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COVID-19 in solid organ transplant recipients: Initial report from the US epicenter

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Solid organ transplant recipients may be at a high risk for SARS-CoV-2 infection and poor associated outcomes. We herein report our initial experience with solid organ transplant recipients with SARS-CoV-2 infection at two centers during the first 3 weeks of the outbreak in New York City. Baseline characteristics, clinical presentation, antiviral and immunosuppressive management were compared between patients with mild/moderate and severe disease (defined as ICU admission, intubation or death). Ninety patients were analyzed with a median age of 57 years. Forty-six were kidney recipients, 17 lung, 13 liver, 9 heart, and 5 dual-organ transplants. The most common presenting symptoms were fever (70%), cough (59%), and dyspnea (43%). Twenty-two (24%) had mild, 41 (46%) moderate, and 27 (30%) severe disease. Among the 68 hospitalized patients, 12% required non-rebreather and 35% required

Abbreviations: BIPAP, bilevel positive airway pressure; COVID-19, coronavirus disease; ECMO, extracorporeal membrane oxygenation; HCQ, hydroxychloroquine; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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intubation. 91% received hydroxychloroquine, 66% azithromycin, 3% remdesivir, 21% tocilizumab, and 24% bolus steroids. Sixteen patients died (18% overall, 24% of hospitalized, 52% of ICU) and 37 (54%) were discharged. In this initial cohort, transplant recipients with COVID-19 appear to have more severe outcomes, although testing limitations likely led to undercounting of mild/asymptomatic cases. As this outbreak unfolds, COVID-19 has the potential to severely impact solid organ transplant recipients.

KEYWORDS

antibiotic: antiviral, clinical research/practice, complication: infectious, immunosuppression/immune modulation, infection and infectious agents – viral, infectious disease, organ transplantation in general

1 | INTRODUCTION

With at least 75 795 cases of COVID-19 and 1550 deaths by March 31, 2020, New York State has become the current epicenter of COVID-19 in the United States.[1] As this pandemic continues to unfold, data on the clinical characteristics and outcomes of COVID-19 are emerging across continents.[2-5] It has been reported that approximately 20% of those with COVID-19 suffer moderate or severe symptoms and 5% progress to critical disease.[6] The case fatality rate so far has ranged widely from 1% to 7.2% overall reaching up to 49% among the critically ill.[6,7] Risk factors identified for severe disease described to date include older age and the presence of comorbidities such as diabetes, hypertension, chronic kidney disease, morbid obesity, coronary heart disease, and chronic lung disease.[3]

The impact of chronic immunosuppression on outcomes of COVID-19 is not known but is potentially highly relevant since host inflammatory responses appear to constitute an important cause of associated organ injury. Most cohorts reported thus far do not include immunosuppressed patients or details about immunosuppression-related risk factors, including a history of solid organ transplantation. While transplant recipients have a high prevalence of the comorbidities that have been established as risk factors for severe disease, as the role of the immune system and inflammatory response to infection is now being elucidated, there is also significant debate regarding the role of immunosuppression in the pathogenesis and outcome of COVID-19. Despite widespread concern about the potential for high prevalence and severity of COVID-19 among transplant recipients, data on this population is lacking so far aside from a few single patient case reports.[8-10] As transplant centers around the United States and the world prepare for a rising incidence of disease, important questions around differences in disease susceptibility, clinical presentation, severity and transplant specific management of both antiviral therapy and immunosuppression remain unanswered. Here we present the clinical characteristics of solid organ transplant recipients with COVID-19 at two large academic centers during the initial 3 weeks of the epidemic in New York City.

2 | METHODS

2.1 | Patients

All adult (age >18 years) solid organ transplant recipients from Columbia University Irving Medical Center (CUIMC) and Weill Cornell Medicine (WCM) with a positive test for SARS-CoV-2 in an inpatient or outpatient setting between March 13, 2020 and April 3, 2020 were retrospectively assessed. Data were extracted from the electronic medical record system. All tests performed at CUIMC or WCM used reverse-transcriptase PCR via Roche 6800 platform of nasopharyngeal swab specimens to diagnose COVID-19. Lower respiratory samples were not tested. Patient characteristics, symptoms and timing of presentation, management of immunosuppression and initial antiviral treatment strategies as well as initial outcomes were characterized. This work was approved by the local institutional review boards.

Patients were categorized as having mild disease (outpatient care only), moderate disease (admission to the general inpatient floor), or severe infection (mechanical ventilation, admission to intensive care unit [ICU] or death). The median (IQR) overall time from the date of the positive SARS-CoV-2 test until death or last follow-up was 20 (14-24).

2.2 | Therapeutic approach

At this time, there are limited data on effective antiviral therapies against SARS-CoV-2. As such, the initial management has been to provide supportive care for patients with mild disease while generally treating those with moderate or severe disease with hydroxychloroquine if those patients were unable to enroll in clinical trials or compassionate use of investigational agents such as remdesivir. Additional therapeutic considerations included the addition of azithromycin to hydroxychloroquine, and/or tocilizumab for patients rapidly decompensating thought due to high and deleterious

cytokine activity. IVIG infusion and bolus steroids were also considered on a case by case basis.

Regarding immunosuppressive therapy, the general approach at our centers was to moderately decrease the overall amount of immunosuppression with a particular emphasis on decreasing or stopping antimetabolite drugs such as mycophenolate or azathioprine. This approach was based on expert opinion developed in conjunction with various organ transplant groups and transplant infectious diseases.

In one of the centers, the clinical protocol for hospitalized patients also included initial measurement of D-dimer, ferritin, procalcitonin, C-reactive protein (CRP), high sensitivity (HS)-troponin and interleukin-6 (IL-6) levels, based on their potential to identify subsequent poor outcomes.[11,12]

2.3 | Medication and dosing

Hydroxychloroquine when given at our institutions was dosed at 600 mg orally twice daily (load) on day 1, then 400 mg orally daily on days 2-5. Caution was advised in individuals with pre-existing QT prolongation or those at risk for QT prolongation. Azithromycin was dosed as 500 mg orally once on day 1, then 250 mg orally daily on days 2-5. Azithromycin was avoided if the patient's QTc interval was >500 ms at baseline or the patient was taking any concurrent QTc prolonging medications. When combined with hydroxychloroquine, QTc was re-assessed by 12-lead ECG on hospital days 2 or 3 of therapy. Tocilizumab was given as a one-time dose of either 400 mg or 8 mg/kg (maximum 800 mg) intravenously once, and a second dose was given in select cases.

2.4 | Statistical approach

Baseline characteristics are compared between groups with mild/moderate and severe COVID-19 infection as defined above. Continuous variables were compared with Wilcoxon rank-sum and proportions with chi-square. For purposes of this analysis, comorbidities were determined from clinical documentation in the medical record. Chronic kidney disease was defined as baseline glomerular filtration rate below 60 mL/min. The subset of patients who were hospitalized were then analyzed for a more detailed description of laboratory abnormalities, inpatient treatment and documentation of clinical outcomes.

3 | RESULTS

3.1 | Patient characteristics

Ninety solid organ transplant recipients from Columbia University Irving Medical Center (CUIMC, n = 72) and Weill Cornell Medicine (WCM, n = 18) tested positive for SARS-CoV-2 between March 10 and April 3, 2020. The overall median age of the cohort was 57 years, 59% were men, 63% Caucasian race, and 42% Hispanic ethnicity (Table 1). There were 46 (51%) kidney transplant recipients, 17 (19%) lung recipients, 13 (14%) liver recipients, 9 (10%) heart recipients, 3 (3%) heart-kidney recipients, 1 (1%) liver-kidney recipient, and 1 (1%) kidney-pancreas recipient. The median time from transplant to COVID-19 diagnosis was 6.64 years. Three (3%) of patients were in the first month posttransplant and 13 (14%) were in the first-year posttransplant. There were no significant differences between baseline immunosuppression and disease severity.

There were 22 (24%) patients with mild disease, 41 (46%) with moderate disease, and 27 (30%) with severe disease. Advanced age was significantly associated with severe disease. However, other baseline demographics including sex, race, ethnicity, type of transplant and time from transplant did not significantly differ between these groups (Table 1). Patients with severe disease were also more likely to have hypertension and active cancer, while other comorbidities so far described in the general population did not significantly differ between the two groups.

The median (IQR) overall follow up time from positive test until death or last follow-up, was 20 (14-24) days.

3.2 | Clinical presentation

The median number of days symptom onset until the positive test for SARS-CoV-2 was four, and there was no difference between the disease groups. The most common presenting symptom reported was fever by 63 patients (70%), followed by cough in 53 (59%), dyspnea in 39 (43%), fatigue in 25 (28%), myalgias in 22 (24%), and diarrhea in 28 (31%). Dyspnea upon presentation was significantly associated with a severe clinical course, while other presenting symptoms were similar between groups (Table 1). Fifteen (17%) reported a known exposure outside the hospital prior to diagnosis—this was almost universally to a sick family member. In addition, three patients (4%) were suspected of having nosocomial transmission, all of whom progressed to severe disease (P = .01). Seven (8%) patients who tested positive had a recently negative initial SARS-CoV-2 PCR test but were retested due to ongoing high clinical suspicion. In addition, eight of the hospitalized patients were initially diagnosed as outpatients, 3-9 days prior to hospitalization.

3.3 | Characteristics of hospitalized patients

Sixty-eight (76%) of all patients were hospitalized. For these patients, additional clinical details including vital signs, laboratory values and outcomes are summarized in Tables 2 and 3. Patients with severe disease had significantly higher respiratory rates (P = .01) and lower oxygen saturation (P = .01) but lower maximum temperatures (P = .03) on initial presentation than those with moderate disease.

Laboratory values at the time of hospitalization were generally similar between those who had moderate and severe disease,

TABLE 1 Baseline demographics and clinical presentation of entire cohort by disease severity

	All (n = 90)	Mild/moderate disease (n = 63)	Severe disease (n = 27)	*P*-value
Age in years, median (IQR)	57 (46-68)	54 (39-64)	67 (56-74)	.001
Age >60 (%)	43 (48)	24 (38)	19 (70)	.005
Male sex (%)	53 (59)	37 (59)	16 (59)	.96
Race (%)				
White	57 (63)	40 (63)	17 (63)	.59
Black	20 (22)	13 (21)	7 (26)	
Asian	5 (6)	5 (8)	0 (0)	
Other	8 (9)	5 (8)	3 (11)	
Hispanic ethnicity (%)	37 (42)	25 (40)	12 (44)	.72
Organ transplant (%)				
Kidney	46 (51)	34 (54)	12 (44)	.90
Lung	17 (19)	10 (16)	7 (26)	
Liver	13 (14)	9 (14)	4 (15)	
Heart	9 (10)	6 (10)	3 (11)	
Heart-kidney	3 (3)	2 (3)	1 (4)	
Liver-kidney	1 (1)	1 (2)	0 (0)	
Kidney-pancreas	1 (1)	1 (2)	0 (0)	
Years from transplant to diagnosis, median (IQR)	6.64 (2.87-10.61)	6.25 (2.6-10.69)	6.86 (2.87-10.16)	.92
Within 1 mo (%)	3 (3)	2 (7)	1 (4)	.90
Within 1 y (%)	13 (14)	8 (13)	5 (19)	.47
Comorbidities (%)				
HTN	58 (64)	37 (60)	19 (78)	.01
DM	41 (46)	27 (43)	14 (52)	.47
CKD	57 (63)	38 (60)	19 (70)	.47
Dialysis	5 (6)	4 (6)	1 (4)	.57
Chronic lung disease	17 (19)	11 (17)	6 (22)	.65
HIV	1 (1)	1 (2)	0 (0)	.51
Active cancer	3 (3)	0 (0)	3 (11)	.01
BMI > 40 kg/m^2	5 (6)	3 (5)	2 (7)	.63
Presenting symptoms (%)				
Fever	63 (70)	50 (79)	13 (48)	.01
Fatigue	25 (28)	20 (32)	5 (19)	.30
Myalgias	22 (24)	18 (29)	4 (15)	.24
Cough	53 (59)	39 (62)	14 (52)	.70
Dyspnea	39 (43)	22 (35)	17 (63)	.01
Diarrhea	28 (31)	21 (33)	7 (26)	.68
Vomiting	7 (8)	5 (8)	2 (7)	.95
Days from symptom onset to test, median (IQR)	4 (2-7)	4 (2-7)	4 (1.5-7)	.46
Report of known exposure outside hospital (%)	15 (17)	12 (19)	3 (11)	.41
Suspected nosocomial transmission (%)	3 (3)	0 (0)	3 (11)	.01

(Continues)

TABLE 1 (Continued)

	All (n = 90)	Mild/moderate disease (n = 63)	Severe disease (n = 27)	*P*-value
Initial SARS-CoV-2 test negative and retested positive (%)	7 (8)	3 (5)	4 (15)	.09
Baseline IS (%)				
CNI	77 (86)	53 (84)	24 (89)	.38
Mycophenolate	65 (72)	44 (70)	21 (78)	.57
Steroids	53 (59)	34 (38)	19 (70)	.18
Azathioprine	4 (4)	4 (6)	0 (0)	.20
Belatacept	5 (6)	4 (6)	1 (4)	.64
IVIG ± Pheresis	3 (3)	1 (2)	2 (7)	.15
mTOR	6 (7)	5 (8)	1 (4)	.24
Hospitalized (%)	68 (76)	41 (65)	27 (100)	<.001
Days from positive SARS-CoV-2 test until death or last follow-up, median (IQR)	20 (14-24)	20 (15-26)	15 (9-23)	.003

except for a lower serum albumin in the severe group (*P* = .048) (Table 2). In one of the centers, initial inflammatory biomarkers were checked for most patients. While the median levels of all biomarkers measured at presentation were well above normal range, procalcitonin was the only marker significantly more elevated in the severe group (Table 2).

All hospitalized patients had abnormal chest radiographs, most commonly characterized by bilateral opacities. As part of infection prevention efforts, computed chest tomography imaging for the management of COVID-19 was strongly discouraged and not performed.

3.4 | Initial treatment approach in hospitalized patients

Immunosuppressive therapy was reduced in the majority of patients. Overall, 42 patients (88%) had antimetabolite doses reduced or held, 3 (7%) had steroids decreased or held and 10 (18%) had calcineurin inhibitor doses decreased or held (Table 3). Almost all patients remain on reduced immunosuppression at the time of last follow-up.

Sixty-two (91%) patients received hydroxychloroquine. Forty-five patients (66%) received azithromycin. No patients developed a documented prolonged QTc interval with the combination of hydroxychloroquine and azithromycin requiring early treatment discontinuation.

Immunomodulatory agents were also used including tocilizumab in 14 patients (nine received one dose, four received two doses and one received three doses) who deteriorated rapidly. For five of these patients, the initial dose was given after the patient was intubated. Of these 14 patients, three have died, four remain in ICU, five remain with moderate disease on the general medical floor and two have been discharged. In addition, 16 patients received bolus steroids, of whom three have died, five remain in ICU, six remain with moderate disease on the general medical floor and two have been discharged.

3.5 | Clinical outcomes for hospitalized patients

Thirteen (19%) patients did not require supplemental oxygen, while 20 (29%) required nasal cannula, 10 (12%) non-rebreather mask, high flow nasal cannula or BIPAP and 24 (35%) mechanical ventilation as their highest level of respiratory support. No patients went on ECMO thus far. Twenty-three patients (26% overall, 34% of inpatients) required ICU admission and sixteen died due to complications of COVID-19 (18% [16/90] overall, 24% [16/68] of all inpatients, 52% [12/23] of ICU patients). Four of the patients who died chose to not be intubated or admitted to ICU. Thirty-seven (54%) patients were discharged with improved condition and one patient was readmitted with worsening symptoms. Only two patients requiring mechanical ventilation have been discharged so far. Fifteen patients currently remain hospitalized, nine in the ICU, at the time of this report.

There were no confirmed cases of thromboembolic complications or rejection after a diagnosis of COVID-19 during this study period.

4 | DISCUSSION

As the COVID-19 pandemic continues to spread and severely impact large parts of the world, solid organ transplant recipients are at high risk of infection and poor outcomes due to high rates of comorbidities, frequent contact with medical care, and chronic immunosuppression. Here we present the first 90 cases COVID-19 among solid organ transplant recipients at two large transplant centers during the initial 3 weeks of the outbreak in New York City. When compared to nontransplant patients hospitalized with COVID-19 in international

TABLE 2 Initial hemodynamic and laboratory values among hospitalized patients with COVID-19

	All (n = 68)	Moderate disease (n = 41)	Severe disease (n = 27)	*P*-value
Vitals, median (IQR)				
Maximum temperature (°C)	37.4 (37.1-37.9)	37.6 (37.1-38.1)	37.2 (36.7-37.4)	.03
Heart rate (per min)	93.5 (83-104)	93 (85-106)	94 (80-101)	.52
Respiratory rate (per min)	20 (18-24)	19 (18-21)	22 (19-39.5)	.01
Lowest O_2 sat (%)	94 (91-96)	95 (92-96)	91 (88-94)	.01
Blood counts, median (IQR)				
WBC × 1000/μL	5.16 (3.5-7.5)	5.66 (3.67-7.4)	4.4 (2.5-10.43)	.63
Hgb g/dL	11.2 (9.4-12.6)	11.4 (10.2-12.9)	9.8 (8.9-12.2)	.20
Platelets × 1000/μL	176.5 (129-221)	174 (138-221)	186 (124-215)	.95
Neutrophils count/μL	3.8 (1.92-5.68)	4.1 (2.02-5.42)	3.64 (1.62-7.27)	.96
Lymphocytes count/μL	0.7 (0.34-1.09)	0.7 (0.39-1.04)	0.80 (0.14-1.26)	.83
Neutrophil to lymphocyte ratio	5.27 (2.89-9.46)	5.14 (3.23-8.39)	6.22 (1.97-14.17)	.70
INR, median (IQR)	1.1 (1-1.2)	1.1 (1-1.2)	1.2 (1.1-1.4)	.06
Chemistries, median (IQR)				
Creatinine, mg/dL[a]	1.89 (1.15-3.85)	1.9 (1.15-3.47)	1.9 (1.47-3.96)	.41
Albumin g/dL	3.6 (3.1-3.9)	3.8 (3.2-4)	3.35 (2.75-3.7)	.048
AST U/L	26 (17-36)	24.5 (18-34)	33 (17-48)	.39
ALT U/L	18 (13-25)	18 (12-25)	18 (14-24)	.51
Total bilirubin mg/dL	0.4 (0.3-0.5)	0.4 (0.3-0.5)	0.5 (0.4-0.6)	.04
Additional labs, median (IQR)[b]				
HS-troponin ng/L	27 (9-58.5)	17.5 (8.5-43.5)	52.5 (9.5-77)	.24
Procalcitonin ng/mL	0.285 (0.15-0.86)	0.205 (0.12-0.7)	0.73 (0.37-3.795)	.003
CRP mg/L	68.5 (15.445-126)	60 (11-110)	97 (18.6-130)	.20
D-dimer μg/mL	1.335 (0.69-3.08)	1.04 (0.66-1.96)	2.2 (0.99-3.81)	.13
Ferritin ng/mL	801.5 (270-1514)	813 (257-1611)	790 (466-1464)	.86
IL-6 level pg/mL	20 (8-51)	18 (5-45)	32 (11-90)	.26

[a]Six patients were on chronic renal replacement therapy and not included in this calculation.
[b]These values were not available for all patients (HS-troponin N = 44, procalcitonin N = 50, CRP N = 48, D-dimer N = 40, ferritin N = 46, IL-6 N = 33).

cohorts, our hospitalized cohort had higher rates of severe disease (39% vs 6.1%) and mortality (24% vs 1.4%-4.3%).[13,14] While we present an overall median follow up time of 20 days, several patients in this cohort remain hospitalized (n = 15), including in the ICU (n = 9). Thus, the estimates for severe disease and mortality may increase with additional follow up. These comparisons should be interpreted with caution as testing limitation in the United States does not allow an assessment of the true rate of infection. In addition, criteria for hospitalization, ICU admission and discharge are likely to be different between countries.

The most common presenting symptoms in our cohort included fever, cough, and dyspnea, similar to the general population so far reported.[2,13] Immunosuppressed patients commonly present with atypical or attenuated signs and symptoms of infection, often leading to late presentations, or missed diagnoses, and potentially leading to worse outcomes overall.[15] Dyspnea was the only symptom that was significantly associated with a severe clinical course, highlighting the fact that respiratory pathology is the main driver of poor outcomes in COVID-19. More atypical presentations were also described in this cohort, including a significant proportion with diarrhea (31%), a symptom increasingly recognized in COVID-19.[13] Some patients with diarrhea subsequently developed cough and dyspnea, including severe hypoxia, much like a recent report from Italy of a renal transplant patient.[9]

When compared to those with mild to moderate presentations, patients with severe disease were older and more likely to have

TABLE 3 Treatment and outcomes to date among hospitalized patients with COVID-19

	All (n = 68)	Moderate disease (n = 41)	Severe disease (n = 27)
Changes in immunosuppression (%)[a]			
Decrease or hold antimetabolite	42/48 (88)	27/32 (84)	15/16 (94)
Decreased or hold steroids	3/43 (7)	1/27 (4)	2/16 (13)
Decrease or hold CNI	10/56 (18)	5/35 (14)	5/21 (23)
Anti-viral treatment (%)			
Hydroxychloroquine	62 (91)	38 (93)	24 (89)
Azithromycin	45 (66)	26 (63)	19 (70)
Remdesivir	2 (3)	1 (2)	1 (4)
Unknown	2 (3)	0 (0)	2 (7)
Immunomodulatory therapy (%)			
Bolus steroids	16 (24)	6 (15)	10 (37)
Tocilizumab	14 (21)	6 (15)	8 (30)
Highest level of respiratory support (%)			
Room air	13 (19)	13 (32)	0 (0)
Nasal cannula	20 (29)	20 (49)	0 (0)
NRB/high flow/BIPAP	10 (12)	6 (15)	4 (15)
Intubation	24 (35)	0 (0)	23 (85)
ECMO	0 (0)	0 (0)	0 (0)
Unknown	1 (1)	1 (2)	0 (0)
ICU admission (%)	23 (34)	0 (0)	23 (85)
Mortality (%)	16 (24)	0 (0)	16 (59)
Discharge (%)	37 (54)	35 (85)	2 (7)
Readmission (%)	1 (6)	1 (2)	0 (0)

[a]Denominator includes patients on the agent at baseline and known adjustment status.

hypertension, similar to reports in the general population. There was no clear difference between disease severity and type of organ transplant in this cohort, though the numbers in each group are relatively small. Patients who progressed to severe disease were often already hypoxic and tachypneic on presentation, highlighting once again that these patients may be presenting at a late stage of their infection, with possibly decreased chance of recovery with currently available off label and investigational therapies. In our cohort, there was no difference in median time from symptoms to diagnosis among those with dyspnea or hypoxia (oxygen saturation <93% on room air).

Among the biomarkers of inflammation measured at presentation, although almost uniformly elevated, none except procalcitonin were significantly different between those with moderate and severe disease. While this could be due to a small sample size, one could also postulate that this chronically immunosuppressed population may undergo a more unique but equally dysfunctional inflammatory response in the setting of SARS-CoV-2 infection. Other reports have also found that high levels of procalcitonin, usually a marker of bacterial infection, can be predictive of severe COVID-19 and potentially related to secondary bacterial infections.[16] It may also be that a more predictive analysis lies in the kinetics of these biomarkers through longitudinal measurements, not in a single point in time. Much remains uncertain about the immune response in COVID-19 and further detailed research on cytokine activation and patterns of T cell migration and signaling are needed.

Most patients in our cohort were thought to be infected via community transmission. Several patients reported family members with either confirmed infection, or symptoms suggestive of COVID-19. This is not surprising and is consistent with the fact that average time from transplant to infection in our cohort was almost 6 years. It is becoming increasingly evident, however, that the risk of nosocomial transmission is a major problem in this outbreak. While it is not possible at this time to be certain that our three cases of suspected nosocomial transmission were in fact hospital acquired, all of whom progressed to severe disease. The first was a heart transplant recipient who had undergone a deceased donor kidney transplant with thymoglobulin induction 5 days prior to symptoms and the second was a kidney transplant recipient undergoing inpatient treatment for antibody mediated rejection with plasmapheresis and IVIG. The third patient was a liver transplant recipient who had also been undergoing inpatient treatment for refractory rejection and was found to be positive 10 days into the admission, after initially testing negative. All were highly immunosuppressed hosts and this may have

contributed to their disease severity. Among the many needs during a surge of SARS-CoV-2 infections, priority must be given to infection prevention and hospital epidemiology efforts.[14]

Another important finding in this report is the presence of initially negative results in seven patients. While it is possible that some patients became infected after the initial negative test, most were likely false negatives that led to a delay in diagnosis. All testing performed via nasopharyngeal swab, which is known to have variability in sensitivity. There are important implications of this delay in diagnosis, for both therapeutic and epidemiological reasons. The possibly significant rate false negative rate of nasopharyngeal swabs has likely compounded the difficulties in understanding the prevalence of COVID-19 in our community that stem from the overall low rate of testing.[17] A major limitation of this report is our current inability to evaluate the impact of transplantation on attributable hospitalizations and mortality due to COVID-19 since there has been profound deficiency in testing availability for outpatients. It is almost certain that a much larger number of transplant recipients have been infected with SARS-CoV-2 but have not been confirmed by formal testing due to milder symptoms and/or benign course as well as instructions from the hospitals and public health community to stay home and not seek testing in this circumstance. Additional delays in diagnosis may have also occurred due to initial long turnaround time of 3-5 days for testing, which has now been reduced to less than 1 day in the final 2 weeks of this cohort. Nevertheless, transplant recipients are usually closely followed and this cohort includes a number of patients who were never hospitalized. As testing continues to improve, there will be a much better understanding of the true impact of transplant recipient status and immunosuppression on COVID-19 outcomes.

At this time, there is much uncertainty in treatment strategies. No significant conclusions can be drawn from this study on the efficacy of a particular therapeutic intervention. Although there were no adverse reactions reported, including no significant QT interval prolongation, in this small cohort in the short term. While there are no approved antiviral agents, many new and old agents are under intense consideration. Investigational agents such as remdesivir are being actively studied for COVID-19 although access remains limited to clinical trials and an expanded access program. Off label use of available drugs such as lopinavir/ritonavir and hydroxychloroquine/chloroquine are being employed in the absence of robust data. While a large trial in China showed a lack of efficacy of lopinavir/ritonavir, no large studies have yet been published on hydroxychloroquine/chloroquine.[18] In both centers, after a careful assessment of the limited existing literature, hydroxychloroquine became the preferred initial therapy. While azithromycin was initially used in combination in one of the centers, this was later discouraged given the lack of evidence to support this approach. Immunomodulation is also being actively evaluated as a therapeutic approach, in particular among those patients experiencing rapid deterioration in the second week of illness. In particular, interleukin-6 receptor blockers such as tocilizumab and sarilumab are currently being explored to address the cytokine storm that has been described as a major driver of this rapid decompensation.[11] At this time, there are very limited data regarding the use of these agents among patients who are already immunosuppressed. In our cohort, 14 patients have received 1-3 doses each of tocilizumab with no adverse events so far noted. In addition, 16 patients received bolus steroids. The indications for using these immunomodulatory therapies, their optimal timing and how they interplay with baseline immunosuppression are currently unknown, despite great early interest.

The optimal management of immunosuppression in transplant recipients with COVID-19 also remains largely uncertain despite the importance and urgency of this question. In this cohort, based upon expert opinion only, the general approach was to decrease or hold the antimetabolite while dosing of other agents was less uniformly decreased. The impact of this approach is not clear. There is concern that immunosuppression may be associated with poor virologic control, leading to more severe disease and more prolonged viral shedding. Conversely, reducing immunosuppression may not only lead to acute rejection but may cause an immune reconstitution-like reaction with a paradoxical worsening of disease. There were no confirmed diagnoses of rejection after COVID-19 in this cohort during the study period, although this certainly may have been due to limited access to biopsies and the short timeframe. Furthermore, immunosuppression may play a role in attenuating a dysfunctional immune response and dampening cytokine release syndrome. There are limited reports addressing this issue. A case report from Wuhan, China, showed successful recovery from COVID-19 of a renal transplant patient from 12 years earlier when his immunosuppression was reduced and methylprednisolone was given.[10] In case of lung transplantation, since the main site of SARS-CoV-2 infection is the allograft with major influx of inflammatory cells, there may be a major role of high dose steroid therapy, particularly after the first several days of the illness. Additional data in this area are urgently needed.

In summary, in a 3-week period at two large academic medical centers in New York City, 90 solid organ transplant recipients were diagnosed with COVID-19, 68 (76%) of them were hospitalized and 16 patients have died thus far (18% of cohort, 24% of hospitalized patients, and 52% of ICU patients). While it is clear that the COVID-19 pandemic will leave many communities devastated, this initial report suggests that transplant recipients may be at high risk of severe disease and poor outcomes. There is an urgent need to investigate and identify the most effective antiviral strategies as well as determine the role of the immune response in order to guide appropriate immunomodulatory therapy which may be different in various solid organ transplant recipients.

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DISCLOSURE

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. ECV is on the

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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