ORIGINAL ARTICLE

COVID-19 in kidney transplant recipients

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There is minimal information on coronavirus disease 2019 (COVID-19) in immuno-compromised individuals. We have studied 10 patients treated at 12 adult care hospitals. Ten kidney transplant recipients tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by polymerase chain reaction, and 9 were admitted. The median age was 57 (interquartile range [IQR] 47-67), 60% were male, 40% Caucasian, and 30% Black/African American. Median time from transplant to COVID-19 testing was 2822 days (IQR 1272-4592). The most common symptom was fever, followed by cough, myalgia, chills, and fatigue. The most common chest X-ray and computed tomography abnormality was multifocal patchy opacities. Three patients had no abnormal findings. Leukopenia was seen in 20% of patients, and allograft function was stable in 50% of patients. Nine patients were on tacrolimus and a mycophenolic antimetabolite, and 70% were on prednisone. Hospitalized patients had their antimetabolite agent stopped. All hospitalized patients received hydroxychloroquine and azithromycin. Three patients died (30%), and 5 (50%) developed acute kidney injury. Kidney transplant recipients infected with COVID-19 should be monitored closely in the setting of lowered immunosuppression. Most individuals required hospitalization and presenting symptoms were similar to those of nontransplant individuals.

KEYWORDS
clinical research/practice, infection and infectious agents - viral, kidney (allograft) function/dysfunction, kidney transplantation/nephrology

1 | INTRODUCTION

Since December 2019, the novel coronavirus (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2) has spread out from a single city in Hubei, China to most of the world.[1] The World Health Organization (WHO) has classified the resulting disease, coronavirus disease 2019 (COVID-19), as a global pandemic. The recently published Chinese experience on COVID-19 has addressed clinical characteristics of the virus, including risk factors and prognosis, in the general population. However, there is little information on the infectious course of COVID-19 in immunocompromised individuals, including transplant recipients.

Given their diminished T cell immunity, transplant recipients are expected to be at higher risk for severe bacterial and viral infections. This would suggest that transplant recipients are at higher risk for infection and mortality from COVID-19. There have, however, been very few reports published on COVID-19 in transplant recipients. A case report described a COVID-19–infected kidney transplant recipient who presented with gastrointestinal (GI) symptoms and fever that progressed to pulmonary findings in 48 hours.[2] Another case report described a male who tested positive for COVID-19 12 years after kidney transplantation and recovered after being treated with reduced immunosuppression and low dose methylprednisolone.[3] Thus far, it is unclear if these are anecdotal cases or whether a tempered immune response is helpful in preventing a severe cytokine storm associated with COVID-19–induced acute respiratory distress syndrome (ARDS).

New York has become the epicenter of the COVID-19 pandemic in the United States. It is also home to many transplant centers. Herein we report our initial series of COVID-19 in kidney transplant recipients and discuss their characteristics, treatment, and evolution.

2 | MATERIALS AND METHODS

We performed an ongoing study at 12 acute care hospitals in Northwell Health. All COVID-19-positive patients with a functioning kidney allograft who presented to the emergency department and were either discharged or hospitalized between March 1, 2020 and March 27, 2020 were included. Data were collected from the enterprise electronic health record (EHR; Sunrise Clinical Manager, Allscripts) reporting database. COVID-19 positivity was defined as a positive result on real-time polymerase chain reaction (PCR) assay of nasal and/or pharyngeal swab specimens. Kidney transplant status was defined as an active International Statistical Classification of Diseases and Related Health Problems 10 code of T86.1, T86.10, T86.11, T86.12, T86.13, T86.19, or Z94.0. All charts were manually reviewed for demographics, history of recent exposure, immunosuppression changes, clinical signs and symptoms, and laboratory findings. Mycophenolic acid (MPA) doses were converted to mycophenolate mofetil (MMF) (360 mg of MPA are equivalent to 500 mg of MMF) for dose analysis. Acute kidney injury was graded according to Kidney Disease Improving Global Outcomes (KDIGO) criteria. The study was approved by the institutional review board of Northwell Health. Written informed consent was waived in light of the urgent need to collect data.

3 | RESULTS

Ten kidney transplant recipients were found to be COVID-19 positive by PCR. Nine of the 10 patients included were hospitalized. Of the 9, 5 were admitted to the intensive care unit (ICU). Three patients who required intubation died.

3.1 | Demographics

The median age of COVID-19 patients was 57 (interquartile range [IQR] 47-67). (Patient demographics can be seen in Table 1.) The majority of patients were male (60%), Caucasian (40%), and Black or African American (30%) All patients had a history of hypertension, with the majority also having diabetes. None were current smokers, although 2 had a history of tobacco use. Five patients had

TABLE 1 Patient demographics

Patient	Age	Gender	Race	Donor type	Time from transplant to infection (d)	Comorbid conditions	Tobacco	F/u (d)
1	50.91	M	Caucasian	DDRT	124	HTN, DM, CAD	Prior	28
2	37.08	M	Black/AA	LDT	2516	HTN, DM	N	27
3	63.06	F	Caucasian	LDT	3366	HTN	N	3
4	30.71	F	Black/AA	LDT	1346	HTN, DM	N	26
5	56.43	M	Caucasian	DDRT	7447	HTN, DM	N	5
6	80.05	M	Asian	LDT	5000	HTN, DM, CAD	Prior	26
7	45.42	M	Black/AA	DDRT	1247	HTN, DM	N	25
8	68.04	Male	Multiracial	unknown	6290	DM, HTN	N	24
9	74.68	Female	Caucasian	LDT	3127	HTN, malignancy	N	21
10	56.94	Female	Multiracial	DDRT	1178	DM, HTN	N	8

Abbreviations: AA, African American; CAD, coronary artery disease; DDRT, deceased donor renal transplant; DM, diabetes mellitus; F, female; F/u, follow-up; HTN, hypertension; LDT, living donor renal transplant; M, male.

undergone living donor transplants, 4 had received deceased donor organs, and 1 had an unknown donor type. Median time from transplant to COVID-19 testing was 2822 days (IQR 1272-4592). The shortest time from transplant to testing was 124 days with the longest time being 6290 days.

3.2 | Presentation and clinical course

The 10 patients with COVID-19 had variable presentations and courses (see Table 2). The most common documented symptom was fever followed by cough, myalgia, chills, and fatigue. Two patients had diarrhea and 1 had nasal congestion. At the time of presentation, 7 patients had a temperature greater than 38.3 degrees Celsius. All patients had a chest X-ray (CXR) obtained at the time of admission and 40% had computed tomography (CT) scans. CXR and CT scan findings varied, with multifocal patchy opacities consistent with COVID-19 pneumonia most commonly seen. Three patients had no abnormal findings on CXR or chest CT. All patients had rapid viral assays performed, and no patients had coexisting viral infections at the time of presentation. One patient had influenza diagnosed 13 days prior to admission and was treated at the time with 5 days of oseltamivir. Three patients (Patients 4, 5, and 10) had positive urine cultures for *Enterococcus*, *Klebsiella pneumonia*, and *E. coli*, respectively. None had urinary symptoms at the time of presentation.

As was previously noted, one patient (Patient 1) was discharged home from the emergency room without treatment or change in immunosuppression; a follow-up 1 week later demonstrated resolution of symptoms. Five patients (Patients 5, 6, 8, 9, and 10) required an ICU stay and the others were admitted to a COVID-19 medical floor. Of the ICU patients, 3 died, and 2 eventually recovered and were discharged. Patient 5 was initially on a medical floor before decompensating and required intubation and vasopressor support. The patient became anuric, was started on continuous renal replacement therapy, and died 2 days later after being made do not resuscitate. Patient 9 never recovered mental status after mechanical ventilation. She was eventually extubated and then died in hospice. Patient 10 developed respiratory decompensation and died of a cardiac arrest. All of the remaining patients were eventually discharged. Median length of stay was 11 days (IQR 4-17 days). One patient resumed MMF at home and was readmitted 2 days later due to fever and shortness of breath. CT upon readmission revealed multifocal pneumonia presumed related to COVID-19. MMF was stopped, fevers resolved, and he was discharged on room air after 7 days. Median follow-up for the entire cohort was 25 days (IQR 11-26 days, 2 patients were lost to follow-up after discharge).

Leukopenia was seen in 20% of patients during hospitalization. Eight of the 9 hospitalized patient had at least 1 ferritin level and C-reactive protein (CRP) checked (see Table 2). Median ferritin was 788 ng/mL (IQR 563-1162) and CRP 13.35 mg/dL (IQR 4.82-23.72). Allograft function was stable in 50% of patients. Five patients had acute kidney injury (AKI): three stage 3, one stage 2, and one stage 1. No kidney biopsies were performed during the hospitalization.

3.3 | Immunosuppression

Immunosuppression at baseline and changes undertaken can be seen in Table 3. At the time of presentation, 9 patients were on tacrolimus (calcineurin inhibitor [CNI]) and either MMF or MPA (antimetabolite). Median tacrolimus trough at presentation was 9.1 ng/mL (IQR 6.3-11.2). A total of 70% of patients were on prednisone. Patient 1 was on everolimus in addition to tacrolimus, MMF, and prednisone. This patient was discharged home from the emergency room without any change in immunosuppression. Patient 9 was on sirolimus and prednisone. The median total daily dose of antimetabolite therapy (MPA was converted to the equivalent dose of MMF) was 1000 mg (IQR of 1000-2000 mg). Induction with an anti-interleukin-2 receptor antibody (IL2rAb) or with antilymphocyte globulin (ATG) was equal in the 6 patients who had known induction therapy. The type of induction was unknown in 4 cases.

All hospitalized patients had their antimetabolite agent stopped. Tacrolimus doses were titrated to a target trough of 3-5 ng/mL. Tacrolimus was stopped for Patients 5 and 6 who were intubated in the ICU and sirolimus was stopped for Patient 9.

3.4 | Treatment

All hospitalized patients received hydroxychloroquine (HCQ) and azithromycin (the latter no longer routinely administered as part of COVID treatment). All patients had an electrocardiogram (EKG) performed before initiation of therapy whereas only 4 had subsequent EKGs performed. No patient had a QTc of 500 or greater. Six patients received at least 1 dose of an additional antibiotic including ceftriaxone, piperacillin/tazobactam, levofloxacin, cefepime, and vancomycin at the time of presentation (see Table 4). Patient 1 was discharged home without any antiviral or antimicrobial agents. Patients 5, 6, and 10 in the ICU were also placed on thiamine. Patients 6 and 7 were given methylprednisolone and Patient 10 was given high-dose prednisone for ARDS.

4 | DISCUSSION

COVID-19 has rapidly spread through the population of the world; almost all people are at risk of infection either directly or indirectly. It is therefore not surprising that COVID-19 has been identified in kidney transplant recipients. We present the first 10 cases of confirmed COVID-19 in kidney transplant recipients at our health network. Although our cohort is small, it is clear that, similar to what occurs in the general population, COVID-19 can present in various fashions and the prognosis can be vastly different among individual kidney transplant recipients. However, overall mortality is high.

Similar to those of the general population, the most frequent presenting symptoms were fever, myalgia, and cough. Most patients had suggestive findings of viral pneumonia on a CXR or CT. Illness acuity at presentation was also highly variable with one patient being

TABLE 2 Presentation and hospital course

Pt	Exposure	Presenting symptom	Fever	CXR findings	CT findings	WBC initial	WBC nadir	Lymph	Ferritin (ng/mL)	CRP (mg/dL)	ICr (mg/dL)	PCr (mg/dL)	O2	Disp
1	Family member	Fever, chills, cough	No	Normal		9.2	n/a	1.14			0.88	n/a	n/a	discharge
2	Community acquired	Cough, chills, nasal congestion, myalgias	Yes	Normal	Patch opacity/multifocal	5.08	2.38	0.81	1664	17.97	1.93	1.9	RA	discharge
3	Healthcare-acquired	Fever, chills, myalgias, cough, headache	Yes	RLL hazy and nodular opacities	Normal	9.1	4.02	1.2	101	3.44	1.2	1.2	RA	discharge
4	Community acquired	Fever, myalgias, headache, emesis	No	RLL hazy and nodular opacities	Patch opacity/multifocal	3.78	2.82	1.22			1.5	1.7	RA	discharge
5	Family member	Fever, cough, fatigue	Yes	Patch opacity/multifocal		4.1	4.1	0.32	2871	30.65	4.85	6.09	MV	ICU/death
6	Healthcare-acquired	Fever, chills, diarrhea, myalgias, fatigue	Yes	Patch opacity/multifocal	Patch opacity/multifocal	5	5	0.26	758	8.72	1.91	2.88	MV	discharge
7	Community acquired	Fever, cough, myalgias, diarrhea	Yes	right middle and lower lung opacities		5.23	4.3	1.13	369	3.86	1.74	2.33	NC	discharge
8	Community acquired	Fever, cough, SOB	No	Interstitial abnormality		6.73	4.79	0.55	627	24.37	1.46	8.01	NRB	discharge
9	Family member	Fever, fatigue, cough, SOB	Yes	Patch opacity/multifocal		6.3	4.44	0.44	817	5.14	1.29	1.37	MV	ICU/death
10	Community acquired	Chills, cough, SOB, fatigue	Yes	Patch opacity/multifocal	Patch opacity/multifocal	11.1	9.41	1.38	994	23.5	1.6	3.54	MV	ICU/death

Abbreviations: CRP, C-reactive protein; CXR, chest X-ray; CT, computed tomography; Disp, disposition; ICr, Initial creatinine mg/dL; ICU, intensive care unit; Lymph, lymphocyte count; MV, mechanical ventilation; NC, nasal cannula; NRB, non-rebreather; O2, oxygen requirement; PCr, peak creatinine mg/dL; RA, room air; RLL, relative radiation level; SOB, shortness of breath; Vent, mechanical ventilation; WBC, white blood cell count K/µL.

TABLE 3 Immunosuppression and management

Patient	Organ type	Time from transplant to infection (d)	Induction	CNI	Antimetabolite	Total daily dose (mg)	mTOR	Pred	Immuno changes
1	DDRT	124	IL2rAb	FK	MMF	1000	EVR	Yes	None
2	LDT	2516	ATG	FK	MPA	1440		Yes	d/c MPA
3	LDT	3366	ATG	FK	MPA	1440		No	d/c MPA
4	LDT	1346	ATG	FK	MMF	2000		Yes	d/c MMF
5	DDRT	7447	Unknown	FK	MMF	1000		Yes	d/c MMF, FK
6	LDT	5000	Unknown	FK	MMF	500		No	d/c MMF, FK
7	DDRT	1247	IL2rAb	FK	MMF	1000		Yes	d/c MMF
8	unknown	6290	Unknown	FK	MMF	1500		Yes	d/c MMF
9	LDT	3127	IL2rAb	N/a	N/a	N/a	SRL	Yes	d/c SRL
10	DDRT	1178	Unknown	FK	MMF	1000		No	d/c MMF

Abbreviations: ATG, antithymocyte globulin; CNI, calcineurin inhibitor; d/c, discontinue; DDRT, deceased donor renal transplant; EVR, everolimus; FK, tacrolimus; IL2rAb, IL2 receptor antibody; LDT, living donor renal transplant; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; Pred, prednisone; SRL, sirolimus.

TABLE 4 Antiviral and antimicrobial treatments

Patient	COVID-19 directed therapy	Antimicrobial agents	Bacterial coinfection
1	none	None	
2	HCQ, azithro	None	
3	HCQ, azithro	Ceftriaxone	*Enterococcus* in urine
4	HCQ, azithro	Ceftriaxone	*Klebsiella pneumonia* in urine
5	HCQ, azithro	Ceftriaxone	
6	HCQ, azithro	Cefepime, vanco	
7	HCQ, azithro	Ceftriaxone, pip/tazo, vanco	
8	HCQ, azithro	pip/tazo, vanco	
9	HCQ, azithro	N/a	
10	HCQ, azithro	Levofloxacin, ceftriaxone	*E. coli* in urine

Abbreviations: azithro, azithromycin; COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine; N/a, nonapplicable; pip/tazo, piperacillin tazobactam; vanco, vancomycin.

urgently intubated and admitted into the ICU whereas another patient was discharged home. Unfortunately several patients decompensated while in the hospital. Of the 5 ICU patients 3 were initially admitted to a medical floor. Three of the 5 ICU patients eventually died, which is consistent with the poor prognosis of patients requiring intensive care in the general population. In comparison, in a study out of Wuhan, China, 52% of the general population of patients with ARDS died.[4] A study in kidney transplant recipients with COVID-19 from China[5] did not report mortalities among 5 patients with non-"severe" infections. Another report from Italy in transplant recipients with COVID-19 described an overall mortality rate among admitted patients of 25%.[6] Larger studies are warranted to fully understand mortality risk of transplant recipients with COVID-19.

It has been hypothesized that immunosuppressed patients may not be at increased risk of complications in the setting of coronavirus infections when compared to the general population.[7] Risk factors for poor outcome among patients in our series were similar to those of the general population, including age, male gender, and preexisting comorbidities.[7-9] Comorbid conditions including hypertension and diabetes were highly prevalent in our population. The overall mortality in our patient cohort was high. In our experience immunosuppression did not seem to reduce the incidence of ARDS or death.

Some risk factors among our recipients were not consistent with those encountered in transplantation. For example, the early posttransplant period is usually characterized by the highest risk of infection. However, only 1 of our patients who received IL2rAb induction acquired COVID-19 within 1 year of transplantation, and this specific patient was among those who were discharged home with resolution of symptoms. Induction with ATG is also traditionally

associated with a higher risk of infection. Our cohort was split evenly between those known with ATG induction and IL2rAb induction.

There is yet no proven treatment for COVID-19. Chloroquine and HCQ have been reported to have antiviral activity, to inhibit cytokine production, and to be associated with improved CT pulmonary images, a rapid decline in fever, and a quicker recovery period.[10-13] The effect seems to be reinforced by azithromycin.[11] Corticosteroids are not routinely recommended but have also been utilized.[14,15] Current treatments include supportive care as well as chloroquine, HCQ, and various agents currently under investigation such as interleukin-6 (IL-6) inhibitors and remdesivir.[8,12,16] All of our hospitalized patients were treated with HCQ and azithromycin. Since the writing of this manuscript, azithromycin has been discontinued as a routine therapy at our institution. Notably both CNI and HCQ can prolong the QT interval, resulting in fatal torsades. For this reason, it is imperative to assess the QT interval before initiation of therapy and possibly monitor posttherapy as well.

It is intuitive that T cell immunity should be important in controlling viral replication and disease. Based on this assumption, antimetabolite therapy was stopped in all patients.[17] The decision whether to hold CNI was based on clinical parameters. Two patients who were critically ill in the ICU eventually had CNI held. It is not clear, however, whether stopping all immunosuppression in transplant recipients is helpful. Most COVID-19 deaths are associated with ARDS.[15] It is likely that the development of ARDS is mediated by the uncontrolled release of cytokines.[10,16] There seems to be evidence pointing to the fact that a subgroup of patients with severe COVID-19 may have a cytokine storm syndrome.[15] Some form of immunosuppression may be of benefit in this setting of hyperinflammation.[15] Interleukin-6 (IL-6) and interleukin-1 (IL-1) blockade is currently being tried with COVID-19. Administration of agents such as immunoglobulin, other cytokine blocking agents, and statins may also be of use.[15]

The current report is based on the experience of a large health system and its transplant center at the epicenter of a pandemic. We believe that kidney transplant recipients infected with COVID-19 should be monitored closely in the setting of a lowered immunosuppression. Most individuals sick enough to present to the emergency room required hospitalization, and rates of ICU admission are high. Presenting symptoms are similar to those of nontransplant individuals. Although all recipients in our series had at least 1 comorbidity, this is an almost universal finding in the transplant population. There were no viral coinfections. In our cohort of hospitalized patients, mortality was high. Home-bound patients (both with and without COVID-19) are being followed via telehealth. Morbidity and mortality rates continue to evolve.

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DISCLOSURE

DATA AVAILABILITY STATEMENT

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