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# COVID-19 in Kidney Transplantation: Epidemiology, Management Considerations, and the Impact on Kidney Transplant Practice

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**Abstract.** The novel severe acute respiratory syndrome coronavirus 2 was identified in the late 2019 as the cause of coronavirus disease 2019 (COVID-19), an acute respiratory viral illness. Patients with chronic underlying conditions may have an increased risk of morbidity and mortality from COVID-19. Kidney transplant recipients may be at a uniquely increased risk of serious complications from COVID-19 as compared to the general population because of a chronically immunosuppressed state and a high prevalence of comorbidities like diabetes, heart disease, and lung disease. Early data suggest that the mortality of patients on dialysis may be comparable to those with kidney transplants, although more research is needed. This concise review aims to describe the epidemiology of COVID-19 in kidney transplant recipients, manifestations, appropriate management, and clinical outcomes based on the available literature. Current evidence on many of the specific antiviral measures against COVID-19 has not shown a clear-cut benefit in smaller studies and the results of several ongoing larger clinical trials are awaited. In addition, we also highlight the impact of COVID-19 on kidney transplant center practice and volumes; potential living or deceased donors, recipients; and induction immunosuppression and surgical strategies.

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The novel coronavirus [severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)] was first identified toward the end of 2019 in Wuhan, Hubei province of China as the cause of a new viral respiratory illness, designated as coronavirus disease 2019 (COVID-19).<sup>1</sup> Despite the worldwide effort to contain COVID-19, new cases were identified all over the world by January 2020 and the World Health Organization designated COVID-19 as a pandemic in March

2020.<sup>2</sup> As of May 12, 2020, there were a total of 4.2 million cases worldwide and 289932 deaths were attributed to COVID-19.<sup>3</sup> The morbidity and mortality from COVID-19 are particularly high among patients with underlying health conditions and chronic diseases.<sup>1,4</sup> Solid organ transplant (SOT) patients including kidney transplant recipients (KTRs) are at a uniquely increased risk of serious complications from COVID-19 because of immunosuppressive (IS) medication use, elderly age (>65 y), and preexisting comorbidities like diabetes, hypertension, and cardiovascular diseases.<sup>5-7</sup> Current literature is sparse on the outcomes and appropriate management of COVID-19 in KTR. The aim of this review is to describe the epidemiology of COVID-19 in KTR, manifestations, appropriate management, outcomes, and its impact on kidney transplant surgery and programmatic modifications based upon the review of the currently available literature.

## Epidemiology in Kidney Transplant Patients

COVID-19 has shown widespread community spread across most countries.<sup>8</sup> The exact prevalence of infection in the general population is unknown since the pandemic is ongoing; however, a case fatality rate of 2%–4% has been described.<sup>9</sup> There is limited literature on the prevalence of COVID-19 in patients with end-stage kidney disease (ESKD) and how it compares to KTR.<sup>10,11</sup> In 1 Chinese retrospective study among ESKD patients, the prevalence of COVID-19 was 2.1%.<sup>12</sup> In another study from Italy, 15% (94/643) patients on maintenance dialysis were diagnosed with COVID-19.<sup>13</sup> In a large study from New York, United States SOT recipients

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comprised 1% of all hospitalized patients with COVID-19.<sup>4</sup> Although these data are not entirely comparable, they suggest that the incidence of COVID-19 in transplant patients is likely to be lower or at least similar to those on dialysis.

In recent studies from New York, the baseline demographic features of KTRs who had COVID-19 were similar to the nontransplant population.<sup>4,6,14</sup> The median age at presentation was 50–60 y and a majority had underlying comorbidities including hypertension (>90%) and diabetes mellitus (>30%). The median duration to disease onset since transplant in these studies was 49 and 76 mo, respectively.

The average incubation period in the general population was reported to be between 5 and 7 d.<sup>15</sup> The incubation period and reproduction number of COVID-19 in KTRs are not exactly known but may be similar to the general population. Contact tracing has identified confirmed exposure to a patient with COVID-19 in only 17% of KTRs in a study from New York.<sup>14</sup> However, in a study from the general population from Wuhan, China, 64% of disease clusters were described among family members.<sup>8,16</sup> Results in these 2 studies may be different because of different degrees of community spread in China and the United States. In addition, patient behavior (with regards to minimizing exposure to infected family members) may also impact these data. In the general population, viral replication typically begins 24–48 h before symptoms and peaks at 3–5 d after symptom onset.<sup>16,17</sup> It has been suggested that compared to the general population, viral shedding may be prolonged to up to 28 d in patients with kidney transplants.<sup>18</sup> Although it is not known whether this virus may be infectious or not, this has implications for patients with regards to return to work, for exposure to clinical environments, and to healthcare providers.<sup>19</sup>

## DIAGNOSIS

Reverse-transcription polymerase chain reaction (RT-PCR) assay of upper respiratory secretions usually collected with a nasopharyngeal swab is the current diagnostic test of choice for COVID-19 patients. This test is >99% specific, although sensitivity may vary by severity of disease, specimen type, and assay type.<sup>20,21</sup> False negatives of up to 30% have been reported although retesting on successive occasions may increase the positive yield.<sup>22,23</sup> In a study of 90 SOT recipients from New York, 8% patients had an initial negative upper respiratory RT-PCR result.<sup>5</sup> The yield of lower respiratory tract specimens has been shown to be higher and this is likely true for transplant patients also.<sup>20,24</sup>

Rapid tests using RT-PCR with point-of-care results for SARS-CoV-2 detection are also becoming available. Mobile platforms like Abbot ID NOW molecular point-of-care device typically run 1 sample at a time and are useful for bedside testing and to perform tests in remote areas. Facility-based platforms like Cepheid GeneXpert Xpress have higher throughput and yield results in less than an hour. In many cases, a presumptive diagnosis may have to be made based upon the clinical picture, characteristic laboratory and lung imaging findings.<sup>23</sup> Serologic IgM and IgG antibody testing is becoming widely available but the indications, validity, and reliability of these tests remain largely unknown. Most of the studies in general population suggest a rapid formation of IgM and/or IgG within a few days of COVID-19 infection, although there is no data to date to suggest that

seroconversion confers definitive immunity to future reinfection.<sup>17,25</sup> Nevertheless, the rates of reported reinfection rates remain extremely low.<sup>26</sup> In addition, emerging data suggest some efficacy for convalescent sera transfusions for patients with serious COVID-19 infections.<sup>27–31</sup> Data on seroconversion among immunosuppressed kidney transplant patients are not available at this time.

Laboratory findings have been generally similar in KTR and nontransplant population.<sup>4</sup> The white cell counts (median 4800–5300/mm<sup>3</sup>) and platelet counts were within normal limits.<sup>6,14</sup> However, a relative lymphopenia (median 600–800 lymphocytes/mm<sup>3</sup>) was more common. Serum ferritin (median 407–1230 ng/mL) and erythrocyte sedimentation rate (median 40 mm/h) were significantly elevated in these studies. The interleukin-6 (IL-6) level was only slightly elevated in these studies (median range 20–24 pg/mL), although it has been noted to be significantly elevated in a few patients.<sup>32</sup> Chest imaging showed variable findings that could include normal/mild focal infiltrates in 33% and diffuse patchy infiltrates in nearly half the patients.

## MANIFESTATIONS AND CLINICAL OUTCOMES

In the general population, COVID-19 could manifest with varying degrees of severity ranging from asymptomatic/mild self-limited infections (~80%) to all the way to severe (14%) and critical ventilator-dependent (5%) illness.<sup>1</sup> Similarly, KTRs with COVID-19 can have varying clinical manifestations and severity, ranging from mild or asymptomatic infections to multiorgan failure resulting in death.<sup>5–7,18,33</sup> The onset of symptoms has ranged widely from 1 d to 3 wk before the diagnosis. In 1 study on KTRs, fevers were noted to be less common (58%) compared with studies from the general population.<sup>6</sup>

Although the initial study by Zhu et al<sup>18</sup> from Wuhan in SOT recipients described disease severity according to the Chinese CDC classification, other disease severity classifications have been used by other authors (Table 1). In the study from New York by Pereira et al,<sup>5</sup> 44% of 46 KTRs had critical and 34 (54%) had mild to moderate disease.<sup>14</sup> On the other hand, in the Wuhan study, 8 of 10 KTRs (80%) had moderate–severe disease. In 2 separate studies from New York, 78% KTRs required hospitalization and 34% required ICU stay.<sup>6,14</sup> The median length of hospital stay has ranged from 4.5 d to a much longer duration in another study with 43% KTRs still hospitalized at a 3-wk period. In a newly published study from New York on the outpatient management of COVID-19, of 41 patients, 13 patients (32%) required hospitalization a median of 8 d (range, 1–16) after symptom onset, and 23 (56%) had outpatient symptom resolution a median of 12 d (4–23) after onset.<sup>34</sup>

Despite the heterogeneity of case descriptions, it does appear that the incidence of severe complications of COVID-19 may be higher in KTRs than the general population in various studies.<sup>5–7,18,33</sup> These complications may include acute respiratory distress syndrome (ARDS) requiring mechanical ventilation (27%–39% patients) and severe acute kidney injury that necessitated the initiation of dialysis (20%–40%). The median time to intubation was reported as 5 d posthospitalization in 1 study.<sup>14</sup> Other reported complications include rhabdomyolysis, myocarditis, bacterial superinfection, and atrial fibrillation.

**TABLE 1.**  
**Classification of COVID-19 severity used in various studies**

Classification	Features	Comments	
Chinese CDC classification <sup>96</sup>	Mild	Most commonly cited in the literature	
	Nonpneumonia or mild pneumonia		
Pereira et al <sup>5</sup>	Severe	Relies on center-specific practices	
	Dyspnea		
	Respiratory rate > 30/min		
	Blood oxygen saturation ≤ 93%		
	PaO <sub>2</sub> /FI <sub>o2</sub> ratio < 300		
	Lung infiltrates > 50% of lung fields within 24–48 h		
	Critical		
	Respiratory failure		
	Septic shock		
	Multiorgan dysfunction or failure		
WHO-China Joint Mission Classification <sup>97</sup>	Mild disease	Similar to Chinese CDC classification	
	Outpatient care only		
	Moderate disease		
	Admission to the general inpatient floor		
	Severe infection		
	Mechanical ventilation, admission to ICU or death		
	Mild		Mild–moderate severity distinction based upon imaging
	Clinical symptoms without manifestation of viral pneumonia on chest CT scans		
	Moderate		
	Symptoms such as fever and respiratory tract symptoms, etc., with manifestation of viral pneumonia on chest CT scans		
Severe			
Patients who met any of the following criteria:			
Respiratory rate > 30/min			
Blood oxygen saturation ≤ 93%			
PaO <sub>2</sub> /FI <sub>o2</sub> ratio < 300			
Lung infiltrates > 50% of lung fields within 24–48 h			
Critical			
Patients that met any of the following criteria: (1) occurrence of respiratory failure requiring mechanical ventilation; (2) shock; and/or; (3) other organ failure that requires monitoring and treatment in the intensive care unit			

COVID-19, coronavirus disease 19; CT, computed tomography; FI<sub>o2</sub>, fraction of inspired oxygen; PaO<sub>2</sub>, partial pressure of oxygen; WHO, World Health Organization.

### Renal Involvement

Early data from the general population suggest that COVID-19 may cause viral infection of different renal cells resulting in nephritis. SARS-CoV-2 uses the receptor angiotensin-converting enzyme 2 (ACE2) for cell entry; both endothelial cells and podocytes express ACE2. Glomerular changes and nephritis-like histology have been described in postmortem samples from patients with COVID-19.<sup>35</sup> A case series from the general population reported that >40% of cases had proteinuria on hospital admission.<sup>36</sup> Acute kidney injury (AKI) has also been reported to be common among critically ill patients with COVID-19, affecting approximately 20%–40% of patients admitted to intensive care.<sup>4</sup> In another study from China, 75% of hospitalized patients had abnormal urinalysis or AKI.<sup>37</sup> Although a majority of these patients had resolution of proteinuria (69%) and/or AKI (46%), renal involvement was associated with an increased mortality (11% versus 1% in those without renal involvement). Recent case reports have described collapsing glomerulopathy as well as thrombotic microangiopathy.<sup>38,39</sup>

The limited literature from kidney transplants suggests a similar or a higher incidence of AKI as well as proteinuria.<sup>7</sup> These data are limited by the absence of previous baseline parameters to clarify whether proteinuria was a new onset. Similarly, it is unclear whether the AKI is secondary to hemodynamic alterations or a direct infection by SARS-CoV-2. An interesting case report from a kidney transplant patient showed evidence of endothelialitis in the transplanted kidney.<sup>40</sup> It is unknown whether COVID-19 may be immunomodulatory and trigger acute rejection. It is, however, plausible that the cytokine release syndrome (CRS) associated with COVID-19 combined with a reduction in IS medications may predispose KTR to AR.<sup>41</sup>

### Outcomes

Various estimates of morbidity and mortality among KTR have been described in the literature. In general, outcomes seem to be worse than those described in the general population. Although adequate data are not available, early reports suggest that the mortality of COVID-19 may be

similar between dialysis-dependent ESKD patients and kidney transplant patients. Xiong et al<sup>12</sup> reported 33 (or 130; 23%) Chinese patients with ESKD had severe or critical disease and a significant proportion of the patients (43/130; 33%) died of complications.<sup>12</sup> Two other studies (1 each from Spain and Italy) also describe a mortality of 29%–30% among maintenance dialysis patients.<sup>13,42</sup> The 3 studies from New York in kidney transplant patients reported a mortality of between 16% and 30%.<sup>6,14,43</sup>

There are 2 ongoing registry studies that may further clarify the outcomes of kidney transplant patients with COVID-19. The first one is an international COVID-19 Solid Organ Transplant Registry ([www.C19TxR.org](http://www.C19TxR.org)).<sup>44</sup> As of May 20, 2020, a total of 592 SOT patients have been reported. A majority of these were reported from the United States and the United Kingdom. Of these 592, 530 (90%) were in kidney transplant patients. Among the 405 KTRs that had received treatment, 46 (15%) have recovered and 58 (14%) died. Another registry study being organized by the University of Washington is actively collecting data. Although published data are not yet available, >300 kidney transplants with COVID-19 were reported to the registry to date.

## MANAGEMENT

### Specific Antiviral Measures

Specific antiviral or immunomodulatory agents against COVID-19 are being rapidly investigated and many are currently being used in approved or experimental settings in the general population. Although a detailed review of these agents is beyond the scope of this article, various agents with their proposed mechanisms of action are listed in Table 2. It should be noted that no single agent has proven to be successful and had reproducible results in long term trials. A summary of the published studies, IS alterations, and other interventions focusing only on kidney transplants is described in Table 3.

One of the first publicized agents against COVID-19, hydroxychloroquine (HCQ) with or without azithromycin, was investigated because of its potential direct antiviral and immune modulation properties.<sup>45</sup> Although a few studies with small sample sizes appeared to have promising results,<sup>46</sup> a randomized, controlled trial of 150 Chinese patients showed no significant difference in the 28-d negative conversion rate between treatment and the control groups.<sup>47</sup>

Tocilizumab, an IL-6 antagonist is being used in patients with COVID-19 in an effort to suppress the CRS.<sup>48</sup> In a single series of 21 patients with severe COVID-19 pneumonia without controls, a single dose of 400 mg tocilizumab showed promising results with faster resolution of fevers, hypoxia, and earlier extubation.<sup>49</sup> Several randomized controlled trials are currently being performed to investigate the role of IL-6 blockade in the treatment of COVID-19. Tocilizumab (and other IL-6 blockers) has been tried with variable success in KTRs with moderate-severe disease or in patients with high IL-6 levels.<sup>50</sup> Whether additional immunosuppression with IL-6 blockade would provide increased benefit in immunosuppressed KTRs is controversial and a subject of ongoing research. It is contraindicated in patients with a suspected or proven coinfection with bacterial or fungal agents and it should be individualized in KTRs in which benefits outweigh the risks.

Remdesivir, a RNA polymerase inhibitor, is also being intensely investigated.<sup>51</sup> Early data from studies in the general population suggest that it may be beneficial in patients with mild–moderate disease, but the data for those with severe or critical disease are less clear.<sup>52–54</sup> There is no data on a possible drug interaction between Remdesivir and calcineurin inhibitor (CNI), making this an attractive choice, although access to the drug is currently limited and there is lack of safety data for patients with a poor kidney function (glomerular filtration rate < 30 mL/min/1.73 m<sup>2</sup>).<sup>55</sup>

In KTRs, other specific antiviral medications have been used with variable success rates in several case series and reports from China and Europe. Several papers reported the use of the protease inhibitor combination of Lopinavir and Ritonavir.<sup>33,56,57</sup> In addition to an unlikely efficacy, their interaction with CNI metabolism suggests that this combination should not be used for the treatment of COVID-19 in KTRs.<sup>58</sup> Additionally, there is no proven benefit (and potential harm) of other agents such as intravenous immunoglobulin, interferon, HCQ, and azithromycin in KTRs except in anecdotal cases and their routine use is not recommended.<sup>59</sup>

Very early data from the general population suggest some efficacy for convalescent sera transfusions for patients with serious COVID-19 infections, although no such data are available yet for KTRs or other immunosuppressed patients.<sup>27–31</sup>

### Maintenance Immunosuppression Management

The management of IS agents in KTRs is complex because the appropriate choice or optimal dosing of individual agents remains mostly unclear. Transplant clinicians have generally extrapolated the evidence in managing other life-threatening infections in KTRs to COVID-19, which involves a reduction of overall IS.<sup>60</sup>

The primary aim of IS management in SOT recipients is a balance between the risk of rejection and complications of overimmunosuppression, such as worsening of COVID-19 complications and superinfections. KTRs with COVID-19 should have their IS management reduced based on factors such as age, time since transplant, sensitization level, previous rejection episodes, and the severity of COVID-19. It has been hypothesized that CNIs can lead to immune modulation against the virus and thus may be beneficial in reducing the cytokine release storm that is frequently seen with COVID-19.<sup>61</sup> Thus, cautious reduction rather than complete elimination of immunosuppression may avoid precipitation of severe complications like ARDS. This, however, remains to be proven in clinical studies.

Here, we propose an algorithm based upon our own experience as well as from published studies.<sup>5,7,33,43,62–64</sup> Patients with mild COVID-19 (minimal or no supplemental O<sub>2</sub> requirement) may benefit from reduction in their target CNI trough concentration to ~75% of their previous goal. In addition, reduction of other agents such as antimetabolites (mycophenolate or azathioprine) by 50% should be considered. Those with moderate–severe disease may benefit from further reduction in IS with target CNI trough goals to ~25%–50% and temporary cessation of their antimetabolites. Steroid dosage ideally should be left unchanged in patients with mild–moderate disease. In those with critical disease (ARDS or requiring mechanical ventilation), consideration may be given to intravenous methylprednisolone or hydrocortisone in an attempt to suppress CRS, although there is inadequate evidence to

**TABLE 2.**  
**COVID-19 pharmacotherapy and immunotherapy considerations**

Agent	Mechanism of action
Drugs with in vivo human data	
Remdesivir	Interference with viral RNA-dependent RNA polymerase; premature termination of viral RNA transcription.
IL-6-specific antibodies	Competitively inhibit IL-6 or IL-6 receptor thereby inhibiting signal transduction involved in cytokine release syndrome
Corticosteroids	Glucocorticoid receptor interactions with transcription factors, especially activator protein 1 and NF- $\kappa$ B <sup>98</sup>
Hydroxychloroquine/chloroquine	Reduces cytokine production, especially IL-1 and IL-6; intracellular alkalization inhibits pH-dependent steps of viral replication as well as viral receptor glycosylation
Azithromycin	Antiviral mechanism is largely unknown
ACE/ARB	Potentially may mitigate ACE2 downregulation caused by viral binding to the enzyme
Lopinavir/ritonavir	May inhibit chymotrypsin-like protease (3CLpro)
Favipiravir	Nucleoside analog prodrug, RdRP inhibitor
Eculizumab	Inhibits cleavage to C5a and C5b and prevents the generation of the terminal complement complex C5b-9, which is involved in cell lysis
Plasma	Hosts development of pathogen-specific antibodies allowing for immune-mediated neutralization and clearance of pathogen
Systemic anticoagulation	May mitigate the inflammatory response and subsequent hemostatic abnormalities such as venous thromboembolism, myocardial infarction, and disseminated intravascular coagulation
In vitro data, animal data, and hypothetical treatments	
Ivermectin	Wide antiviral activity by nuclear transport inhibition
Ribavirin	Direct antiviral activity via inhibition of RNA polymerase chain termination, inhibition of RNA capping activity, and lethal mutagenesis of RNA genome
Nitazoxanide	Interferes with pyruvate ferredoxin oxidoreductase enzyme-dependent electron transfer reaction, which is essential to anaerobic metabolism
Zinc	May reduce RNA synthesis catalyzed by an RdRP
Interferon	May bind to specific plasma membrane receptors and activate JAK-STAT signaling pathway
Doxycycline	Anti-inflammatory via inhibitory action on metalloproteases and modulating effects of proinflammatory cytokines IL-6, IL-8, and tumor necrosis factor-alpha.
Anakinra	Blocks biological activity of IL-1 $\alpha$ and IL-1 $\beta$

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; COVID-19, coronavirus disease 2019; IL, interleukin; RdRP, RNA-dependent RNA polymerase.

support this practice.<sup>6,50</sup> Patients who have a rapid clinical deterioration to ARDS or septic shock may need withdrawal of all immunosuppression, especially if they are coinfecting with other organisms and/or stress dose steroids are being concomitantly administered.<sup>4,12</sup> Patients on maintenance belatacept may need to have their monthly dose held especially if they have moderate or severe disease. Therapy could generally be resumed on their previous monthly schedule once they are symptom free. For patients that have recovered, it remains unknown whether and when the CNI and antimetabolite dose should be reincreased back to baseline. Extrapolation from the management of other infections suggests that it should be reasonable to cautiously reinstitute the preinfection IS regimen once the patients starts improving clinically.

### Renin-Angiotensin-Aldosterone System Inhibitors

SARS-CoV-2 enters human cells by binding of its viral spike protein to the membrane-bound form of the monocarboxypeptidase ACE2.<sup>65</sup> Studies in animals have suggested that ACE inhibitors and angiotensin-receptor blockers (ARBs) may upregulate ACE2 expression, thus increasing the availability of target molecules for SARS-CoV-2.<sup>66</sup> These considerations led to speculation that ACE inhibitors and ARBs might be harmful in patients with COVID-19.<sup>67</sup> Despite this, there are now evolving data to suggest that this may not be true and in fact there may be some benefit to RAAS blockade.<sup>68</sup> Thus, stopping RAAS blockade in patients with COVID-19 cannot be recommended.

### Anticoagulation and Complement Blockade

Thrombophilia has been commonly associated with COVID-19 and various postmortem studies have shown the presence of macrothrombi and microthrombi in both venous and arterial systems.<sup>69</sup> Critically ill COVID-19 patients have been reported to have significant elevation in D-dimer levels and a very high risk of deep venous and pulmonary thromboembolism of up to 30%.<sup>70</sup> Various approaches to the prevention of thromboses ranging from prophylactic to therapeutic anticoagulant strategies are being employed and are described elsewhere.<sup>71,72</sup> At this time, there is no evidence to suggest that kidney transplant patients are at an increased risk of thrombotic events compared with the general population for disease of similar severity. Thus, we recommend standard prophylactic anticoagulation with low-molecular heparin (adjusted for renal function) or unfractionated heparin for hospitalized KTR with no active thromboses. Some authors describe the use of direct thrombin inhibitors among patients with severe disease and D-dimer >3  $\mu$ g/mL.<sup>5</sup>

Complement is an integral component of the innate immune response to viruses and an instigator of proinflammatory responses.<sup>73</sup> A recent study of SARS-CoV, which is closely related to SARS-CoV-2, found that activation of complement component C3 exacerbates disease in SARS-CoV-associated ARDS.<sup>74</sup> Although there are numerous pathways for renal injury due to coronavirus, complement activation may play a significant role. Case reports describing renal endothelialitis and thrombotic microangiopathy support this association.<sup>38,40</sup> Currently, there are no published data on the effect of complement inhibitors, but there are several ongoing clinical trials that may shed some light on the topic.<sup>75</sup>

**TABLE 3.****Summary of kidney transplant studies: immunosuppressive changes, antiviral agents, and outcomes**

Author	sample size	Country of origin	Change in immunosuppression	Antiviral treatment	Immunomodulatory therapy <sup>a</sup>	Outcomes
Pereira et al <sup>5a</sup>	46 <sup>b</sup>	New York City, USA	Hospitalized patients (75%) CNI dose decreased or held (18%) Antimetabolite reduction or held (87%) Corticosteroids decreased or held (7%)	Azithromycin (66%) HCQ (91%) Remdesivir (3%)	Bolus steroids (23%) Tocilizumab (20%)	Hospital admissions (75%) ICU admission (34%) Mortality (27%) Discharged from the hospital (54%) Hospital readmissions (1%)
Alberici et al <sup>99</sup>	20	Brescia, Italy	Complete withdrawal of CNIs and antimetabolites. All patients received methylprednisolone 16 mg daily or prednisone equivalent	HCQ (95%) Lopitavir/ritonavir (79%) Darunavir plus ritonavir (21%)	Dexamethasone (55%) Tocilizumab (30%)	Hospital admissions (100%) ICU admission (20%) Treated on general ward (60%) Mortality (20%) Discharged from the hospital (15%)
Akalin et al <sup>6</sup>	36	New York City, USA	Withdrawal of antimetabolites (67%) Withdrawal of tacrolimus (17%)	HCQ (67%) Azithro (36%)	Leronlimab (CCR5 antagonist; 17%) Tocilizumab (5%) High-dose glucocorticoids (5%)	Hospital admissions (78%) Intubation required (30%) Mortality (28%) Mortality after intubation (7/11; 67%) Renal replacement therapy (17%) Remained hospitalized (12/28; 43%)
The Columbia University Kidney Transplant Program <sup>14</sup>	15	New York City, USA	Antimetabolite discontinuation (71%) Prednisone decreased (10%) Belatacept infusion postponed (1/2; 50%) Discontinued all immunosuppression (13%) No change in immunosuppression (7%) Replaced tacrolimus and MMF with prednisone (7%)	HCQ without Azithro (27%) HCQ plus Azithro (60%)	Tocilizumab (7%)	Hospital admissions (100%) Intubation required (27%) Mortality (14%) Discharged from the hospital (53%)
Nair et al <sup>43</sup>	10	New York City, USA	MMF discontinuation (89%) Discontinue tacrolimus (9%) Discontinue sirolimus (1/1) No changes (10%)	HCQ plus Azithro (90%)	None reported	Hospital admissions (100%) ICU admission (30%) Mortality (30%) Discharged from the hospital (70%)
Fernandez-Ruiz <sup>33</sup>	8	Madrid, Spain	MMF discontinuation (4/5; 80%) Reduction in tacrolimus (6/7; 86%) Discontinuation of prednisone (2/8; 25%)	Lopinavir/ritonavir plus HCQ (100%)	Methylprednisolone (38%) Intravenous immune globulin (38%) Tocilizumab (12%)	Hospital admissions (100%) Mortality (25%) Discharge from the hospital (25%)
Banerjee et al <sup>7</sup>	7	London, UK	Reducing tacrolimus dose, stopping MMF	None reported	None reported	Hospital admissions (71%) ICU admissions (28%) Intubation required (28%) Mortality (14%) Managed on general ward (28%) Managed outpatient (28%)
Kates et al <sup>88</sup>	1	Wisconsin, USA	Reduced tacrolimus dose, MMF stopped, prednisone 10 mg daily started	HCQ + Azithro	None	Hospitalized and discharged from the hospital
Zhong et al <sup>62</sup>	1	Wuhan, China	Discontinued MMF	Oseltamivir	Intravenous immune globulin Methylprednisolone Recombinant interferon alpha	Hospitalized, discharged home and symptoms resolved
Meziyerh et al <sup>63</sup>	1	Leiden, Netherlands	Everolimus and pred continued	Lopinavir/ritonavir plus HCQ	None	Hospitalized and discharged from the hospital
Marx et al <sup>64</sup>	1	Strasbourg, France	MMF discontinuation, belatacept held and switched to cyclosporine, prednisone continued	None reported	None reported	Hospitalized and discharged from the hospital

<sup>a</sup>Data only on hospitalized patients.<sup>b</sup>Study included non-kidney transplant recipients. Sample size is kidney transplant recipients only, but therapies and outcomes reported includes overall cohort of all solid organ transplant recipients. Azithro, azithromycin; CNI, calcineurin inhibitor; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil.

### Augmentation of Immune System, Specific immunotherapy, and Adoptive Immune therapy

Although a functional immune system is essential for combating infection, the role of augmenting the immune response is still unclear. Several vitamins, nutrients, and cofactors are thought to improve immune function. For example, zinc-deficient patients may be at an increased risk of viral infections.<sup>76</sup> It seems reasonable to test for deficiencies and provide supplementation to those patients, but there are no data on safety and efficacy of these approaches.

Specific immune therapies such as the use of convalescent plasma have been met with early success,<sup>77</sup> and larger studies are underway.<sup>78,79</sup> Other directions in future therapeutics include the use of monoclonal antibodies against the viral spike protein<sup>80</sup> and adoptive T cell therapy. Adoptive T cells with a chimeric antigen receptor or a T-cell receptor have been successfully developed against other viruses like Epstein barr virus<sup>81</sup> and severe acute respiratory syndrome coronavirus-1.<sup>82</sup> Use of adoptive T cell therapy may be particularly helpful in SOT recipients with COVID-19 in reducing the risk

of serious complications and are in the developmental stage (<https://www.fiercebitech.com/research/scientists-explore-using-engineered-t-cells-to-target-covid-19>).

### Future Trials and Vaccines

The race for a successful vaccine has been going on for several months now, and several candidate vaccines ranging from mRNA to DNA vaccines and from injectables to tablets are in initial planning or early testing phases.<sup>83</sup> Historically, vaccine deployment is delayed in the immunocompromised because of concerns of safety and efficacy and this remains an area of active concern in protecting KTRs from COVID-19. Similarly, there is a lack of planned interventional clinical trials focused on transplant patients. A review of the US and European clinical trial databases ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) and <https://eudract.ema.europa.eu>) reveals only 10 listed studies, all of which are observational in design. Some of these key studies are listed in Table 4.

### Impact on Induction Immunosuppression Strategies

COVID-19 patients have been reported to develop profound lymphopenia. Akalin et al<sup>6</sup> reported infected KTRs had

**TABLE 4.**

#### List of ongoing clinical studies on COVID-19 among transplants

Study features	Intervention and primary outcome (s)	Current status
Blood innate biomarkers (IL-6) as predictors of COVID-19 disease progression in recently infected KTRs  ClinicalTrials.gov Identifier: NCT04369456 N = 115, single intervention arm Multicentric	Intervention: quantity of IL-6 in of whole blood samples after ex vivo costimulation with lipopolysaccharide and adenosine triphosphate in COVID-19 kidney transplant patients  Outcome: clinical outcomes	Recruiting
AlloSure guided immuno-optimization for COVID-19: an early experience  ClinicalTrials.gov Identifier: NCT04341103 N = 500, observational Multicentric	Patients with solid organ transplants who have been admitted with suspected COVID-19 utilizing AlloSure donor derived cell-free DNA to help guide immunosuppression management balancing the treatment of sepsis and avoiding allograft rejection	Not yet recruiting
A prospective noninterventional study to evaluate the role of immune and inflammatory response in recipients of allogeneic hematopoietic stem cell transplantation (SCT) affected by severe COVID-19 infection  ClinicalTrials.gov Identifier: NCT04349540 N = 40, observational, single-center	Comparison of inflammatory/immunological biomarkers <72 h after development of oxygen requirement  Compliance precautions with COVID-19 and clinical outcomes	Active, not recruiting
Assessment of the impact of COVID-19 on transplant patients and on patients awaiting transplantation  ClinicalTrials.gov Identifier: NCT04376775 N = 2000, observational, multicentric	Surveys to be distributed to patients awaiting transplantation	Recruiting
COVID-19 in liver transplant recipients in Spain: a nationwide prospective study  ClinicalTrials.gov Identifier: NCT04361591 N = 400, observational, multicentric	Incidence, clinical characteristics, and outcomes in liver transplant patients	
Development and persistence of humoral immunity against SARS-CoV2 in liver transplanted patients in comparison with immunocompetent patients  ClinicalTrials.gov Identifier: NCT04410471 N = 300, observational	Incidence, titration, and evolution of IgG an IgM in a prospective cohort of liver transplant patients surviving to the first wave of COVID-19, in comparison to not immunosuppressed patients	Recruiting
COVID-19 research in organ transplant recipients  ClinicalTrials.gov Identifier: NCT04407221 N = 1100, observational	Clinical, immunological response, and seroconversion kinetics for COVID	Not yet recruiting
Consequences of the COVID-19 pandemic on worldwide organ procurement and transplantation  ClinicalTrials.gov Identifier: NCT04416256 N = Observational 230 000	Organ transplantation activity during COVID	Recruiting

COVID-19, coronavirus disease 2019; IL-6, interleukin 6; KTR, kidney transplant recipient; SARS-CoV2, severe acute respiratory system coronavirus 2; SCT, stem cell transplantation.

lower CD3, CD4, and CD8 cell counts and more rapid clinical progression than persons with COVID-19 in the general population. It is unclear if the increased mortality in KTRs noted in this study (as opposed to the general population) was due to the overall frailty of the transplant patients or due to the impact of IS drugs, for example, the use of T-cell depleting induction agents that are the standard of care in a majority of the US kidney transplant centers. Although no definite recommendations can be provided, in case induction immunosuppression is indicated, it seems reasonable to consider non-T-cell depleting agents (basiliximab or other IL2 receptor antagonists), especially in low immunologic risk kidney transplant patients wherein the risk of acute rejection is lower and the risk of COVID-19 is significant based upon population characteristics.

### IMPACT OF COVID-19 ON KIDNEY TRANSPLANT CENTER VOLUME

After the COVID-19 outbreak, a significant decline (25%–90% reduction) in both deceased donor and living donor kidney transplants was reported by several hyper endemic countries including Italy, France, and the United States.<sup>84–86</sup> Surprisingly, a reduction in transplantation rates was noted even in regions where COVID-19 cases are low, suggesting a global and nationwide effect beyond the local COVID-19 infection prevalence. Many transplant programs reported using a staged approach to transplant volume considerations with suspension of living donor surgeries and limitation of deceased donor transplants because of the risk of transmission to procuring teams, kidney donors, and kidney recipients.<sup>87</sup> Transplant professionals will continue to need to adapt to these rapidly changing circumstances, and remain poised to reinvigorate transplant infrastructure to avoid losing opportunities to transplant valuable deceased donor organs.

### RISKS OF DONOR TRANSMISSION TO RECIPIENTS AND SURGICAL TEAMS

At this time, there are no confirmed reports of transmission of SARS-CoV-2 from a live or deceased donor to the recipient.<sup>88</sup> Theoretically, viral transmission could happen via donor blood or the organ itself. Limited data have shown that viral RNA could be detected in plasma or serum from COVID-19 patients. In the first 41 patients in the city of Wuhan, viremia was found only in 6 of 41 (15%) patients.<sup>89</sup> The following points may be relevant to considerations regarding organ transplantation: (1) viral RNA in plasma or serum could be detected in COVID-19 patients on the first 2 or 3 d after the onset of symptoms; (2) most patients, especially younger adults who can donate organs, had milder symptoms than the older adults; and (3) the rate of infectivity of patients who are in the incubation period remains uncertain, and there are no data on the viral load in plasma, serum, or lymphocytes among individuals in the incubation period. Despite this, there are no reported cases of transfusion transmission of SARS-CoV-2 to date. Nevertheless, COVID-19 testing for all asymptomatic live kidney and most deceased donors before transplantation is currently being recommended, especially when the turnaround time is reasonable.<sup>90</sup> However, its impact on organ utilization rates and actual transmission is unknown owing to the presence of false negatives. The use of chest computerized

tomography scans on deceased donors who test PCR negative should be based on individual donor's history and the level of community spread.

The virus has been isolated in the kidney and urine of some COVID-19 patients, and thus, the use of deceased organs with diagnosed COVID-19 patients remains controversial.<sup>91,92</sup> Of particular relevance are laparoscopic living donor procurements and transplant surgeries. It has been theorized that the pneumoperitoneum induced during a laparoscopic procedure may increase the risk of aerosolization of COVID-19.<sup>93</sup> Thus, routine testing for COVID-19 with nasopharyngeal swabs before all elective surgeries is rapidly becoming the norm in many hyperendemic areas.

### CONCLUSIONS AND THE FUTURE

Various transplant organizations have published best practice guidelines to guide transplant programs during the pandemic and to minimize the spread of COVID-19 to living donors, recipients, and the treating providers.<sup>87,94</sup> Transplant programs will need to individualize their approaches in navigating through individual aspects of transplant operations by prioritizing patients requiring urgent transplantation, carefully selecting which organ offers to accept (local donors, avoiding long travel of the procuring team, and minimizing delayed graft function to reduce the recipient's hospital stay), enhancing tele-visits for stable outpatients,<sup>95</sup> establishing careful triage systems, and balancing the risk of excessive immunosuppression against allograft rejection. The COVID-19 pandemic has resulted in unprecedented challenges that include unclear efficacy of current investigational therapies in transplant populations, lack of data driven optimal immunosuppression management, historic delay in vaccine deployment for immunocompromised hosts related to safety or efficacy, and ethical dilemmas in organ allocation and health-care resource constraints.

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