

# Coronavirus-19 infection in kidney transplant recipients: A comprehensive review

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## ABSTRACT

The COVID-19 pandemic has disrupted health care across the globe. Since the beginning of the pandemic, there have been substantial changes in the approach toward kidney transplantation and management of the virus in transplant recipients. Chronic immunosuppression and comorbidities in renal transplant recipients place them at risk during the pandemic. Data on the risk factors, presentation, and management of kidney transplant patients have become more robust over time. Relevant data on this topic was procured and synthesized with the aid of a comprehensive Medline search on all published studies that investigated COVID-19 infection in kidney transplant recipients. This comprehensive review summarizes the current literature on the epidemiology, clinical features, complications, graft outcomes, and current management of COVID-19 infection in kidney transplant recipients. We further summarize published literature on immunization in kidney transplant recipients.

## INTRODUCTION

In December 2019, the Municipal Health Commission in Wuhan, China, reported its first cases of a viral pneumonia that would later be attributed to severe acute respiratory syndrome-coronavirus2 (SARS-CoV-2).<sup>[1]</sup> Since the virus has reached global pandemic proportions, with recurrent waves of increasing cases owing to new variants of the virus.<sup>[2]</sup> Many organ transplant centers around the world initially stopped doing transplants due to a variety of risks, including but not limited to the risk of transmission to healthy living donors, concern for donor-to-recipient transmission, and limited available COVID testing.<sup>[3]</sup> Since the first case report of COVID-19 in a kidney transplant patient in China was published in March 2020, researchers have been working to gather, analyze, and share knowledge.

## METHODOLOGY

A literature search was performed using PubMed databases to identify relevant English language articles

published from December 2019 to July 2021. Search terms included COVID-19, coronavirus, SARS coronavirus 2, 2019-nCoV, SARS-CoV-2, SARS-CoV, and transplantation. We divided our referenced studies into three categories: case reports consisting of one patient, small-to-medium-sized cohorts consisting of under 100 patients, and large, usually multicenter, cohorts consisting of over 100 patients. We focused on compiling demographic information, risk factors, and clinical outcomes from patients worldwide.

## POPULATION OVERVIEW

The proportion of confirmed COVID-19 (with reverse transcription-polymerase chain reaction testing via nasopharyngeal swab) among kidney transplant patients has been reported to be from 1.42 to 16% among multicenter cohort studies.<sup>[4-8]</sup> Table 1 describes the patient characteristics of the reviewed studies. The cohorts were mostly males in their 50s–60s. The most common patient comorbidity was

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Type of Study	Patient characteristics			Reported patient comorbidities				
	Sex (male)	Age (years, median, (IQR))	HTN	DM	Obesity	Heart Dx	Lung Dx	
Case reports (52), n (%)	67%	49 (36-56.5)	40%	16%	8%	12%	6%	
Medium-sized (63), n (%)	64% (56-75)	53.9 (47.6-58)	73% (60-91)	30% (21-40)	30% (19-43)	20% (9-35)	11% (4-19)	
Multi-center (15), n (%)	65.4% (62-67)	60 (57.4-51.4)	86% (83-91)	33% (31-46)	27% (23-56)	26% (21-29)	11% (7-15)	

  

Type of Study	Transplant age			Symptoms on presentation			
	(Months, median, (IQR))	Fever	Dyspnea	Cough	Myalgia	N/V	Diarrhea
Case reports (52), n (%)	48 (15-112.5)	75%	40%	48%	12%	12%	23%
Medium-sized (63), n (%)	66 (42.5-89.5)	76% (63-92)	50% (35-68)	62% (50-75)	37% (25-50)	15% (7-21)	27% (18-43)
Multi-center (15), n (%)	72 (59.75-75.75)	75% (70-80)	40% (38-45)	67% (65-68)	29% (27-33)	16% (13-18)	34% (31-38)

DM = Diabetes mellitus, HTN = Hypertension, IQR = Interquartile range, N/V = Nausea/vomiting

reported to be hypertension, consistent across case reports, medium-sized studies, and multicenter cohorts. Diabetes and obesity were also commonly reported comorbidities. These patient characteristics are similar to those in the general population, which are mostly male,<sup>[9,10]</sup> advanced in age and with hypertension, obesity, and diabetes as common comorbidities.<sup>[11,12]</sup> The age of transplant at the time of COVID-19 infection or median transplant vintage was 48, 66, and 72 months among case studies, medium-sized studies, and multicenter cohorts, respectively.

## CLINICAL PRESENTATION

Patients in the general population most commonly present with fever, followed by cough, dyspnea, and myalgia or fatigue.<sup>[1]</sup> Similar patterns of presentation were seen in the kidney transplant recipient population, described in Table 2. It appears that among kidney transplant patients with COVID-19, patients also frequently complain of diarrhea and other gastrointestinal symptoms on presentation; 23%, 27%, and 35% of patients reported with diarrhea among case reports, medium-sized reports, and multicenter cohorts, respectively. This presentation could be influenced by the usage of mycophenolate mofetil (MMF), a frequently prescribed immunosuppressant with a known side effect of diarrhea. Diarrhea in the general population has been reported to be a presenting symptom in between 3 and 10.4% of patients among more recent meta-analyses.<sup>[1,9,13]</sup>

## DISEASE COURSE AND CLINICAL OUTCOMES

In the kidney transplant population, considerable proportions of those who had contracted SARS-CoV-2 developed an acute kidney injury (AKI). Among 52 case reports reviewed, 63% of patients had been diagnosed with an AKI during their hospitalization. Among medium-sized and multicenter cohorts, the median proportion of patients who had developed an AKI was 51% and 44%, respectively. This is in stark comparison to renal manifestations in the general population, of which studies have reported 0.5%–7% of COVID-19 cases developing an AKI.<sup>[1,14,15]</sup> This highlights our population's increased vulnerability to kidney insult.

Among medium-sized and multicenter cohort studies, median of 20% and 21% of kidney transplant patients with COVID-19, respectively, succumbed to the disease. Rates of intensive care unit admission among kidney transplant patients were noted to be 21%–27%. Table 2 describes the disease course and clinical outcomes for kidney transplant patients with SARS-CoV-2 infection.

There are four reported cases of graft loss and two cases of *de novo* chronic antibody-mediated allograft rejection following SARS-CoV-2 infection among kidney transplant patients.<sup>[16-19]</sup> Of the four graft losses, two had a history of graft rejection prior to COVID-19 and a decreased baseline

**Table 2: Clinical outcomes in kidney transplant recipients infected with COVID-19**

Type of Study	Clinical outcomes				
	AKI	ICU admission	Intubation	Loss of allograft	Mortality
Case reports (52)	63%	27%	17%	8%	10%
Medium-sized (63), <i>n</i> (%)	51% (34-60)	26% (14-46)	20% (7-29)	0% (0-5)	20% (12-31)
Multi-center (15), <i>n</i> (%)	44% (29-47)	21% (18-23)	18% (14-25)	4% (3-5)	21% (14-23)

AKI=Acute kidney injury, ICU=Intensive care unit

**Table 3: Immunosuppression modifications and COVID-19 treatment**

Type of Study	Withdrawal MPA/MMF	Withdrawal CNI	Withdrawal mTORi	Hydroxy chloroquine	Azithromycin	Tocilizumab	Antivirals (lopinavir/ritonavir)	Increased dose of steroids
Case reports (52)	73%	33%	75%	40%	54%	17%	31%	54%
Medium-sized (63), <i>n</i> (%)	88% (63-100)	50% (24-71)	80% (50-100)	78% (38-99)	55% (40-85)	12% (4-39)	37% (12-84)	45% (20-93)
Multi-center (15), <i>n</i> (%)	74% (70-86)	23% (13-27)	62% (37-49)	73% (52-87)	58% (28-72)	13% (10-14)	16% (9-21)	46.5% (37.9-54.4)

CNI=Calcineurin inhibitors, MPA=Mycophenolic acid, MMF=Mycophenolate mofetil

**Table 4: Immune response to SARS-CoV-2 vaccination**

Reference	<i>n</i>	Percentage seronegative after 1 dose	Percentage seronegative after 2 doses
Husain <i>et al.</i> <sup>[48]</sup>	28	-	75
Benotmane <i>et al.</i> <sup>[45]</sup>	241	89	-
Benotmane <i>et al.</i> <sup>[49]</sup>	204	-	52
Chavarot <i>et al.</i> <sup>[46]</sup>	101	98	94
Yi <i>et al.</i> <sup>[47]</sup>	145	93.80	-
Rozen-Zvi <i>et al.</i> <sup>[50]</sup>	308	-	63.60

glomerular filtration rate. Further large volume studies may reveal if the graft outcomes in patients with graft dysfunction prior to COVID-19 are different from recipients with healthy graft function. *De novo* anti-donor-specific antibodies have been reported following SARS-CoV-2 infection.<sup>[20]</sup>

Predictors of mortality among kidney transplant patients with SARS-CoV-2 infection were generally similar to those of the general population. In factors specific to kidney transplant recipients, shorter span of time between transplant and COVID-19 infection, deceased donor transplant, diabetic etiology of end-stage renal disease, and previous antirejection therapy were associated with increased mortality.<sup>[6,21,22]</sup> Active cytomegalovirus coinfection and bacterial coinfections were also shown to complicate and worsen the prognoses of kidney transplant patients.<sup>[23]</sup>

## IMMUNOSUPPRESSION MODIFICATION AND OTHER TREATMENTS

Immunosuppression regimens for kidney transplant patients frequently consist of a combination of calcineurin inhibitors (CNIs), azathioprine, mycophenolic acid/MMF (MPA/MMF), mammalian target of rapamycin-inhibitors, prednisone, and belatacept.<sup>[24]</sup> The combination most frequently seen in case reports and cohort studies included tacrolimus, mycophenolate, and prednisolone. In the management of COVID-19 in kidney

transplant patients, MPA/MMF was discontinued in most cases due to its implications in suppressing the response of T-lymphocytes needed to mount an immune response to SARS-CoV-2.<sup>[25]</sup> Withdrawal of MPA/MMF was seen in 73% of case reports and a median of 88% and 74% in medium-sized and multicenter cohorts, respectively. The withdrawal of a CNI was reported in 33% of case studies, a median of 50% in medium-sized cohorts, and a median of 23% in multicenter cohorts. More frequently, it was found that in patients who received anti-COVID-19 therapeutics, the tacrolimus doses had to be adjusted due to drug-drug interaction.<sup>[26-28]</sup>

In the treatment of COVID-19 in kidney transplant patients, reports of use of tocilizumab,<sup>[29-37]</sup> remdesivir,<sup>[38]</sup> low-dose methylprednisolone,<sup>[39]</sup> convalescent plasma therapy,<sup>[40-42]</sup> colchicine,<sup>[43]</sup> and favipiravir have been published.<sup>[36,44]</sup> However, most of these positive outcomes were observed in either case studies or small cohorts, and the use of any of these treatments should be considered on a case-by-case basis. Table 3 describes the reported frequency of immunosuppression regimen modification and treatment attempts among kidney transplant patients with COVID-19.

In kidney transplant patients, there have been multiple reports of limited immune response to the SARS-CoV-2 vaccine. Investigators have reported 89%–98% of kidney transplant recipients are seronegative after their first dose,<sup>[45-47]</sup> and 52%–94% remain seronegative after their second dose.<sup>[46,48-50]</sup> Table 4 describes the articles that have been published investigating immunological responses in vaccinated kidney transplant patients.

The limitations of our study include our use of descriptive studies comprising varied cohorts, which do not enable us to make any statements on causation. Furthermore, we must consider that we lack results from the era of unavailable to limited testing during the pandemic. It is difficult to compare patient outcomes holistically, as many patients

who died may not have been tested, and only patients who were fit enough to go to access testing were included. Outcomes due to changes in immunosuppression regimens are largely unstudied and warrant investigation. Finally, our data is largely from the prevaccination era. Studies from the post-vaccination era are awaited.

## CONCLUSION

As COVID-19 and its underlying virus become more understood, our ability to better protect our kidney transplant patients grows. We must continue to contribute to the evolving literature and clinical guidelines available on the treatment of COVID-19.

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