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ORIGINAL ARTICLE

Influence of patient characteristics and immunosuppressant management on mortality in kidney transplant recipients hospitalized with coronavirus disease 2019 (COVID-19)

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Abstract

The influence of patient characteristics and immunosuppression management on COVID-19 outcomes in kidney transplant recipients (KTRs) remains uncertain. We performed a single-center, retrospective review of all adult KTRs admitted to the hospital with confirmed COVID-19 between 03/15/2020 and 05/15/2020. Patients were followed from the date of admission up to 1 month following hospital discharge or study conclusion (06/15/2020). Baseline characteristics, laboratory parameters, and immunosuppression were compared between survivors and patients who died to identify predictors of mortality. 38 KTRs with a mean baseline eGFR of 52.5 ml/min/1.73 m^2 were hospitalized during the review period. Maintenance immunosuppression included tacrolimus (84.2%), mycophenolate (89.5%), and corticosteroids (81.6%) in the majority of patients. Eleven patients (28.9%) died during the hospitalization. Older age (OR = 2.05; 1.04-4.04), peak D-dimer (OR = 1.20; 1.04-1.39), and peak white blood cell count (OR = 1.11; 1.02-1.21) were all associated with mortality among KTRs hospitalized for COVID-19. Increased mortality was also observed among KTRs with concomitant HIV infection (87.5% vs. 36.1%; $p < .01$). Conversely, immunosuppression intensity and degree of reduction following COVID-19 diagnosis were not associated with either survival or acute allograft rejection. Our findings potentially support a strategy of individualization of immunosuppression targets based on patient-specific risk factors, rather than universal immunosuppression reduction for KTRs at risk from COVID-19.

KEYWORDS
COVID-19, immunosuppressive agents, kidney transplantation, transplant recipients

1 | INTRODUCTION

The novel SARS-CoV-2 virus and resulting infectious syndrome termed coronavirus disease 2019 (COVID-19) has spread rapidly across the world, leading the World Health Organization to declare a global pandemic in March 2020.[1,2] SARS-CoV-2 transmission occurs primarily through respiratory droplets, with symptoms developing following a median incubation period of 4-5 days.[1,3,4] Disease severity ranges from mild or asymptomatic in the majority of patients, to a severe respiratory and inflammatory syndrome and ultimately death in 1%-3% of patients.[1] Solid organ transplant recipients are thought to be at high risk for morbidity and mortality from COVID-19 due to the necessity for chronic immunosuppressive therapy to prevent allograft rejection.[5,6] However, the optimal immunosuppressant management strategy and potential risk factors for severe COVID-19 disease in solid organ transplant recipients remain relatively unknown.

The majority of documented SARS-CoV-2 infections in solid organ transplant patients have been reported in kidney allograft recipients, with mortality rates ranging from 22% to 28% among hospitalized patients.[7-9] A number of risk factors have been purported to be associated with progression to severe COVID-19 in transplant recipients, including increased age, the presence of chronic comorbidities, and active malignancy; however, the role of chronic immunosuppression remains controversial.[3,7-10] A retrospective cohort study by Chaudhry et al[9] did not find a difference in the composite outcome of escalation of care, mechanical ventilation, or in-hospital all-cause mortality between kidney transplant recipients (KTRs) and non-transplant controls. Alternatively, a study of the UK transplant registry reported a 10.2% mortality rate among patients waitlisted for kidney transplant compared with 25.8% in post-transplant kidney allograft recipients.[10] These divergent findings could potentially be explained by underlying differences in baseline immunosuppression intensity and dose modulation following COVID-19 diagnosis. To examine the impact of immunosuppressant management on COVID-19 outcomes in transplant recipients, we provide a comprehensive retrospective review of all adult KTRs with confirmed COVID-19, managed at a single academic medical center during peak SARS-CoV-2 transmission within New York City. We explore immunosuppressant management strategies and potential clinical variables associated with COVID-19 related mortality in order to provide insight for clinicians attempting to manage KTRs during the ongoing SARS-CoV-2 pandemic. Additionally, we provide follow-up of allograft outcomes beyond index hospitalization in order to assess the impact of SARS-CoV-2 viral infection and immunosuppressant dose adjustment on the risk of acute allograft rejection.

2 | MATERIALS AND METHODS

This was an IRB-approved, single-center, retrospective cohort study of adult kidney or simultaneous kidney-pancreas transplant recipients with a functioning kidney or pancreas allograft who were admitted to the Mount Sinai Health System with confirmed COVID-19 during a two-month period between 03/15/2020 and 05/15/2020. A waiver of informed consent was granted by the local IRB. Patients were excluded from the review if they received a combined organ transplant other than pancreas or were chronically followed by an outside transplant center. Confirmation of COVID-19 diagnosis was based on RT-PCR testing of a nasopharyngeal swab specimen, using the Roche dual-target assay (one target specific to SARS-CoV-2 and second target for pan-Sarbecovirus), Cobas 6800 instrument. The United States Food and Drug Administration approved an emergency use authorization for the assay. All patients meeting the inclusion criteria, regardless of symptoms, had baseline demographic, transplant, and immunosuppressant data collected at the time of hospital admission and were subsequently evaluated up until study conclusion (06/15/2020), to ensure all patients had 1 month of follow-up. A pre-admission baseline estimated glomerular filtration rate (eGFR) was calculated by the modification of diet in renal disease equation (MDRD), using the median of the three most recently recorded serum creatinine values.

Standard immunosuppression at our institution includes rabbit anti-thymocyte globulin (rATG) induction, with maintenance tacrolimus, mycophenolate, and tapering corticosteroids based on perceived immunologic risk. Induction with the IL-2 inhibitor basiliximab may be considered for patients with a history of human immunodeficiency virus (HIV) or human leukocyte antigen (HLA)–identical sibling pairs. Belatacept and mechanistic target of rapamycin (mTOR) inhibitors are considered as alternative maintenance immunosuppressive agents for patients with a compelling indication for calcineurin inhibitor reduction or avoidance. For standard-risk transplant recipients maintained on tacrolimus therapy, 12-hour whole-blood tacrolimus trough targets are as follows: 10-12 ng/ml for months 1-3, 8-10 ng/ml for months 3-6, 6-8 ng/ml for months 6-12, and 4-6 ng/ml beyond 12 months. A baseline tacrolimus level prior to COVID-19 diagnosis was established for all study patients on maintenance tacrolimus therapy using the median trough value from all reported troughs during the 3 months prior to hospital admission.

General institutional recommendations for immunosuppression management upon hospital admission for COVID-19 included a 50% reduction in anti-metabolite dosing as well as a tacrolimus or mTOR target trough level of 4-6 ng/ml. For patients receiving monthly belatacept, doses were held up to 2 weeks from the original scheduled date of administration prior to re-dosing. If COVID-19 symptoms had not improved by 2 weeks, temporary conversion to tacrolimus with a trough target of 4-6 ng/ml was considered. Maintenance corticosteroid doses were continued following hospital admission for COVID-19, and adjunctive corticosteroid boluses were considered for patients with acute respiratory distress syndrome at the recommendation of pulmonary and infectious disease consultants. Protocols regarding antiviral and immunomodulatory treatments for COVID-19 disease evolved over the course of the review period as new data became available. Briefly, a 5-day course of off-label hydroxychloroquine was recommended for patients admitted to hospital with COVID-19 up until 5/4/2020 based on early in vivo

reports of efficacy, with the addition of a 3-day course of azithromycin based on the clinical discretion of the treating physician.[11] Either prophylactic or therapeutic anticoagulation was prescribed for patients based on clinical risk, and investigational therapies including convalescent plasma, remdesivir, and interleukin-6 (IL-6) or interleukin-1 (IL-1) inhibitors were considered in consultation with infectious disease and hematology experts.

Treatment response was monitored by routine clinical assessment, daily complete blood counts and metabolic chemistries, serum inflammatory markers (including C-reactive protein, D-dimer, and ferritin), and a one-time cytokine profile (including IL-6, interleukin-8, tumor necrosis factor-alpha, and IL-1 beta). For study purposes, COVID-19 disease severity was assigned at 1 month following diagnosis based on the published criteria proposed by Cao et al[12] and ranged from 1 (not hospitalized) to 7 (death during hospitalization). Serologic testing for the development of SARS-CoV-2 antibodies following infection consisted of an enzyme-linked immunosorbent assay to detect neutralizing antibody formation to the SARS-CoV-2 spike protein. Emergency use authorization for the assay was approved by the United States Food and Drug Administration.[13]

The primary outcome assessed in this review was in-hospital all-cause mortality among KTRs diagnosed with COVID-19. Additional secondary endpoints evaluated included patient and allograft survival at 1 month following hospital discharge or study conclusion (6/15/2020), incidence of acute kidney injury during hospitalization (AKI; based on the KDIGO definition of 1.5× increase in baseline serum creatinine over the course of 7 days or urine output <0.5 ml/kg/h for 6 hours), change in eGFR at 1 month following COVID-19 diagnosis, and the incidence of biopsy-proven acute rejection (BPAR) at any point during the review period. Categorical variables were expressed as raw numbers with percentages, and continuous variables were reported using mean ± standard deviation (SD) or median with interquartile range (IQR). Baseline characteristics and laboratory parameters of KTRs who died in the hospital following admission for COVID-19 were compared with survivors to identify potential predictors of mortality. Continuous variables were compared using the Wilcoxon rank-sum test for non-parametric data, and Fisher's exact test was utilized for categorical variables at $\alpha < .05$ for significance. Logistic regression generated odds ratios with 95% confidence intervals for pertinent variables, and a multivariable model was built testing all variables significant at the univariate level with a p-Value ≤ .05. Variables were added to the multivariable model sequentially based on univariate p-Values, and the impact on model performance was assessed via likelihood ratio testing. All data were collected and analyzed in accordance with local ethics guidelines and the Helsinki Declaration of 1975. Complete data analysis was conducted using Stata system software, version 14 (StataCorp LLC.).

3 | RESULTS

Between 03/15/2020 and 05/15/2020, 95 out of 2,126 (4.5%) KTRs followed longitudinally at our transplant center were diagnosed with RT-PCR–confirmed SARS-CoV-2 infection. Of these patients, 69 (72.6%) required hospital admission, 38 of whom were admitted to the Mount Sinai Hospital and comprised the study cohort. The mean age of the cohort was 53.8 ± 13.6 years, and the majority were African American (44.7%) or Hispanic/Latino (34.2%) [complete baseline characteristics are summarized in Table 1]. The mean baseline eGFR prior to hospital admission for COVID-19 was 52.5 ± 29.9 ml/min/1.73 m^2, and maintenance immunosuppression included tacrolimus, mycophenolate, and corticosteroids in 84.2%, 89.5%, and 81.6% of patients, respectively.

The median time from transplantation to COVID-19 diagnosis for the study cohort was 69.6 months (IQR = 18.5-114.2), and hospital admission occurred a median of 6 (IQR = 2-7) days following the onset of symptoms. Respiratory symptoms including cough and dyspnea were the most common presenting clinical manifestations (71.1%), followed by subjective fevers (63.2%), and gastrointestinal symptoms (28.9%). An interstitial infiltrate was present on chest radiography in the majority of cases (86.8%), but only 8 patients were found to have a peripheral oxygen saturation <90% on ambient air at the time of admission. Serum inflammatory markers including C-reactive protein (CRP), D-dimer, and ferritin were elevated upon presentation in the majority of cases and peaked following hospital admission (Table 2). Lymphopenia was also common, with a mean absolute lymphocyte count (ALC) of 587 ± 344 cells/μL observed on admission.

3.1 | Immunosuppression and antiviral management

Tacrolimus was the primary immunosuppressive agent in 32/38 patients at the time of COVID-19 diagnosis, while 4 patients were receiving belatacept, 1 patient was receiving sirolimus, and 1 patient was on a combination of corticosteroids and immune globulin. Of the 4 patients receiving belatacept, only 1 patient was converted back to tacrolimus during hospitalization. Median tacrolimus trough levels during the hospitalization were reduced by −11% from baseline, although significant variability was observed between patients (IQR = −26% to 17%). Antimetabolite doses were reduced by at least 50% in all but one patient receiving mycophenolate, and 13 (34.2%) patients had their antimetabolite discontinued entirely (Table 3). Twelve (31.6%) patients received pulse corticosteroids during hospitalization with total doses ranging from 555 to 1914 milligrams (mg) of prednisone equivalents. The most frequently prescribed corticosteroid regimen was methylprednisolone 80 mg daily for a duration ranging from 5 to 10 days. All corticosteroids were prescribed for the indication of COVID-19 pneumonia, and 3 patients additionally received stress-dose hydrocortisone. No patients received pulse corticosteroids for prophylaxis of allograft rejection at any point during the study period.

Empiric COVID-19–targeted therapy included hydroxychloroquine in 68.4% of patients, and 57.9% received concomitant azithromycin. Four patients were enrolled in a clinical trial, and 10 patients

TABLE 1 Baseline Characteristics and Immunosuppression for Patients Hospitalized with COVID-19

Demographics	All patients (*n* = 38)	Survived[a] (*n* = 27)	Died (*n* = 11)	*p*-Value
Mean age, years ± SD	53.8 ± 13.6	50.7 ± 13.2	61.5 ± 11.0	.03
Male sex	25 (65.8%)	17 (63.0%)	8 (72.7%)	.71
Ethnicity				
White/European	5 (13.2%)	4 (14.8%)	1 (9.1%)	.94
African American	17 (44.7%)	11 (40.7%)	6 (54.5%)	
Hispanic/Latino	13 (34.2%)	10 (37.0%)	3 (27.3%)	
Asian/Pacific Islander	3 (7.9%)	2 (7.4%)	1 (9.1%)	
Mean body mass index, kg/m^2 ± SD	28.3 ± 6.2	28.4 ± 6.0	28.1 ± 6.7	.66
Median time post-transplant, months (IQR)	69.6 (18.5-114.2)	67.0 (16.1-111.8)	103.5 (35.8-131.4)	.20
Etiology of kidney disease				
Hypertension	7 (18.4%)	5 (18.5%)	2 (18.2%)	.81
Diabetes mellitus	13 (34.2%)	8 (29.6%)	5 (45.5%)	
Glomerulonephritis	12 (31.6%)	10 (37.0%)	2 (18.2%)	
Polycystic kidney disease	3 (7.9%)	2 (7.4%)	1 (9.1%)	
Other	3 (7.9%)	2 (7.4%)	1 (9.1%)	
Underlying comorbidities				
Hypertension	34 (89.5%)	24 (88.9%)	10 (90.9%)	1.00
Diabetes mellitus	19 (50.0%)	13 (48.1%)	6 (54.5%)	1.00
Interstitial lung disease	3 (7.9%)	2 (7.4%)	1 (9.1%)	1.00
HIV	3 (7.9%)	0 (0.0%)	3 (27.3%)	.02
ACEI/ARB prescription	10 (26.3%)	7 (25.9%)	3 (27.3%)	1.00
Prior transplantation	4 (10.5%)	2 (7.4%)	2 (18.2%)	.56
Kidney donor type				
Living donor	17 (44.7%)	13 (41.8%)	4 (36.4%)	.72
Deceased donor	21 (55.3%)	14 (51.9%)	7 (63.6%)	
Combined kidney-pancreas transplant	2 (5.3%)	2 (7.4%)	0 (0.0%)	1.00
Induction immunosuppression				
Lymphocyte depleting	30 (78.9%)	24 (88.9%)	6 (54.5%)	.01
IL-2 inhibitor	3 (7.9%)	0 (0.0%)	3 (27.3%)	
None	2 (5.3%)	1 (3.7%)	1 (9.1%)	
Unknown	3 (7.9%)	2 (7.4%)	1 (9.1%)	
Maintenance immunosuppression				
Tacrolimus + mycophenolate	7 (18.4%)	6 (22.2%)	1 (9.1%)	.39
Tacrolimus + mycophenolate + corticosteroid	22 (57.9%)	14 (51.9%)	8 (72.7%)	
Tacrolimus + corticosteroid	3 (7.9%)	2 (7.4%)	1 (9.1%)	
mTOR + mycophenolate + corticosteroid	1 (2.6%)	1 (3.7%)	0 (0.0%)	
Belatacept + mycophenolate + corticosteroid	4 (10.5%)	4 (14.8%)	0 (0.0%)	
Corticosteroid + IVIG	1 (2.6%)	0 (0.0%)	1 (9.1%)	
Maintenance tacrolimus therapy	32 (84.2%)	22 (81.5%)	10 (90.9%)	.65
Maintenance corticosteroid therapy	31 (81.6%)	21 (77.8%)	10 (90.9%)	.65
Receiving triple immunosuppression therapy	27 (71.1%)	19 (70.4%)	8 (72.7%)	1.00
Median baseline tacrolimus trough, ng/ml (IQR)	6.5 (5.0-8.7)	6.8 (5.1-9.2)	6.4 (5.0-7.6)	.46

(Continues)

TABLE 1 (Continued)

Demographics	All patients (*n* = 38)	Survived[a] (*n* = 27)	Died (*n* = 11)	*p*-Value
Mycophenolate dose prior to diagnosis, mg				
No antimetabolite	4 (10.5%)	2 (7.4%)	2 (18.2%)	.76
≤1000 per day	19 (50.0%)	14 (51.9%)	5 (45.5%)	
>1000 per day	15 (39.5%)	11 (40.7%)	4 (36.4%)	
Mean baseline eGFR, ml/min/1.73 m^2 ± SD	52.5 ± 29.9	54.2 ± 31.2	48.2 ± 25.9	.69
Any treated rejection post-transplant	10 (26.3%)	5 (18.5%)	5 (45.5%)	.12
Treated malignancy within 1 year	3 (7.9%)	1 (3.7%)	2 (18.2%)	.20
Hospitalization for infection during the past year	7 (18.4%)	6 (22.2%)	1 (9.1%)	.34

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ESRD, end-stage renal disease; IQR, interquartile range; IVIG, intravenous immunoglobulin; SD, standard deviation.

[a]As of June 15, 2020.

received convalescent plasma therapy through an institutional research protocol (Table 3). Treatment-dose anticoagulation was prescribed for 20 (52.6%) patients and included treatment with an anti-Xa inhibitor in 10 (26.3%) patients.

3.2 | Patient and Allograft outcomes

Of the 26 out of 95 (27.4%) KTRs who did not require hospitalization, all patients were alive with functioning allografts at 1 month following COVID-19 diagnosis. Conversely, 20 of 38 KTRs (52.6%) admitted to hospital developed severe COVID-19 at 1 month defined by a COVID-19 severity score ≥ 5, and 11 of 38 (28.9%) patients died during hospitalization.[12] Of the 24 patients surviving to hospital discharge (3 patients remain hospitalized), 18 were able to be discharged home, while 6 required temporary transfer to a rehabilitation facility (Table 4). A follow-up SARS-CoV-2 RT-PCR was checked in 18 of the 27 patients alive at the time of study conclusion, 15 of which were found to be undetectable after a median of 45 days (IQR = 33-60). SARS-CoV-2 serology was assessed in 15 of 27 surviving patients, 14 of which reported serum antibody titers >1:80.

Overall kidney allograft survival at 1 month following hospital discharge or study conclusion was 67.6%, but increased to 96.2% when censored for patient death. One patient survived with new allograft failure, although this patient had a baseline serum creatinine of 5.6 mg/dl prior to hospitalization and was already in the process of relisting for kidney transplant. Both recipients of combined kidney-pancreas transplants continued to have functioning pancreas allografts at the conclusion of the study, but one patient had a prior failed kidney transplant and subsequently was excluded from all kidney analyses. AKI was common and occurred in 22 (59.5%) patients, with 12 (32.4%) patients requiring renal replacement therapy during hospitalization. However, among patients who maintained a functioning allograft at 1 month following COVID-19 diagnosis, the mean change in eGFR from baseline was −1.6 ± 19.5 ml/min/1.73 m^2, and kidney function returned to baseline in the majority of cases following viral recovery. Additionally, no cases of suspected or biopsy-proven allograft rejection occurred at any point during the study period.

3.3 | Risk factors for hospital mortality

3.3.1 | Baseline characteristics

Patients experiencing in-hospital mortality were generally older (61.5 vs 50.7 years; $p = .03$) and were more likely to have a history of HIV and had subsequently received IL-2 inhibitor-based induction therapy (27.3% vs 0.0%; $p = .01$). The Cox regression analysis demonstrated that each decade of life was associated with a 2.05 higher odds of mortality in our patient cohort (OR = 2.05; 95% CI: 1.04, 4.04). Concomitant HIV infection could not be evaluated in the multivariable modeling due to the low event rate; however, as all 3 HIV-positive KTRs admitted at our center died, we additionally examined the mortality rate for any HIV-positive patients followed at our transplant center who were admitted to outside hospitals with COVID-19. We identified an additional 5 cases, 4 of whom died due to complications related to severe COVID-19. When all 69 hospitalized patients followed at our center were analyzed (8 HIV-positive vs. 61 HIV-negative), KTRs with concomitant HIV had a significantly higher mortality rate compared with their HIV-negative counterparts (87.5% vs. 36.1%); $p < .01$, Table S1).

3.3.2 | Symptoms/Laboratories

We did not find that presenting symptomatology or hypoxia on admission was associated with in-hospital mortality in our patient cohort. Despite similar serum inflammatory markers at baseline, patients who died demonstrated higher peak CRP (255.0 vs 183.6 mg/L; $p = .04$), D-dimer (12.6 vs 5.4 mg/L; $p = .01$), and white blood cell (24.4 vs 14.2 cells/L; $p = .01$) counts as well as a lower

TABLE 2 Symptoms and Laboratory Parameters Following Hospital Admission for COVID-19

Variables	All patients (*n* = 38)	Survived (*n* = 27)	Died (*n* = 11)	*p*-Value
Median days of symptoms (IQR)	6 (2-7)	6 (1-8)	5 (2-7)	.87
Patient-reported symptoms on admission				
Respiratory (cough/dyspnea)	27 (71.1%)	21 (77.8%)	6 (54.5%)	.24
Gastrointestinal (diarrhea/vomiting)	11 (28.9%)	8 (29.6%)	3 (27.3%)	1.00
Subjective fevers	24 (63.2%)	15 (55.6%)	9 (81.8%)	.16
Interstitial infiltrate on chest X-ray	33 (86.8%)	22 (81.5%)	11 (100.0%)	.29
Oxygen saturation < 90% at admission	8 (21.1%)	6 (22.2%)	2 (18.2%)	1.00
qSOFA score ≥ 2 at admission	3 (7.9%)	2 (7.4%)	1 (9.1%)	1.00
Mean procalcitonin on admission, ng/ml ± SD	0.76 ± 1.20	0.55 ± 0.83	1.47 ± 1.92	.16
Mean C-reactive protein, mg/L ± SD				
Admission	111.5 ± 80.7	104.5 ± 70.0	132.3 ± 109.3	.73
Peak	201.4 ± 100.1	183.6 ± 104.3	255.0 ± 64.2	.04
Mean D-dimer, mg/L ± SD				
Admission	1.7 ± 1.4	1.7 ± 1.2	1.9 ± 1.9	.72
Peak	7.3 ± 7.4	5.4 ± 6.5	12.6 ± 7.3	.01
Mean ferritin, ng/ml ± SD				
Admission	2310 ± 2821	2080 ± 2047	2976 ± 4479	.88
Peak	5832 ± 7516	4796 ± 7009	8824 ± 8544	.21
Mean peak IL-6, mg/L ± SD	218.0 ± 538.6	221.5 ± 630.6	209.5 ± 209.9	.06
Mean peak tumor necrosis factor, ng/ml ± SD	31.5 ± 14.9	30.2 ± 14.1	35.0 ± 17.5	.58
Mean white blood cell count, cells/L ± SD				
Admission	8.3 ± 4.9	8.8 ± 4.9	7.1 ± 4.5	.26
Peak	17.1 ± 11.5	14.2 ± 8.9	24.4 ± 13.7	.01
Mean absolute lymphocyte count, cells/μL ± SD				
Admission	587 ± 344	630 ± 358	482 ± 296	.26
Discharge/death	850 ± 609	1011 ± 637	455 ± 277	<.01
Microbiologically documented bacterial, viral, or fungal co-infection	5 (13.2%)	4 (14.8%)	1 (9.1%)	.65
Highest level of respiratory support				
None	8 (21.1%)	8 (29.6%)	0 (0.0%)	.09
Nasal cannula	10 (26.3%)	8 (29.6%)	2 (18.2%)	
BiPAP/high-flow nasal cannula	6 (15.8%)	3 (11.1%)	3 (27.3%)	
Mechanical ventilation	14 (36.8%)	8 (29.6%)	6 (54.5%)	
Acute kidney injury or dialysis requirement	23 (60.5%)	16 (59.3%)	7 (63.6%)	1.00
Mean peak serum creatinine, mg/dl ± SD	4.4 ± 3.3	4.3 ± 3.7	4.4 ± 2.3	.46
Mean peak ALT, U/L ± SD	70.7 ± 92.1	73.9 ± 96.7	63.0 ± 83.7	.55

Abbreviations: BiPAP, bilevel positive airway pressure; IL-6, interleukin-6; IQR, interquartile range; SD, standard deviation.

ALC at discharge/death or study conclusion (455 vs 1011 cells/μl; $p < .01$). We did not observe a statistically significant difference in admission procalcitonin or peak IL-6, tumor necrosis factor-alpha, or serum creatinine levels between survivors and patients who died of severe COVID-19. In the final regression model, after adjusting for age, peak D-dimer (OR = 1.20; 95% CI: 1.04, 1.39) and WBC levels (OR = 1.11; 95% CI: 1.02, 1.21) remained independent predictors of COVID-19–related mortality (Table 5).

3.3.3 | Immune modulation

Immunosuppressant and antiviral management were largely similar between survivors and patients who died, with the exception of higher total corticosteroid doses and more frequent prescription of treatment-dose anticoagulation in patients who died. However, as this likely reflects differences in underlying disease severity rather than treatment efficacy, we performed a subgroup analysis for the

TABLE 3 Antiviral and Immunomodulatory Management during Hospitalization for COVID-19

Characteristics	All patients (*n* = 38)	Survived (*n* = 27)	Died (*n* = 11)	*p*-Value
Median tacrolimus trough during admission, ng/ml				
Alternative therapy during admission	5 (13.2%)	4 (14.8%)	1 (9.1%)	.77
1.0-5.0	10 (26.3%)	7 (25.9%)	3 (27.3%)	
5.1-10.0	19 (50.0%)	14 (51.9%)	5 (45.5%)	
>10.0	4 (10.5%)	2 (7.4%)	2 (18.2%)	
Percentage reduction in median tacrolimus trough				
Alternative therapy prior to admission	6 (15.8%)	5 (18.5%)	1 (9.1%)	.83
No reduction	15 (39.5%)	10 (37.0%)	5 (45.5%)	
10%-30%	12 (31.6%)	8 (29.6%)	4 (36.4%)	
>30%	5 (13.2%)	4 (14.8%)	1 (9.1%)	
Percentage change in tacrolimus trough (IQR)	−11% (−26% to 17%)	−11% (−28% to 11%)	−6% (−22% to 33%)	.32
Mycophenolate dose				
Off antimetabolite	4 (10.5%)	2 (7.4%)	2 (18.2%)	.68
Same dose	1 (2.6%)	1 (3.7%)	0 (0.0%)	
50%-75% dose reduction	20 (52.6%)	14 (51.9%)	6 (54.5%)	
Hold antimetabolite	13 (34.2%)	10 (37.0%)	3 (27.3%)	
Total prednisone equivalents administered during hospitalization, mg				
<500	25 (65.8%)	20 (74.1%)	5 (45.5%)	.15
500-1000	8 (21.1%)	5 (18.5%)	3 (27.3%)	
>1000	5 (13.2%)	2 (7.4%)	3 (27.3%)	
Mean prednisone equivalents per day during hospitalization, mg	17.2 ± 18.6	12.9 ± 16.5	27.7 ± 19.2	.04
Enrolled in clinical trial	4 (10.5%)	4 (14.8%)	0 (0.0%)	.18
Antiviral and immunomodulatory therapies				
Hydroxychloroquine	26 (68.4%)	18 (66.7%)	8 (72.7%)	.71
Azithromycin	22 (57.9%)	14 (51.9%)	8 (72.7%)	.24
Remdesivir	3 (7.9%)	2 (7.4%)	1 (9.1%)	.86
IL-6 or IL-1 inhibitor	3 (7.9%)	2 (7.4%)	1 (9.1%)	.86
Convalescent plasma	10 (26.3%)	6 (22.2%)	4 (36.4%)	.37
Anticoagulation therapy				
None	2 (5.3%)	1 (3.7)	1 (9.1%)	.37
Prophylactic dose	16 (42.1%)	13 (48.1%)	3 (27.3%)	
Treatment dose	20 (52.6%)	13 (48.1%)	7 (63.6%)	
Prescription of anti-Xa inhibitor	10 (26.3%)	8 (29.6%)	2 (18.2%)	.46

20 patients with severe COVID-19 (severity score ≥ 5) at 1 month. Among these patients, only the mean prednisone equivalents administered per day during hospitalization were different between survivors and those who died (15.4 vs 37.0 mg/day; $p = .02$; Table S2). No statistically significant differences were observed in baseline immunosuppressant regimen, dosing intensity, or percentage reduction in immunosuppression following hospital admission among survivors. The administration of hydroxychloroquine, convalescent plasma, and treatment dose anticoagulation was also not found to be associated with improved survival among our KTRs with severe COVID-19 (Table S2).

4 | DISCUSSION

The SARS-CoV-2 pandemic has placed a particular burden on immunosuppressed patient populations, including the organ transplant community.[6,14] Transplant volumes declined by nearly 50% in March and April during the early phase of the pandemic in the United States, and in a national survey of the largest kidney transplant centers, 85.1% of respondents reported being extremely or highly concerned about the impact of COVID-19 on transplant recipients.[14,15] We observed a wide spectrum of disease severity in KTRs diagnosed with COVID-19 at our center, with 26 (27.4%) patients able

TABLE 4 Patient and Allograft outcomes following COVID-19 infection

Outcomes	All patients (*n* = 38)
Hospital discharge disposition	
Still hospitalized	3 (7.9%)
Home	18 (47.4%)
Rehabilitation	6 (15.8%)
Expired	11 (28.9%)
Allograft survival	
1 month following hospital discharge or study conclusion	25/37 (67.6%)
1 month following hospital discharge or study conclusion censored for death	25/26 (96.2%)
Acute kidney injury	
KDIGO criteria (*n* = 37)	22 (59.5%)
Requiring renal replacement therapy (*n* = 37)	12 (32.4%)
Mean change in eGFR at 1 month following COVID-19 diagnosis, ml/min/1.73 m^2 ± SD	−1.6 ± 19.5
BPAR during study review period	0 (0.0%)

Abbreviations: BPAR, biopsy-proven acute rejection; eGFR, estimated glomerular filtration rate.

TABLE 5 Risk Factors for Mortality Following Hospitalization for COVID-19

	Unadjusted OR (95% CI)	*p*-Value	Adjusted OR[a] (95% CI)	*p*-Value
Baseline characteristics				
Age (per 10 years)	2.05 (1.04, 4.04)	.04		
History of HIV	22.65 (1.06, 483.71)	.04		
Laboratory parameters				
Peak D-dimer (per 1 mg/L increase)	1.14 (1.03, 1.27)	.01	1.20 (1.04, 1.39)	.01
Peak WBC (per 1 cell/L increase)	1.08 (1.01, 1.16)	.03	1.11 (1.02, 1.21)	.02

[a]Adjusted for age.

to be managed remotely with 100% patient and allograft survival at 1 month. Alternatively, in our cohort of KTRs admitted to hospital, we observed an overall mortality rate of 28%, which is similar to previous reports, and is 2-3× higher than mortality rates reported in the general hospitalized population.[3,4,7-9] While these findings should not preclude kidney transplantation, there is a suggestion that KTRs may be at high risk of significant morbidity and mortality following hospitalization for COVID-19. Among our cohort of KTRs, as has been previously reported, age was independently associated with an approximately 2× higher odds of mortality for each decade of life.[7,16,17] We also observed a remarkably high mortality rate in hospitalized KTRs with COVID-19 and HIV co-infection, despite all patients having undetectable viral loads prior to hospitalization and a mean CD4 count of 373 ± 185 cells/mm^3. This potentially warrants further investigation in a multi-center study as prior publications in non-transplant populations have reported equivalent COVID-19 outcomes in HIV-positive and HIV-negative patients.[18] Based on our findings, older KTRs and patients with concomitant HIV and transplantation appear to be at particular risk for in-hospital mortality from COVID-19 and warrant prompt medical referral and aggressive monitoring for signs of clinical deterioration.

There was a high incidence of AKI in our cohort of KTRs (59.5%). In a meta-analysis by Robbins-Juarez *et al*, the incidence of AKI following COVID-19 diagnosis ranged from 0.5% to 80.3%, with a mean of 17%.[19] Additionally, a prior report from our own center in non-KTRs reported a 46% incidence of AKI.[20] These results suggest that KTRs may be particularly susceptible to COVID-19–mediated kidney injury, although whether this damage is the result of direct viral injury to the allograft or secondary to other mechanisms remains a matter of debate. Autopsies of patients with COVID-19 and AKI have demonstrated endothelial injury with severe acute tubular necrosis and lymphocyte and macrophage infiltration, although how this translates to KTRs is unknown.[21] Encouragingly, at 1 month post–COVID-19 diagnosis, eGFR returned to pre-infection levels in nearly all patients with a functioning allograft. Additionally, no cases of acute rejection following COVID-19 infection were observed for the duration of the study period in spite of immunosuppressant reduction. These results suggest that if KTRs can be supported through

the acute illness, COVID-19 disease may not pose prolonged risk to the transplant allograft.

The optimal treatment strategy for KTRs infected with COVID-19 remains unknown. A number of antiviral and immunomodulatory therapies are currently under investigation for the treatment of COVID-19 and are beyond the scope of this study. In the absence of a well-defined treatment standard, most transplant centers reduce immunosuppression as a component of COVID-19 management; however, this practice is based on expert consensus, without explicit treatment targets.[7-9] The findings from our study are generally consistent with those reported by Kates *et al*, which concluded that the presence of patient comorbidities was more predictive of COVID-19 mortality than the intensity of immunosuppression at diagnosis.[16] In our review, we did not find that the choice or number of immunosuppressants, baseline tacrolimus levels or antimetabolite dose, or the use of maintenance corticosteroids were associated with COVID-19 mortality. Similarly, we also did not observe that degree of immunosuppressant reduction following hospitalization or lower calcineurin inhibitor trough levels was associated with reduced mortality in KTRs with severe COVID-19. The only significant difference in immunosuppressant dosing between groups was a higher mean daily corticosteroid dose among patients who died. Given the reduction in mortality demonstrated with the use of dexamethasone in patients requiring supplemental oxygen in the RECOVERY study, it is likely that this finding reflects differences in disease severity in our patient cohort as well as the use of stress-dose hydrocortisone in critically ill patients.[22] Additionally, methylprednisolone was the corticosteroid of choice for COVID-19 treatment at our center and may have differential pharmacologic effects compared with dexamethasone which has a longer duration of action and more potent systemic glucocorticoid effects.[23] Future studies are still needed to clarify the optimal agent, dose, and duration of corticosteroids for severe COVID-19 in KTRs already receiving chronic maintenance corticosteroids in order to minimize the potential detrimental effects associated with glucocorticoids, including delayed viral clearance.[24,25] Although there is no definitive evidence that immunosuppression reduction improves mortality in the setting of COVID-19 pneumonia, we did not observe a signal for increased allograft rejection following infection.[26] Hence, we continue to consider immunosuppression reduction at the time of COVID-19 diagnosis on a case-by-case bases, taking into account markers of COVID-19 disease severity, patient-specific comorbidities, and markers of systemic inflammation.

We acknowledge that there are limitations to consider when extrapolating our findings. This was a relatively small patient cohort at a single transplant center and was not adequately powered to detect small differences in patient characteristics that may influence COVID-19 outcomes. The effects of multiplicity and multicollinearity also cannot be excluded based on the number of independent variables examined and clinical overlap between biomarkers of systemic inflammation. Additionally, although patient management and treatment selection were guided by institutional protocols, these protocols were subject to individual clinician judgment and evolved over the course of the pandemic as further data became available. As a result, a significant number of our patients received courses of off-label hydroxychloroquine ± azithromycin, which have subsequently been shown to lack efficacy. Finally, our understanding of SARS-CoV-2 and COVID-19 is continually evolving, raising the possibility that additional confounding variables that were not considered may influence treatment outcomes. Despite these limitations, our study provides a detailed analysis of immunosuppression dosing in KTRs hospitalized with confirmed COVID-19 and found no association between baseline immunosuppression intensity or dose modifications following COVID-19 diagnosis and subsequent in-hospital mortality. Additionally, we confirm the findings that older age as well as increasing peak serum inflammatory markers and persistent lymphopenia may be able to identify KTRs at high risk for mortality following hospitalization for COVID-19.

5 | CONCLUSIONS

Kidney transplant recipients diagnosed with COVID-19 are at high risk of poor outcomes following hospitalization, with mortality rates ranging from 22% to 28%. Older age is a significant risk factor for COVID-19–related mortality that has been replicated in a number of studies and was associated with approximately 2× higher odds of death in our patient cohort for each decade of life. We also observed an unusually high rate of mortality in HIV-infected KTRs at our center, which warrants additional study. Baseline symptoms and laboratory values at the time of hospitalization have not been shown to predict COVID-19 mortality, but serum inflammatory markers including D-dimer, CRP, and white blood cell counts should continue to be monitored longitudinally to assess disease course and treatment response. While it has not been explicitly shown to reduce mortality, immunosuppression reduction was not associated with allograft rejection in our study and could be considered on a case-by-case basis.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Andrew Santeusanio, PharmD, BCPS *(corresponding author)*, Arjun Bhansali, MD, Fahima Mahir, MD, and Niralee Patel, MD, participated in research design and involved in data collection. Madhav C. Menon, MD *(co-corresponding author)* participated in research design, assisted with statistical analysis, and assisted with editing of the manuscript. Caroline Liu, MHS, performed statistical analysis and assisted with editing of the manuscript. Meenakshi Rana, MD, Ahmad Mahamid, MD, Yaniv Fenig, MD, and Alexey Zendel, MD, participated in research design, involved in data collection, and assisted

with editing of the manuscript. Sander Florman, MD, assisted with editing of the manuscript. Fasika Tedla, MD, Veronica Delaney, MD, Graciela De Boccardo, MD, Samira S. Farouk, MD, Vinita Sehgal, MD, Rafael Khaim, DNP, Samantha E. Jacobs, MD, Dallas Dunn, MD, Timothy Sullivan, MD, Sarah Taimur, MD, Emily Baneman, MD, and Ron Shapiro, MD, participated in research and assisted with editing of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author (Andrew Santeusanio, PharmD; Andrew.Santeusanio@mountsinai.org). The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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