Effect of COVID-19 on Kidney Disease Incidence and Management

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Abstract

The COVID-19 outbreak has had substantial effects on the incidence and management of kidney diseases, including acute kidney injury (AKI), End-Stage Kidney Disease (ESKD), glomerulonephritis, and kidney transplantation. Initial reports from China suggested a lower AKI incidence in patients with COVID-19, but more recent studies from North America reveal a much higher incidence, likely due to higher prevalence of comorbid conditions such as hypertension, diabetes, and chronic kidney disease (CKD). AKI in this setting is associated with worse outcomes, including requirement for vasopressors or mechanical ventilation and death. Performing renal replacement therapy in those with AKI poses challenges such as limiting exposure of staff, preserving PPE, coagulopathy, and hypoxemia due to Acute Respiratory Distress Syndrome. Continuous Renal Replacement Therapy is the preferred modality, with sustained low-efficiency dialysis also an option, both managed without 1:1 hemodialysis nursing support. Regional citrate is the preferred anticoagulation, but systemic unfractionated heparin may be used in cases of coagulopathy. Ultrafiltration rate has to be set carefully, taking into consideration hypotension, hypoxemia, and responsiveness to presser and ventilatory support. Chance of transmission puts in-center chronic hemodialysis and other immunosuppressed patients at particularly increased risk. Limited data show that patients with CKD are also at increased risk for more severe disease if infected. Little is known about the virus’s effects on immunocompromised patients with glomerular diseases and kidney transplants, which introduces challenges for management of immunosuppressant regimens. While there are no standardized guidelines regarding the management of immunosuppression, several groups
recommend stopping the anti-metabolite in hospitalized transplant patients and continuing a reduced dose of calcineurin inhibitors. This comprehensive review critically appraises the best available evidence regarding the effect of COVID-19 on the incidence and management of kidney diseases. Where evidence is lacking, current expert opinion and clinical guidelines are reviewed and knowledge gaps worth investigation are identified.
Introduction

COVID-19, the disease caused by the novel coronavirus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first described in Wuhan, China but rapidly affected >40 million people worldwide (1). The clinical presentation is highly variable in symptoms, severity, and organ involvement, ranging from asymptomatic to multi-organ failure. One of the major organs involved is the kidney, which manifests as COVID-19-related Acute Kidney Injury (AKI) in hospitalized patients, especially in those requiring Intensive Care Unit (ICU) management. Another important aspect of COVID-19 as relates to kidney disease is, given the highly infectious nature of SAR-CoV-2, patients with End Stage Kidney Disease (ESKD), kidney transplantation recipients, and those with glomerular diseases and other Chronic Kidney Diseases (CKD) may be at increased risk for infection and associated morbidity, especially in the light of the underlying immunocompromised state. The global COVID-19 pandemic has had significant influence on clinical aspects and management of these patient populations. Here, we evaluate the current evidence about the impact of COVID-19 on AKI, CKD, ESKD, renal transplantation, and glomerulonephritis and address specific management challenges of these vulnerable patient populations.

Acute Kidney Injury

Epidemiology and Outcomes

Early reports from Wuhan, China, concluded that COVID-19 does not result in significant AKI (2), with zero cases reported among 119 hospitalized patients, ranging up to 15% in other publications (2-15). Subsequent U.S. studies reported higher incidences of 14-69% in hospitalized patients, especially if requiring ICU and mechanical ventilation (Figure 1A) (15-23). One study reported a higher incidence of
AKI among patients hospitalized for COVID-19 vs. for non-COVID indications (17). These differences could be explained by the varying prevalences of comorbidities among Chinese vs. U.S. cohorts, with the U.S. reporting a higher presence of hypertension, diabetes mellitus, and CKD, found to be risk factors for SARS-CoV-2 infection (Figure 1C, Figure 1D) (3-14, 24-28). Diabetes was present among 16%-49% and hypertension among 31%-74% of patients with COVID-19 (15-17, 19-22, 29-31) in U.S. cohorts, but in only 7%-24% and 15%-38% in Chinese counterparts. These variations may be, in part, due to differences in racial composition, healthcare access, and hospitalization thresholds for disease acuity. There was also heterogeneity across studies, with some comprised of all hospitalized patients, while others only those requiring ICU and, therefore, reporting higher AKI incidence. This is congruent with findings identifying requirement for vasopressors or mechanical ventilation as independent risk factors for COVID-related AKI (18). Another factor could be the lack of a standardized method for defining AKI. Most studies used standard Kidney Disease: Improving Global Outcomes (KDIGO) (32) criteria but varied in how “baseline creatinine” was established.

Reported mortality is also variable, ranging from 1%-28% in Chinese (2, 3, 5, 6, 8-11, 14, 26), and 15%-24% in U.S. studies (15-18, 20-22, 31). Factors implicated for heterogeneity may include case-mix, socioeconomic status, hospitalization criteria, and availability and delivery of COVID-specific treatments. Comorbidities are also considered an important risk factor for COVID-19 disease severity and outcomes, and patients who die have a higher prevalence of hypertension and diabetes vs. those who recover (24, 25).
Patients with COVID-19-associated AKI have worse outcomes than those without AKI, with higher incidences of ICU admission, Acute Respiratory Distress Syndrome (ARDS), mechanical ventilation, and death (27-29). Yang and Xu reported AKI incidences of 29% and 50% in patients admitted to the ICU (27, 28). AKI incidence was about 50% in a larger U.S. multicenter cohort of >3,000 ICU patients (30). Two studies from China reported AKI occurring more frequently in patients who died than who recovered from COVID-19 (24, 25). Association of AKI with poor outcomes in the setting of COVID-19 may be confounded by factors that cause or correlate with AKI and also with adverse outcomes among acutely ill patients.

AKI Requiring Renal Replacement Therapy (RRT)

In China, the incidence of AKI requiring RRT ranged from 0%-7% (2, 6, 7, 9-11, 13, 14, 24, 27). In one cohort of only ICU patients, the incidence was 17% (28). In the U.S., the incidence ranged from 3.1%-15.5% in all-comers (Figure 1A) (16-20, 22) but higher at 20% in ICU patients (30). The higher utilization of RRT in the U.S. vs. China may be due to higher AKI incidence, availability of RRT, or severity of disease or comorbidities. Specific RRT modalities were not always reported, but acute peritoneal dialysis (PD) is utilized in some centers due to concern for lack of resources (33). Performing PD in patients who are placed in the prone position for ARDS brings up the concern for increased intra-abdominal pressures and subsequent decreased ultrafiltration. PD has been successfully used in prone position, and proning is not an absolute contraindication for PD (34). The risk of intra-abdominal hypertension and decreased ultrafiltration can be mitigated by suspension of the abdominal cavity and using low volume continuous PD (35).
Delivering RRT in those with COVID-19 poses several challenges (Figure 2) (36-38). In addition to utilization of acute PD, various strategies were implemented to help ease the impending resource shortages. Many centers utilize continuous RRT (CRRT) or prolonged intermittent daily RRT (PIRRT), including sustained low efficiency dialysis (SLED), instead of intermittent hemodialysis (IHD), which can be managed without 1:1 HD nursing. Other strategies included using a shorter CRRT duration, 10-12 hours, at a higher effluent rate of 40-50 ml/kg/hr, to rotate the same machine for multiple patients. Reducing the effluent dose once the patient becomes stable was recommended to preserve dialysis solutions (37-41).

The virus is easily transmitted which raises challenges regarding safety, complicated by declining personal protective equipment (PPE). Shortages of healthcare workers due to illness and need to quarantine poses additional challenges. Solutions include isolation of patients in aggregate in COVID-only ICUs or using individual isolation rooms. Training non-dialysis staff to assist with dialysis treatments has also been undertaken. Decreasing the IHD length and number of weekly sessions in stable hospitalized patients is another option (38, 39). Additional challenges for CRRT include an underlying hypercoagulable state, which can cause increased circuit and filter clotting. Addition of systemic unfractionated heparin to regional citrate may be required, and argatroban has also been successfully used for anticoagulation (36, 42, 43). To minimize catheter length, vascular access using the right internal jugular vein is preferred, anchored firmly in place, and position checked after pronation. Ultrafiltration rate has to be carefully adjusted, taking into account hypotension, ARDS, and responsiveness to presser and ventilator support.
Renal Outcomes following AKI

Limited long-term data exist regarding AKI recovery vs. continued dialysis-dependence. One study, median follow-up 12 days, reported 18% recovery rate in patients with AKI by KDIGO criteria and 46% by expanded criteria (change in serum creatinine ≥0.3 mg/dl) (8). A multicenter U.S. study of >3000 ICU patients reported that 63% with AKI-RRT died, 34% were discharged, and 3% remained hospitalized at 17 days. Of those discharged, 34% remained RRT-dependent at discharge, and 18% remained RRT-dependent 60 days after ICU admission (30). More information is needed on long-term renal outcomes of patients with COVID-19.

Potential Mechanisms for AKI

Mechanisms are likely multifactorial, with usual suspects including prerenal azotemia from intra-vascular volume depletion; ischemic acute tubular necrosis (ATN) from hypotension and shock; and acute interstitial nephritis from antibiotics, antivirals, and other medications (Figure 3) (19). Other mechanisms include a hypercoagulable state causing kidney ischemia (44). There is increasing evidence that much of the organ dysfunction is due to complement activation and cytokine release (45). Levels of Interleukin-6 (IL-6) along with other inflammatory biomarkers are elevated, especially in patients with ARDS (46). The presence of SARS-CoV-2 in endomyocardial biopsies in patients with myocarditis or unexplained heart failure suggests SARS-CoV-2 can cause cardiomyopathy (47). Acute heart failure can result in Type 1 cardio-renal syndrome (Figure 3).
In an autopsy series of 42 patients, ATN was the most predominant histological finding (23). Evidence of glomerulosclerosis, myoglobin cast nephropathy, thrombotic microangiopathy, crescentic glomerulonephritis, cortical necrosis, and collapsing glomerulopathy were also reported. The latter was associated with presence of high-risk APOL1 genotype, suggesting that individuals with APOL1 risk alleles are at increased risk (48-52).

There is evidence that SARS-CoV-2 may exert direct cytopathic effects on kidney tissue, although data are not consistent. This is thought to be possible due to binding of the virus to host angiotensin-converting enzyme 2 (ACE2) which is expressed in the kidney (53). In 26 postmortem cases from China, all revealing ATN, Coronavirus-like particles were reported by electron microscopy (EM) in podocytes foot processes and the glomerular basement membrane. There was also immunofluorescent staining for anti-SARS-CoV nucleoprotein antibody in 3 of 7 cases (54). In biopsy findings of 6 deceased individuals with AKI, SARS-CoV-2 nucleocapsid protein was found in the renal tubules of all. Virus-like particles were seen by EM in 2 (55). Post-mortem findings in another 63 patients revealed detectable SARS-CoV-2 ribonucleic acid (RNA) in kidney tissue of 72% of those with AKI and 43% of those without AKI (56). These findings do bring up the possibility that the virus may be causing direct tubular damage (23, 57). Another case series of 10 kidney biopsies reported that staining by immunohistochemistry for SARS-CoV-2 was negative in all cases with COVID-19 and tubular injury. These disparate results may be due to viral levels being below the detection threshold in the kidney or that virus-like particles seen on EM may be intracellular components that exhibit viral-like morphology (48).
Chronic Kidney Disease-Non-dialysis (CKD-ND)

Limited data exist regarding COVID-19 infection and morbidity in patients with CKD-ND. The prevalence of CKD-ND among patients with COVID-19 varies from 3.5% to 48% in U.S. cohorts (15-17, 19-22, 29-31). Higher rates were from smaller cohorts, while larger samples had a prevalence ranging from 5-20% (16, 21, 30, 31). Cohorts from China, however, reported lower rates of pre-existing CKD-ND, 0.7% to 4.3% (Figure1B) (3-5, 7, 9-14, 24, 26).

One Chinese meta-analysis of four studies (N=1,389), found an association between CKD-ND and more severe COVID-19 disease (58). Other meta-analyses showed that CKD was associated with an increased risk of mortality in patients hospitalized with COVID-19, although it is not clear whether models were adjusted for hypertension or diabetes mellitus (59, 60). A large, multi-center U.S. study of COVID-positive ICU patients also revealed that patients with pre-existing CKD-ND vs. without had a higher risk of in-hospital mortality (61). While more data are needed to confirm findings, it is important to educate CKD patients about proper precautions to decrease risk.

End Stage Kidney Disease (ESKD)

Epidemiology and Outcomes

The COVID-19 outbreak brings up increased concern for ESKD patients who are intrinsically immunocompromised and have underlying comorbidities (62). Those who receive outpatient in-center HD are in close contact with other patients and staff multiple
times a week, putting them at even greater risk. Clinical presentation is atypical when compared to non-dialysis patients, with ESKD patients presenting without typical symptoms of cough and fever but instead, fatigue and anorexia (63, 64). Risk of in-hospital death is significantly higher among ESKD patients as compared to non-ESKD patients, with older age and need for mechanical ventilation increasing risk (63, 65, 66) (Table 2). Most early reports of mortality came from small cohorts, where mortality ranged from 14-30% (66-69). A more recent larger cohort reported mortality of 31.7% in ESKD patients as compared to 25.4% in non-ESKD patients (65).

**Management of Outpatient Dialysis**

How to best handle outpatient dialysis becomes imperative due to the propensity of COVID-19 to cause cluster outbreaks. A study from London reported cluster outbreaks at specific centers within their network (67). This and other reports illustrated a need for HD center protocols to limit transmission, and subsequently, several opinion-based editorials were published. As Wuhan saw an increase in cases in dialysis patients and staff, preventative measures, including limiting in-person provider rounds, limiting number of patients on individual shifts, temperature and symptom checks at entry, and increased PPE utilization, were implemented. COVID-positive dialysis shifts were set up in designated hospitals where large numbers of dialysis patients with the infection were treated centrally (70). If this was not feasible, then separate COVID-positive dialysis shifts were recommended, preferably utilizing the day’s last shift (71-73). Cohort isolation for in-center HD, screening protocols, and adequate PPE are agreed upon by many nephrologists (71, 73, 74). The Center for Disease Control (CDC)
has provided guidance and commented on when to transition infected patients to outpatient dialysis units after recovery (75). No clear correlation was found between length of illness and post-recovery shedding of virus in dialysis patients, but recent data suggest replication-competent virus likelihood approaches zero by 10 days of symptoms in the general population (76). Currently, the strategy for transitioning patients to outpatient dialysis is either test-based, requiring two negative tests >24 hours apart and being symptom-free; or, if testing is not available, fever-free for ≥72 hours and ≥14 days since symptom onset (77).

Management of Inpatient Dialysis

In anticipation of increased numbers of affected dialysis patients requiring hospitalization, there was concern for limited resources, e.g., dialysis machines, filters, and solutions, and decreased number of available staff due to illness or quarantine. Hospitals admissions will include both COVID-infected patients with AKI and maintenance dialysis patients requiring RRT. Similar strategies were proposed to what was discussed regarding AKI, including decreasing number of weekly dialysis sessions and shortening treatments. Given mandates to defer elective non-urgent surgeries, some centers were having issues with patients not being scheduled for procedures to place or repair vascular access. This prompted the Centers for Medicare & Medicaid Services (CMS) to release a statement iterating that procedures to establish dialysis access were essential and should be treated as such (78). Transitioning patients from in-center HD to home dialysis modalities, such as home HD or PD, can also be considered (Figure 3) (64).
Kidney Transplantation

Epidemiology and Outcomes

It would be logical to assume that kidney transplantation recipients are at increased risk for contracting COVID-19 and having more severe disease based on their immunocompromised state and common comorbidities of hypertension and diabetes. However, current evidence based on several case series is unclear. Presentation of COVID-19 in transplant recipients appears to be similar to that in non-immunosuppressed patients, with typical symptoms being cough, fever, and shortness of breath (Table 1) (39, 79-81). One study of 36 patients reported a mortality rate of 28%, substantially higher than that in the general population (82). Similarly, Alberici described a 25% mortality rate among 20 transplant recipients, and Naira rate of 30% in 10 (39, 83). Both groups also found an increased rate of clinical deterioration. Given small sample sizes, it is difficult to conclude whether kidney transplant recipients are in fact at an increased risk of death from COVID-19.

Immunosuppression Management in Transplant Recipients

While there are no standardized guidelines regarding the management of immunosuppression in patients with COVID-19, several groups recommended stopping the anti-metabolite in hospitalized patients, following the thought process that T-cell immunity is likely important for fighting the virus (39, 79, 82, 84). However, there is also concern that the release of cytokines is responsible for many of the severe manifestations of COVID-19, including ARDS (79). Some form of immunosuppression could, therefore, be of benefit. In addition, new data support using corticosteroids in patients ventilated or with increased oxygen requirements (85). Many transplant centers
have practiced continuing corticosteroids and, in some cases, increasing the dose; and continuing a reduced dose of calcineurin-inhibitors (unless the patient is severely ill) (39, 82, 84). One study of 40 patients hospitalized with COVID-19 from multiple sites reported that the majority were maintained on corticosteroids alone (86). Overall, it is agreed that the specific clinical scenario should guide immunosuppression, including any recent treatments for rejection which would result in further decline in immunity. Of note, patients in many of these early case series were treated with hydroxychloroquine and azithromycin, which are no longer being recommended. More contemporary data with larger numbers are needed to determine outcomes of patients treated with other agents, including Remdesivir, IL-6 inhibitors, and convalescent plasma.

As the pandemic continues, it is important to know how to manage those who may not need hospitalization. The transplant nephrology group at Columbia evaluated outpatients with known or suspected COVID-19, and of 41 patients, 32% required hospitalization, the remaining managed as outpatients. After a median follow-up of 12 days, 23 of 41 had resolution of symptoms. However, due to lack of testing availability at the time, not all patients were tested to confirm COVID-19 (80). The ideal outpatient management has not yet been determined, as very limited follow-up data exist on kidney transplant recipients, in particular, and patients recovering from COVID-19 in general. More information is also needed to determine the optimal timing for reintroduction of immunosuppressants.

Performance of New Transplantations

Most transplant centers had limited or temporarily stopped performing kidney transplantations during the pandemic due risk of transmission to donors with healthcare
contact and recipients who would be immunosuppressed. One report noted that the rate of U.S. deceased donor kidney transplants decreased by 50% (64). Alternatively, transplantation could mean no further need for in-center dialysis, which would reduce risk. In a recent statement, CMS reiterated that organ transplantation is an essential procedure (78). The availability of resources is also a consideration (87). There needs to be a balance between the benefit of transplantation for individual patients and risks of nosocomial COVID-19 spread and resource utilization. Massie developed a tool using machine learning to determine the benefit vs. harm of kidney transplantation and found that, in 72% of simulated scenarios, immediate transplantation provided a survival benefit to deferring transplantation and remaining on the wait list (88). This tool may be used by transplant centers to individualize transplantation decisions.

**Glomerulonephritis**

Initiating or continuing immunosuppression in patients with glomerular disease is also concerning in this pandemic. There are no evidence-based recommendations, and there is very little information regarding the prevalence of COVID-19 or outcomes of infected patients. One group in Italy prospectively evaluated patients with nephrotic syndrome on chronic therapy with anti-CD20 antibodies, the majority of which were pediatric patients. Thirty-four percent were also being treated with other immunosuppressants (corticosteroids, calcineurin-inhibitors, and anti-metabolites). All patients had received treatment with B-cell depleting therapy, with median time since last treatment of 18 months. At follow-up, none developed signs of COVID-19. Six were living with an individual who was found to be COVID-positive. Based on these observations, the authors recommended not to preemptively alter the
immunosuppression regimen in children with nephrotic syndrome, regardless of possible COVID-19 exposure (89).

To strike a balance between COVID-19 complications and kidney outcomes, the glomerular disease group at Columbia proposed recommendations based on their experience in a COVID-19 hot spot (90). For patients with rapidly progressing glomerular disease and severe nephrotic syndrome who have decreased kidney function and/or complications of nephrotic syndrome, initiate standard-of-care. For patients who do not meet this criteria but who would typically be started on immunosuppression, defer treatment. For those who had begun treatment prior to the pandemic onset, decision to continue treatment would be made on a case-by-case basis, weighing risks and benefits. For patients started on intravenous protocols, switch to oral regimens to decrease healthcare visits. Consider home infusions when no equivalent oral regimen exist. For patients in remission on maintenance regimen, stop anti-metabolites and avoid maintenance B-cell depleting infusions. Tapering and discontinuing corticosteroids has also been suggested for stable patients, while calcineurin-inhibitors are continued based on experience in the transplant community. Immunosuppression adjustments for patients with confirmed COVID-19 should be based on specific clinical scenarios. Other strategies to decrease exposure include limiting kidney biopsies to only those necessary for critical decision-making, using home urine dipsticks vs. those done at a laboratory, and utilizing telemedicine (90).

**Conclusion**

The impact of the COVID-19 pandemic has been felt in all facets of kidney disease management. There is still much to be learned, including the long-term kidney
outcomes in patients with COVID-19-related AKI. The best strategies for managing immunosuppression in kidney transplant recipients and patients with glomerulonephritis are unknown. Similarly, strategies on how to best manage patients with ESKD receiving outpatient in-center dialysis or hospitalized COVID-positive patients with ESKD or AKI requiring RRT are anecdotal. As new experiences and data become available, it becomes paramount to continue sharing and publication of evidence, and to be hyper-vigilant in adjusting our practice to provide the best clinical care.
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N Rajora: Writing - original draft; Writing - review and editing
SS Hedayati: Conceptualization; Investigation; Methodology; Resources; Supervision; Validation; Writing - original draft; Writing - review and editing
References


Table 1. Summary of studies reporting AKI and outcomes in patients with COVID-19.

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Patients (N)</th>
<th>Sample</th>
<th>Black N (%)</th>
<th>Hispanic N (%)</th>
<th>CKD N (%)</th>
<th>AKI N (%)</th>
<th>AKI-RRT N (%)</th>
<th>Mortality N (%)</th>
<th>Geographic Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen24</td>
<td>113 deceased and 161 recovered</td>
<td>Hospitalized</td>
<td>0</td>
<td>0</td>
<td>4(1)</td>
<td>28(25) vs 1(1)</td>
<td>3(1)</td>
<td>113(41.2)</td>
<td>China</td>
</tr>
<tr>
<td>Cheng3</td>
<td>701</td>
<td>Hospitalized</td>
<td>0</td>
<td>0</td>
<td>14(2)</td>
<td>36(5.1)</td>
<td>NA</td>
<td>113(16.1)</td>
<td>China</td>
</tr>
<tr>
<td>Deng25</td>
<td>109 deceased and 116 recovered</td>
<td>Hospitalized</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>20 (18.3) vs 0</td>
<td>NA</td>
<td>109(49)</td>
<td>China</td>
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<td>Guan4</td>
<td>1099</td>
<td>Hospitalized and outpatients</td>
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<td>6(3.2)</td>
<td>18(14.6)</td>
<td>NA</td>
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<td>3(7)</td>
<td>3(7)</td>
<td>6(15)</td>
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<tr>
<td>Lei7</td>
<td>34</td>
<td>Underwent elective surgery prior to diagnosis</td>
<td>0</td>
<td>0</td>
<td>1(2.9)</td>
<td>2(5.9)</td>
<td>1(2.9)</td>
<td>7(20.6)</td>
<td>China</td>
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<tr>
<td>Pei8</td>
<td>333</td>
<td>Hospitalized</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>35(10.5)</td>
<td>NA</td>
<td>29(8.7)</td>
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<tr>
<td>Shi9</td>
<td>416</td>
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<td>14(3.4)</td>
<td>8(1.9)</td>
<td>2(0.5)</td>
<td>57(13.7)</td>
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<td>Wang26</td>
<td>107</td>
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<td>0</td>
<td>0</td>
<td>3(2.8)</td>
<td>14(13.1)</td>
<td>NA</td>
<td>19(17.7)</td>
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<tr>
<td>Wang10</td>
<td>138</td>
<td>Hospitalized</td>
<td>0</td>
<td>0</td>
<td>4(2.9)</td>
<td>5(3.6)</td>
<td>2(1.45%)</td>
<td>6(4.3)</td>
<td>China</td>
</tr>
<tr>
<td>Wang1</td>
<td>116</td>
<td>Hospitalized</td>
<td>0</td>
<td>0</td>
<td>5(4.3)</td>
<td>0(0)</td>
<td>0 (0)</td>
<td>7(6)</td>
<td>China</td>
</tr>
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<td>Location</td>
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<td>ED or hospitalized</td>
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<tr>
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<tr>
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<td>0</td>
<td>0</td>
<td>6(2.7)</td>
<td>10</td>
<td>5</td>
<td>12(5.4)</td>
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<td>0</td>
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<td>NA</td>
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<td>Zhang</td>
<td>645</td>
<td>Hospitalized</td>
<td>0</td>
<td>0</td>
<td>6(0.9)</td>
<td>2</td>
<td>33</td>
<td>NA</td>
<td>China</td>
</tr>
<tr>
<td>Zhou</td>
<td>191</td>
<td>Hospitalized</td>
<td>0</td>
<td>0</td>
<td>2(1)</td>
<td>27</td>
<td>10</td>
<td>54(28.3)</td>
<td>China</td>
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<tr>
<td>Aggarwal</td>
<td>16</td>
<td>Hospitalized</td>
<td>0</td>
<td>0</td>
<td>6(38)</td>
<td>11</td>
<td>NA</td>
<td>3(19)</td>
<td>Iowa</td>
</tr>
<tr>
<td>Arentz</td>
<td>21</td>
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<td>NA</td>
<td>NA</td>
<td>10(47.6)</td>
<td>4</td>
<td>11</td>
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<tr>
<td>Argenziano</td>
<td>1000</td>
<td>ED or hospitalized</td>
<td>181</td>
<td>248</td>
<td>137(13.7)</td>
<td>288</td>
<td>117</td>
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</tr>
<tr>
<td>Fisher</td>
<td>3345</td>
<td>Hospitalized</td>
<td>1201</td>
<td>1247</td>
<td>409(12.2)</td>
<td>1903</td>
<td>164</td>
<td>775(23.2)</td>
<td>New York</td>
</tr>
<tr>
<td>Gupta</td>
<td>3099</td>
<td>ICU</td>
<td>952</td>
<td>1045</td>
<td>897(28.9)</td>
<td>1685</td>
<td>637</td>
<td>350/637(54.9)</td>
<td>U.S., multicenter</td>
</tr>
<tr>
<td>Imam</td>
<td>1305</td>
<td>Hospitalized</td>
<td>862</td>
<td>NA</td>
<td>228(17.5)</td>
<td>76</td>
<td>63</td>
<td>200(15.3)</td>
<td>Michigan</td>
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<tr>
<td>Mohamed</td>
<td>575</td>
<td>Hospitalized</td>
<td>414</td>
<td>9(1.57)</td>
<td>172(29.9)</td>
<td>161</td>
<td>89(15.5)</td>
<td>80/161(50)</td>
<td>New Orleans, LA</td>
</tr>
<tr>
<td>Pelayo</td>
<td>223</td>
<td>Hospitalized</td>
<td>152</td>
<td>14(6)</td>
<td>39(17)</td>
<td>110</td>
<td>9(4)</td>
<td>44(19)</td>
<td>Philadelphia, PA</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Diagnosis Status</td>
<td>Hospitalized or Outpatient</td>
<td>Hospitalized (n, %)</td>
<td>Hospitalized only (n, %)</td>
<td>Outpatient (n, %)</td>
<td>Discharged or Died (n, %)</td>
<td>Excluded (n, %)</td>
<td>Other (n, %)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------</td>
<td>---------------------------</td>
<td>---------------------------</td>
<td>---------------------</td>
<td>-------------------------</td>
<td>------------------</td>
<td>---------------------------</td>
<td>----------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Price-Haywood</td>
<td>3481</td>
<td>Hospitalized and outpatient</td>
<td>2451 (70.4)</td>
<td>0</td>
<td>278 (8)</td>
<td>197 (14.25)</td>
<td>NA</td>
<td>326 (23.6)</td>
<td>Louisiana</td>
</tr>
<tr>
<td>Richardson</td>
<td>5700</td>
<td>2634 discharged or died</td>
<td>1230 (23)</td>
<td>1230 (23)</td>
<td>186 (3.5)</td>
<td>523/2634 (20)</td>
<td>81/2634 (3.2)</td>
<td>553/2634 (21)</td>
<td>New York</td>
</tr>
<tr>
<td>Grasselli</td>
<td>1591</td>
<td>ICU</td>
<td>NA</td>
<td>NA</td>
<td>36 (3)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Italy</td>
</tr>
<tr>
<td>Lim</td>
<td>164</td>
<td>Hospitalized</td>
<td>0</td>
<td>0</td>
<td>Excluded</td>
<td>30 (18.3)</td>
<td>5 (3)</td>
<td>44 (164)</td>
<td>South Korea</td>
</tr>
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</table>

### Kidney Transplant Recipients

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Diagnosis Status</th>
<th>Hospitalized or Outpatient</th>
<th>Hospitalized (n, %)</th>
<th>Hospitalized only (n, %)</th>
<th>Outpatient (n, %)</th>
<th>Discharged or Died (n, %)</th>
<th>Excluded (n, %)</th>
<th>Other (n, %)</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akalin</td>
<td>36</td>
<td>Confirmed COVID</td>
<td>14 (39)</td>
<td>15 (42)</td>
<td>NA</td>
<td>NA</td>
<td>6 (21)</td>
<td>10 (28)</td>
<td>New York</td>
<td></td>
</tr>
<tr>
<td>Alberici</td>
<td>20</td>
<td>Hospitalized, confirmed COVID</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>6 (30)</td>
<td>1 (5)</td>
<td>5 (25)</td>
<td>Italy</td>
<td></td>
</tr>
<tr>
<td>Banerjee</td>
<td>7</td>
<td>Confirmed COVID</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1 (14)</td>
<td>London</td>
<td></td>
</tr>
<tr>
<td>Columbia Transplant Program</td>
<td>15</td>
<td>Confirmed COVID</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>6 (40)</td>
<td>2 (13)</td>
<td>2 (13)</td>
<td>New York</td>
<td></td>
</tr>
<tr>
<td>Husain</td>
<td>41</td>
<td>Confirmed or suspected COVID</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>New York</td>
<td></td>
</tr>
<tr>
<td>Maritati</td>
<td>5</td>
<td>Hospitalized, confirmed COVID</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1 (20)</td>
<td>0</td>
<td>2 (60)</td>
<td>Italy</td>
<td></td>
</tr>
<tr>
<td>Nair</td>
<td>10</td>
<td>Confirmed COVID</td>
<td>3 (30)</td>
<td>NA</td>
<td>NA</td>
<td>5 (50)</td>
<td>NA</td>
<td>3 (30)</td>
<td>New York</td>
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</table>

AKI, Acute kidney injury; AKI-RRT, Acute Kidney Injury requiring renal replacement therapy; CKD, Chronic Kidney Disease. Note that references 18 and 22 come from the same institution and the cohorts overlap.
<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Patients (N)</th>
<th>Sample</th>
<th>Dialysis Modality N (%)</th>
<th>Black N (%)</th>
<th>Hispanic N (%)</th>
<th>ARDS/MV</th>
<th>CRRT N (%)</th>
<th>Death N (%)</th>
<th>Geographic Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberici⁹⁴</td>
<td>21</td>
<td>Hospitalized, COVID+</td>
<td>21 (100) HD</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>5 (24)</td>
<td>Italy</td>
</tr>
<tr>
<td>Corbett⁶⁷</td>
<td>1530</td>
<td>ESKD from 1 large center, 300 with COVID</td>
<td>290 (97) in-center HD8(2.7) PD2(0.7) home HD</td>
<td>75/300(25)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>61/300 (20)</td>
<td>London</td>
</tr>
<tr>
<td>Fisher⁹⁵</td>
<td>114</td>
<td>Hospitalized, COVID+</td>
<td>114 (100) HD</td>
<td>56 (49)</td>
<td>45 (40)</td>
<td>19 (17)</td>
<td>2 (2)</td>
<td>32 (28)</td>
<td>New York</td>
</tr>
<tr>
<td>Flythe⁶¹</td>
<td>143 ESKD 4121 non-ESKD</td>
<td>COVID+, in ICU. Multicenter</td>
<td>128 (90) in-center HD 9 (6) PD 2 (1) home HD 4 (3) unknown</td>
<td>71 (50)</td>
<td>29 (20)</td>
<td>106 (74)* *on day 14</td>
<td>NA</td>
<td>72 (50)* *at day 28</td>
<td>US</td>
</tr>
<tr>
<td>Goicoechea⁶⁸</td>
<td>36</td>
<td>ESKD hospitalized, COVID+</td>
<td>36 (100) HD</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>11 (30.5)</td>
<td>Spain</td>
</tr>
<tr>
<td>Ng⁶⁵</td>
<td>419 ESKD, 10,063 non-ESKD</td>
<td>Hospitalized, ESKD and non-ESKD, all COVID+</td>
<td>408 (97) HD 11 (2.6) PD 152 (36) ESKD</td>
<td>87 (21)</td>
<td>89 (21)</td>
<td>NA</td>
<td>133 (31.7)</td>
<td>New York</td>
<td></td>
</tr>
<tr>
<td>Scarpioni⁹⁶</td>
<td>42</td>
<td>ESKD, COVID+</td>
<td>41 (98) HD 1(2) PD</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>18 (41)</td>
<td>Italy</td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Description</td>
<td>Hospitalized, ESKD, all COVID+</td>
<td>57 (97) HD 2(3) PD</td>
<td>15 (25)</td>
<td>44 (75)</td>
<td>NA</td>
<td>3 (5)</td>
<td>18 (31)</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td>-------------</td>
<td>--------------------------------</td>
<td>---------------------</td>
<td>----------</td>
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<tr>
<td>Valeri(^{66})</td>
<td>59</td>
<td>Hospitalized, ESKD, all COVID+</td>
<td>57 (97) HD 2(3) PD</td>
<td>15 (25)</td>
<td>44 (75)</td>
<td>NA</td>
<td>3 (5)</td>
<td>18 (31)</td>
<td>New York</td>
</tr>
<tr>
<td>Wu(^{63})</td>
<td>49 on HD, 52 controls</td>
<td>Hospitalized, ESKD and non-ESKD, all COVID+</td>
<td>49 (100) HD</td>
<td>0</td>
<td>0</td>
<td>10 (20) ESRD 3 (6) Controls</td>
<td>17 (35) ESRD</td>
<td>7 (14) ESRD 2 (4) Controls</td>
<td>China</td>
</tr>
<tr>
<td>Xiong(^{69})</td>
<td>131</td>
<td>ESKD, all COVID+</td>
<td>131 (100) HD</td>
<td>0</td>
<td>0</td>
<td>16/116 (13.8)</td>
<td>36 (28)</td>
<td>41 (31)</td>
<td>China</td>
</tr>
<tr>
<td>Yau(^{97})</td>
<td>330</td>
<td>237 HD patients, 93 HD staff, 22 COVID+</td>
<td>237 (100) HD</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>Toronto</td>
</tr>
</tbody>
</table>

ARDs, Acute Respiratory Distress Syndrome; MV, mechanical ventilation; CRRT, Continues Renal Replacement Therapy; HD, Hemodialysis; PD, Peritoneal Dialysis. Of studies that reported data on ESKD and non-ESKD, only values for ESKD patients are included.
Figures and Legends

Figure 1. Differences in Acute Kidney Injury (AKI), renal replacement therapy (RRT), and comorbidities in patients with COVID-19 in the United States (U.S.) and in China. Percentages calculated as proportion of COVID-19 positive individuals in each study, with data from China shown in red and data from the U.S. shown in blue. (A) Incidence of AKI in patients with COVID-19 (blue for the U.S. and red for China), with percentage of AKI patients requiring RRT depicted in light blue for the U.S. and light red for China. Prevalence of underlying (B) Chronic Kidney Disease (CKD), (C) Hypertension, and (D) Diabetes Mellitus in patients with COVID-19. This figure does not include data from cohorts that only reported patients admitted to intensive care units. AKI, Acute kidney injury; CKD, Chronic kidney disease; HTN, Hypertension; DM, Diabetes Mellitus.

Figure 2. Special challenges and strategies for renal replacement therapy (RRT) delivery in patients with COVID-19. Various challenges noted in the delivery of RRT and solutions that have been implemented and suggested are depicted. CRRT, continuous renal replacement therapy; SLD, sustained low efficiency dialysis; HD, hemodialysis; ICU, intensive care unit.

Figure 3. Potential mechanisms of COVID-19-related kidney injury. Diagram showing possible mechanisms of kidney injury in the setting of infection with SARS-CoV-2. ATN, acute tubular necrosis; AIN, Acute interstitial nephritis.
Figure 1.
Figure 2.

- **Limited PPE**: Isolate COVID-19 only HD Shifts, Open CRRT units in ICUs, Utilize CRRT vs. intermittent HD, Train non-HD nurses to assist with HD, Ultrafilter using presser support.

- **Limited Staff**: Limited Staff.

- **Limited Resources**: Shorter and less frequent HD, Decrease dose of CRRT once stable, Rapid start acute PD for AKI.

- **ARDS**: ARDS.

- **Clothing**: Use CRRT or SLD vs. HD, Place CRRT machine outside of room, Place right internal jugular catheter, Regional citrate + systemic heparin as needed.

- **Safety of Staff**: Limited Staff.
Figure 3.