renal replacement therapies in severely ill patients—particularly those with strong inflammatory reactions or a cytokine storm [42,43].

To date, there is no specific treatment for COVID-19 induced AKI, and management of COVID-19 associated AKI is generally similar to patients with AKI associated with other etiologies such as sepsis [44,45]. Current management of COVID-19 associated AKI includes supportive treatment, avoiding nephrotoxic drugs, and, if possible, an early application of RRT [46,47]. Implementation of the KDIGO supportive care guideline (e.g., avoidance of nephrotoxins, regular monitoring of serum creatinine and urine output, consideration of hemodynamic monitoring) in critically ill patients with kidney involvement is likely to reduce both occurrence and severity of AKI in COVID-19, but requires validation [41,48].

Evidence suggests that conservative management of volume overload, metabolic acidosis, and hyperkalemia can be attempted before implementing kidney replacement therapy (KRT). Shaikh et al. describe methods for potentially delaying KRT to conserve valuable resources during hospital surges,

including escalating dosages of IV loop diuretics in patients with volume overload, IV sodium bicarbonate solution in patients with severe metabolic acidosis, and use of rapid-acting potassium binders such as sodium zirconium cyclosilicate for hyperkalemia [45]. Careful fluid management is important to consider as a modality to reduce the risk of noncardiogenic pulmonary edema, commonly associated with ARDS [49–51]. In the absence of shock and hypotension, fluid conservative therapy is recommended to achieve a negative fluid balance of 0.5–1.0 L per day [46,51]. Strategies for adjusting fluid balance according to volume responsiveness and tolerance assessment aim to restore normal volume status and prevent volume overload, to reduce the risk of pulmonary edema, right ventricular overload, congestions, and subsequent AKI. It is important to note that patients admitted with COVID-19 can often present with volume depletion due to pyrogenic effects and GI disturbances, and pre-hospital fluid resuscitation is rarely performed. These cases warrant the correction of hypovolemia to prevent AKI [41]. In the presence of shock, fluid balance may be achieved with RRT, especially if there is associated AKI and oliguria [51]. SARS, MERS, and sepsis have been successfully treated in the past with continuous renal replacement therapy (CRRT), as CRRT by hemofiltration and hemodiafiltration can contribute to the improvement of organ failure in these cases. Therefore, CRRT may be beneficial in patients with COVID-19 and sepsis syndrome, but it needs to be further evaluated carefully considering the logistical limitations during the current pandemic [46].

Unfortunately, well-established RRT programs have struggled due to a lack of machines, supplies, and personnel [52]. The COVID-19 Treatment Guidelines Panel recommends CRRT, if available, for critically ill patients who have AKI and develop indications for RRT. Suppose CRRT is either not available or not possible due to a lack of resources, including equipment and staff. In that case, the Panel recommends prolonged intermittent renal replacement therapy (PIRRT) rather than intermittent hemodialysis (IHD) [53]. The scarcity of resources has necessitated novel approaches to RRT programs, including “sharing” CRRT machines between patients with each patient receiving a daily 10–12 h session and utilizing peritoneal dialysis—a delivery not traditionally used in North American ICUs for treatment of AKI [52]. Beyond the selection of RRT modalities, the dialysis prescription in COVID-19-associated AKI presents unique considerations, and the ideal ultrafiltration target also remains uncertain. Hypoxemic respiratory failure and ARDS, both cardinal features of severe COVID-19 cases, can be exacerbated by a fluid accumulation that is subsequently worsened by AKI. The decision to remove fluid via ultrafiltration and how fast to do so is still uncertain as it may present with a trade-off in complications. For example, rapid fluid removal may improve oxygenation and accelerate removal of mechanical ventilation, but this ultrafiltration may, in turn, predispose patients to hypotension and secondary organ injury [52]. Furthermore, RRT has been presented with obstacles related to a state of hypercoagulability in severe COVID-19 cases that results in intra- and extracorporeal clotting events with subsequent early termination of treatment. Termination can reduce the gross quality of dialysis, metabolic imbalances, fluid overload increased blood loss due to more frequent changes in the system and is likely to promote further complications for patients [54]. Therefore, specialists have acknowledged the urgent need to establish specific anticoagulation regimens in patients with COVID-19 requiring RRT [41,54]. Nadim et al. has suggested the use of continuous veno-venous hemodialysis or continuous veno-venous hemodialysis filtration to decrease filtration fraction and reduce the risk of circuit clotting if using CRRT [48].

Given that the optimal approach to COVID-19-related kidney injury treatment is still uncertain, decisions for RRT modalities and prescriptions remain largely dependent on clinical judgment and resources available. One avenue that can be explored for tailoring clinical interventions specific to patients includes the use of kidney biopsies, which would help understand the histological pattern of injury (tubular, glomerular, and vascular) and the pathogenesis that could lead to AKI [46]. In a case report of granulomatous interstitial nephritis, Szajek et al. described a SARS-CoV-2-positive patient with severe ARDS and multi-organ failure, who developed oliguric AKI requiring analysis. Given the broad differential diagnoses for AKI, they performed a kidney biopsy that ultimately directed their treatment strategy. Based on findings, the decision was made to adjust medications and initiate corticosteroids, and his individually tailored clinical management plan resulted in recovery, discharge from rehabilitation, and no longer required dialysis. This case highlights the significant value of kidney biopsies in clinical diagnoses and may impact patient outcomes if a treatable cause is identified. They also highlighted the more frequently recognized drug interactions in COVID-19 that can potentially be

reversible, given the correct histopathology is determined [55]. Unfortunately, various factors specific to COVID-19 including the respiratory and hemodynamic instability of AKI patients, anticoagulation that increases the risk of bleeding, and use of mechanical ventilation make obtaining kidney biopsies of suspected AKI patients very difficult. Additionally, the risk of exposure to hospital personnel has severely limited the nonessential procedures performed in infected patients [46,48]. The use and criteria for warranted kidney biopsies are an important area that needs to be further evaluated and can potentially be informative in developing targeted biomarker therapies.

Conclusion

On December 31, 2019, a cluster of pneumonia cases out of Wuhan City, Hubei Providence of China were reported to the WHO China Country Office and later identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [56]. From January 21, 2020 to January 11, 2021, the CDC reported 22,322,956 SARS-CoV-2 cases and 373,167 deaths in the United States, with the current count of deaths exceeding 500,000 [57]. Although SARS-CoV-2 predominately causes acute respiratory illness, it can involve damage to other organs such as the kidneys, heart, gastrointestinal tract, immune, blood, and nervous system [8,58].

Kidney involvement is common in COVID-19, and the affected patients have hallmarks of kidney injury such as proteinuria, hematuria, and elevated BUN and creatinine in up to 60% of affected patients. Postmortem studies reveal elements of renal injury, including acute tubular injury, collapsing glomerulopathy, and the presence of viral particles within both tubular epithelium and podocytes. The exact method by which COVID-19 causes renal injury has yet to be fully elucidated. However, kidney injury pathogenesis appears to be multifactorial, with multiple direct and indirect mechanisms being implicated. SARS-CoV-2 may have the ability to directly affect the kidney by viral tropism, binding of spike protein to ACE2, which is highly expressed in the kidneys. Other direct mechanisms postulated include endothelial dysfunction, coagulopathy, direct viral complement activation, and high levels of circulating cytokines leading to an exaggerated inflammatory response termed “cytokine storm.” Indirect pathogenic mechanisms of kidney injury may include systemic effects of COVID-19 infection coupled with resultant critical care interventions including volume depletion due to hyperpyrexia and the GI effects of COVID-19, nephrotoxic medications used in the treatment of critically ill patients, and mechanical ventilation ultimately, leading to increased venous pressure and reduced filtration, as well as organ crosstalk.

Much is still unknown about the resultant impact of kidney dysfunction on mortality, but current research suggests the renal impairment in patients is associated with increased mortality. Additionally, COVID-19 patients with AKI or CKD exhibited greater in-hospital mortality, and the mortality rates between these two groups were comparable. Notably, the highest mortality rates were observed in patients who previously underwent renal transplant, with increased KDIGO stage associated with increased mortality, and significant proportions of these patients requiring RRT after discharge.

Special considerations and unique clinical presentations can be noted in patients with pre-existing kidney impairment, including those on hemodialysis and kidney transplant recipients. Due to the high rate of comorbidities in patients undergoing hemodialysis with COVID-19, vigilance on preventative measures for the perioperative and intensive care setting remains integral. Uremic patients, and hemodialysis patients with COVID-19, in particular, carry impaired immune responses and demonstrate greater fluctuations in infectivity and clinical symptoms. In–center hemodialysis centers risk of infection in an already impaired immune system patient population. Therefore, utilization of home dialysis remains crucial in protecting this at-risk patient population and healthcare workers from transmission.

Managing kidney transplant patients with COVID-19 requires balancing chronic immunosuppression in the setting of COVID-19 and preventing transplant graft rejection. The medical decision to withdraw immunosuppression in kidney transplant patients remains heavily debated, leading to providers needing to reduce dosages of immunosuppressants on a case-by-case basis carefully. Additionally, reports of AKI in transplant patients seem to be at a higher rate than the general population and are at a higher mortality rate from COVID-19.

To date, there is no specific treatment for COVID-19-induced AKI and management of COVID-19-associated AKI is generally similar to patients with AKI associated with other etiologies such as sepsis [44,45]. Current management of COVID-19-associated AKI includes supportive treatment, avoiding nephrotoxic drugs, and, if possible, an early start of RRT [46,47]. Conservative management of volume overload, metabolic acidosis, and hyperkalemia can be attempted before considering initiation of kidney replacement therapy (KRT) [45]. Careful fluid management is important to consider as a modality to reduce the risk of noncardiogenic pulmonary edema, commonly associated with ARDS [49–51]. SARS, MERS, and sepsis have been successfully treated in the past with CRRT. Therefore COVID-19 patients can benefit, although it needs to be evaluated more carefully and has many logistical limitations during the current pandemic, including transmission, lack of resources, and experienced personnel [46]. Specialists have also acknowledged the need to establish specific anticoagulation regimens in COVID-19 patients with a predisposition for hypercoagulability [41,54]. Future research should include the use of kidney biopsies to elucidate the specific histopathology of a patient's AKI, the potential to target treatments, and the cost-benefit of performing these procedures in at-risk patient populations.

The potential impact of SARS-CoV-2 on the kidneys is still undetermined. Still, emerging evidence indicates that kidney complications are frequent, and COVID-19 disease may have unique features in individuals on chronic dialysis and kidney transplant recipients, requiring increased vigilance in limiting viral transmission in perioperative, in-patient, and dialysis center settings [46].

Practice points

- Current evidence shows that acute kidney injury (AKI) in COVID-19 patients is as high as 25% and up to 60% patients experience proteinuria
- Risk factors for severe COVID-19 infections and AKI are similar, including older age, diabetes mellitus, hypertension and cardiovascular disease.
- AKI in COVID-19 patients may be associated with increased mortality, particularly in patients who require escalating treatment such as renal replacement therapy.
- In–center hemodialysis may raise the risk of infection transmission due to densely populated outpatient units. The management of these at-risk patients must follow stringent guidelines to reduce the transmission risk to other patients and healthcare workers.
- Best practices of handling immunosuppression in kidney transplant patients with COVID-19 remain controversial

Research agenda

- While some evidence sheds light on the multifactorial impact of COVID-19 on renal physiology, the definitive pathophysiologic mechanisms are yet to be defined.
- Meta-analyses of emerging data will reveal the effect of AKI in the setting of COVID-19 on mortality.
- The pandemic might boost home dialysis utilization, although clinical and economic implications are yet to be determined.
- Future trials will clarify some controversial current guidelines on how to manage immunosuppression in kidney transplant patients with COVID-19.

Declaration of competing interest

Richard Urman reports unrelated research funding from AcelRx and fees from Medtronic, Merck, Pfizer, Heron, and Takeda. Alan Kaye reports fees from Merck. Other authors report no conflicts of interest.

Acknowledgement of Funding

No funding was received for this work.

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