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Kidney Transplant Recipients Infected With Coronavirus Disease 2019: Retrospective Qatar Experience

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ABSTRACT

Background. This study aimed to evaluate the incidence of coronavirus disease 2019 (COVID-19) infection on kidney transplant, mortality, and risk factors associated with infection acquisition and severe illness in kidney transplant recipients with COVID-19.

Methods. Of 693 kidney transplant recipients who reported to our center, 249 were tested for COVID-19 by throat and nasal swab reverse transcription polymerase chain reaction. Of these, 43 recipients tested positive and 206 recipients tested negative. Among the 43 positive recipients, 9 were treated within an isolation facility, 25 were admitted to the hospital, and 9 were admitted to the intensive care unit (ICU). Risk factors associated with positive results and ICU admission were evaluated.

Results. COVID-19 was found in 6% of transplant recipients. Asian ethnicity ($p = .003$), history of hypertensive nephropathy ($p = .01$), AB blood group ($P = .04$), and higher tacrolimus trough levels ($P = .007$) were more frequent in the COVID-19 positive than in the COVID-19 negative group. ICU admission was more frequent in recipients presenting with fever, shortness of breath, and acute allograft dysfunction. Renal replacement therapy was required in 3 (7%) of 43 recipients, and mortality was reported in 1 (2.3%) recipient. Acute allograft dysfunction was an independent risk factor for severe COVID-19 (odds ratio, 93.7; 95% confidence interval, 2.37-3710.94; $P = .02$).

Conclusions. Higher tacrolimus targets may be associated with COVID-19 development. Acute kidney injury during the COVID-19 course may be a sign of severe disease. Prognostication of COVID-19 severity in kidney transplant recipients is crucial for early recognition of critical illness and may ensure early intervention.

THE world is confronting the rapid spread of coronavirus disease 2019 (COVID-19), with more than 135 million cases reported as of April 2021 [1]. Although most patients remain asymptomatic or develop only a mild form of COVID-19, approximately 5% develop a severe form that usually requires intensive care support for complications of acute respiratory distress syndrome (ARDS) and multiple-organ failure [2]. Mortality is associated with old age, diabetes mellitus, hypertension, cardiovascular disease, and chronic kidney disease. The effect of COVID-19 on kidney transplant recipients has not been well investigated. It is assumed that the high prevalence of cardiometabolic comorbidities and impaired immune defenses make this population more susceptible to severe illnesses. However, there is also a suggestion that immunosuppression may reduce the cytokine-mediated inflammation associated with COVID-19 and, therefore, reduce the severity

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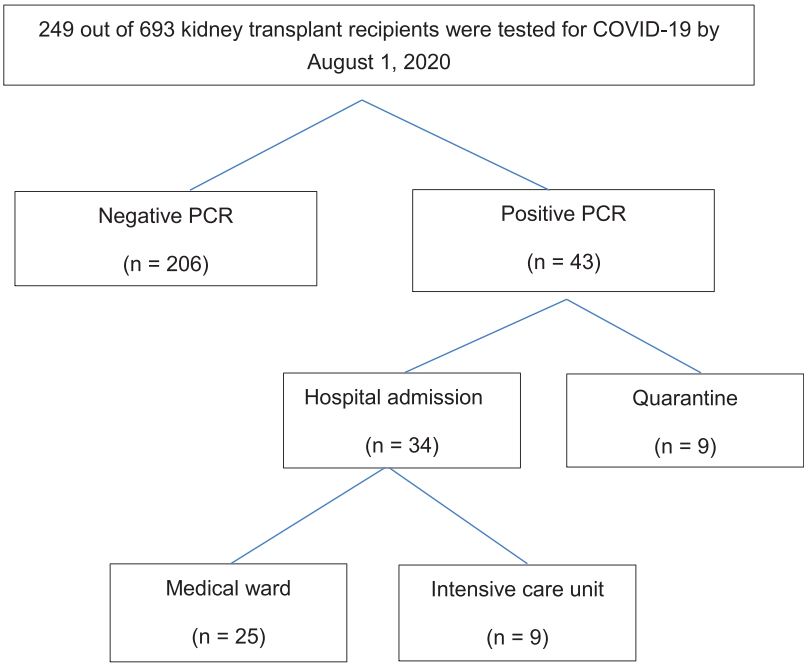

Fig. 1. Flow chart showing study design. COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction.

of the disease [2-5]. The primary aim of this study was to determine the incidence of COVID-19 in the state of Qatar and its 60-day mortality in kidney transplant recipients. The secondary aim was to evaluate the predisposing factors associated with infection development, clinical course of patients with COVID-19, and risk factors for their admission to the intensive care unit (ICU).

MATERIALS AND METHODS

Since the start of the COVID-19 pandemic, testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Qatar was carried out exclusively by the Ministry of Public Health by various manual and automated reverse transcription polymerase chain reaction assay platforms. All platforms were validated in line with the College of American Pathologists' accreditation standards .

A national lockdown, social distancing measures, and mandatory face masks in public areas were enforced across the country. Work-from-home facilities were provided to immunocompromised patients. To minimize the risk of health care−associated viral transmission, telemedicine clinics were introduced, and a special laboratory service dedicated to transplant recipients was created in an isolated area of the hospital. Furthermore, a home delivery medication service was provided.

Patients requiring hospitalization were admitted to 1 of the COVID-19−designated government hospitals to limit the spread of the infection across health care facilities in the country. All government hospitals and primary health care centers shared the same electronic medical record system, which included all hospitalization details such as medical notes, laboratory investigations, and imaging studies.

Patient Selection and Study Design

We retrospectively reviewed the medical records of all kidney transplant recipients in our national registry. The study design is summarized in Fig 1. This study was approved by the ethics review board of Hamad Medical Corporation Medical Research Center (MRC-01-20-679). The study protocol complies with the ethical standards set forth in the Declaration of Helsinki.

Criteria and Definitions

The criteria for admission to ICU were septic shock requiring vasopressor support or hypoxia requiring at least 6 L of oxygen per minute, noninvasive mechanical ventilation, or intubation. Hypoxia was defined as oxygen saturation <94% requiring supplemental oxygen, noninvasive mechanical ventilation, or intubation. Acute kidney injury (AKI) was defined as an increase in the serum creatinine level ≥26.5 μmol/L from baseline, as per the *Kidney Disease: Improving Global Outcomes 2012* guidelines [6]. Lymphopenia was defined as having <1000 lymphocytes per microliter. Calcineurin inhibitor (CNI) trough levels were reported as the average of the last 3 CNI levels beforeSARS-CoV-2 testing.

Immunosuppression Management

The dosages of antimetabolites such as mycophenolate mofetil and azathioprine were reduced by 50% in patients admitted to medical wards and stopped in those admitted to the ICU. CNI trough levels were maintained between 4 and 7 ng/mL and 50 and 100 ng/mL for tacrolimus and cyclosporine, respectively. However, CNI was discontinued in septic patients requiring vasopressor support. Prednisolone dosage was increased to 10 mg daily unless the patient was receiving IV dexamethasone.

Statistical Analysis

Data were summarized using frequency measures for categorical variables and mean and standard deviation (SD) for continuous variables. Fisher exact test and Mann-Whitney *U* test were used to compare

categorical and continuous variables, respectively, between COVID-19 negative and positive groups. Risk factors associated with the severity of COVID-19 were compared among the 3 severity groups using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Risk factors for ICU admission were determined by univariate and multivariate analyses. Variables with a P value < .1 were included in the multivariate analyses. The significance level was set at 5%.

RESULTS

Testing and Incidence of COVID-19

Of the 693 patients, 249 underwent SARS-CoV-2 polymerase chain reaction testing by August 1, 2020. A total of 43 patients tested positive and 34 required admission. Most of the confirmed patients who were positive were male (81%), were Middle Eastern (60%), had undergone living unrelated kidney transplant (63%), and had hypertension (91%) and diabetes mellitus (51%) (Table 1).

Asian ethnicity (37% vs 16%, P = .003), AB blood group (12% vs 3%, P = .04), hypertensive nephropathy (23% vs 9%, P = .01), deep vein thrombosis (DVT) (21% vs 1%, P = .002), and higher tacrolimus trough levels (7.6 ng/mL vs 6.7 ng/mL, P = .007) were significantly higher in the COVID-19 positive group than in the COVID-19 negative group. By contrast, the age, sex, and donor type were similar in both groups. The indication for COVID-19 testing played a significant role in test results, with significantly more positive COVID-19 test results in symptomatic patients (84% vs 18%, P = .0001) and significantly more negative results in patients who had undergone random screening (0% vs 34%, P = .0001). We observed a similar proportion of recipients who had come into contact with a patient positive for COVID-19 in both the positive and negative groups (14% vs 14%, P = .9). Asian ethnicity, AB blood group, hypertensive nephropathy, and higher tacrolimus trough levels were found to be independent variables of susceptibility prediction for COVID-19 (Table 2).

Course of COVID-19

Of the 43 patients positive for COVID-19, 9 (21%) were admitted to a COVID-19 isolation facility, and the remaining 34 (79%) required hospital admission, compared with 28.5% in our general population [7]. Among the 34 admitted recipients, 9 (21%) required ICU treatment, compared with 7.6% in our general population [7]. Twenty-five patients (73.5%) were discharged without ICU treatment. The median length of hospital stay was 14 days.

Predictors of Hospital Admission During the COVID-19 Course

We evaluated the predictors of COVID-19 severity by comparing recipients admitted to the ICU, recipients admitted to the hospital only, and recipients admitted to an isolation facility. We observed that older age showed a significantly higher association with patients in the ICU group than those in the hospital and isolation groups, as shown in Table 3 (57 vs 53 vs 45, P = .03). Sex, ethnicity, and type of transplant were comparable among the 3 groups. In addition, the tacrolimus trough level (7.3 vs 7.9 vs 7.0, P = .7), mycophenolate mofetil dose >1500 mg/day (56% vs 52% vs 56%, P = .6), and baseline creatinine levels (138 μmol/L vs 117 μmol/L vs 124 μmol/L, P = .4) were not significantly different among the 3 groups.

A significantly higher number of patients presented with fever (89% vs 36% vs 11%, P = .002) and shortness of breath (44% vs 12% vs 0, P = .02) in the ICU group than in those in the hospital and isolation groups. A high proportion of asymptomatic recipients who tested positive for COVID-19 were admitted to the isolation facility (P = .0006). Laboratory findings showed a significantly more frequent occurrence of lymphopenia (P = .02), low albumin (P = .01), high c-reactive protein (P = .02), and high procalcitonin (P = .01) levels on presentation in the ICU group.

We performed a multivariable analysis to predict ICU admission among recipients who tested positive for COVID-19, as shown in Table 4. In model 1, we evaluated age, history of diabetes mellitus, and fever on presentation, which revealed fever on presentation as a significant independent risk factor (odds ratio [OR], 17.2; 95% confidence interval [CI], 1.79-164.14; P = .02). After the addition of acute graft dysfunction to model 1, model 2 revealed only acute graft dysfunction as a significant independent variable for ICU admission (OR, 37.3; 95% CI, 2.63-527.13; P = .007). Similarly, in model 3, after the addition of lymphopenia, c-reactive protein, and ferritin to model 2, we still observed only acute graft dysfunction as an independent variable (OR, 93.7; 95% CI, 2.37-3710.94; P = .007).

Treatment of COVID-19 in Hospitalized Recipients

Treatment with hydroxychloroquine, oseltamivir, ritonavir, and azithromycin was more frequent in the ICU group than in the hospital and isolation groups (Table 5). In addition, mycophenolate mofetil and tacrolimus reduction or discontinuation were more frequent in the ICU group than in the hospital and isolation groups (89% vs 32% vs 11%, P = .003 and 100% vs 60% vs 0, P < .0001, respectively). Suspension of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blocker was also more frequent in the ICU group (100% vs 10% vs 0, P = .0002) than in the non-ICU and isolation groups.

COVID-19 Outcomes

In this study, 14 (32%) patients developed acute allograft dysfunction: 8 (89%) in the ICU group and 6 (24%) in the hospital group. An augmented cytosorb filter was used in 2 out of 3 patients who required renal replacement therapy. Five recipients admitted to the ICU required mechanical ventilation, and 1 required extracorporeal membrane origination. Only 1 (2.3%) death at 60-day follow-up, which occurred in the ICU group, was recorded among all recipients who developed COVID-19, compared with 0.28% in the general population [7].

Moreover, 11 of 14 patients with AKI had renal recovery at 30 days postinfection, whereas 2 recipients became dialysis-

Table 1. Baseline Characteristics of Kidney Transplant Recipients Tested for SARS-CoV-2 Infection

Variable	Negative n = 206	Positive n = 43	*P* value
Number of years since transplant, n (%)			
<1 y	12 (6)	1 (2)	.7
1-5 y	71 (34)	14 (33)	.9
5-10 y	45 (22)	14 (33)	.2
>10 y	78 (38)	14 (33)	.6
Age (y), mean ± SD	53.7 ± 13.9	52 ± 10.6	.2
Sex, n (%)			
Male	143 (69)	35 (81)	
Female	63 (31)	8 (19)	.1
Race, n (%)			
Middle Eastern	149 (72)	26 (60)	.1
Asian	33 (16)	16 (37)	.003
African	23 (11)	1 (2)	.09
Other	1 (1)	0	.9
Blood group, n (%)			
A	77 (37)	11 (26)	.2
B	38 (18)	13 (30)	.1
AB	7 (3)	5 (12)	.04
O	84 (41)	14 (33)	.4
Native kidney disease, n (%)			
Diabetic kidney disease	66 (32)	8 (19)	.1
Hypertensive kidney disease	18 (9)	10 (23)	.01
Glomerulonephritis	44 (21)	8 (19)	.8
Retransplantation	7 (3)	3 (7)	.4
Others	35 (17)	4 (9)	.3
Unknown	36 (17)	10 (23)	.4
Comorbid conditions, n (%)			
Diabetes mellitus	126 (61)	22 (51)	.2
Hypertension	182 (88)	39 (91)	.8
Ischemic heart disease	38 (18)	5 (12)	.4
Heart failure	4 (19)	1 (2)	.9
Atrial fibrillation	6 (3)	1 (2)	.9
Asthma	11 (5)	3 (7)	.7
COPD	1 (0)	1 (2)	.3
Deep vein thrombosis	2 (1)	5 (12)	.002
Pulmonary embolism	1 (0)	0	.9
Donor type, n (%)			
Living related	65 (32)	9 (21)	.2
Living unrelated	121 (59)	27 (63)	.7
Deceased	20 (10)	7 (16)	.3
Other transplanted organs, n (%)	3 (1)	1 (2)	.5
Maintenance immunosuppression, n (%)			
Prednisolone	192 (93)	42 (98)	.5
Tacrolimus	164 (80)	33 (77)	.7
Cyclosporine	31 (15)	9 (21)	.4
Mycophenolate mofetil	168 (82)	40 (93)	.07
Azathioprine	12 (6)	1 (2)	.7
Sirolimus	9 (4)	1 (2)	.9
Everolimus	3 (1)	0	.9
CNI trough level (ng/mL), mean ± SD*			
Tacrolimus	6.7 ± 1.6	7.6 ± 2.2	.007
Cyclosporine	105 ± 30	111 ± 42	.7
Mycophenolate daily dosage (mg), mean ± SD	1280 ± 492	1388 ± 431	.2
ACEI or ARB use before COVID-19, n (%)	87 (42)	21 (49)	.5
Flu vaccine within 1 year of COVID-19 testing, n (%)	156 (76)	30 (70)	.4
Reason for COVID-19 testing, n (%)			
Symptomatic	38 (18)	36 (84)	.0001

(*continued*)

Table 1 (*Continued*)

Variable	Negative n = 206	Positive n = 43	*P* value
Contact with COVID-19 patient	28 (14)	6 (14)	.9
Medical or surgical procedure	28 (14)	0	.006
Travel	18 (9)	0	.05
Random testing by MOPH	70 (34)	0	.0001
Personal decision	17 (8)	0	.05
work requirement	7 (3)	1 (2)	.9

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CNI, calcineurin inhibitor; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; MOPH, Ministry of Public Health in the state of Qatar; SD, standard deviation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

* Average of the last 3 CNI trough levels before SARS-CoV-2 testing

dependent after diagnosis with COVID-19. One of these 2 patients underwent kidney biopsy, which showed grade Ia acute cellular rejection.

DISCUSSION

Kidney transplant recipients have been thought to have an increased risk of incidence, severity, and death from SARS-CoV-2 infection given their immunosuppression and comorbid condition [8]. We observed a higher incidence of SARS-CoV-2 infection of 6.1% in our transplant recipient population when compared with 3.8% in the country's general population since the start of the pandemic [7]. In addition, hospitalization, ICU admission, and mortality rates were higher in our transplant recipients than in the general population. SARS-CoV-2 predisposition, presentation, and outcomes vary among the kidney transplant population [9]. In this study, risk factors associated with susceptibility to COVID-19 were Asian ethnicity, history of hypertension, history of DVT, AB blood group, and higher levels of tacrolimus. Furthermore, acute allograft dysfunction was found to be an independent predictor of ICU admission.

Experts recommend a reduction of CNIs and even discontinuation of antimetabolite drugs in severe COVID-19 cases. Based on extrapolated data from studies on other infections, it is unclear if similar approaches have any role in the prevention of COVID-19 [10−13]. Similar to opportunistic viral infections such as BK or cytomegalovirus, a low tacrolimus trough level is desirable to prevent SARS-CoV-2 in high-risk recipients [14,15].

The mechanistic reasoning behind the reduction of CNIs is to improve the probability of T-cell activation and, in turn, disease clearance in patients exposed to viral antigens [10]. However, in vivo studies have shown that CNIs, such as cyclosporine, have the ability to suppress SARS-CoV-2 viral replication, and hence, have a protective effect [16,17]. We observed that patients had an increased susceptibility to tacrolimus but not cyclosporine. However, it is unclear whether a false-negative effect of cyclosporin was observed because only a limited number of patients were taking the medication.

The effect of blood group on COVID-19 has been evaluated in several studies [18,19]. Zhao et al [19] reported that patients with blood group AB or A have higher susceptibility to COVID-19 than do those with blood group O or B. Similar observations were made in severe acute respiratory syndrome (SARS) in 2005 [20]. O and B blood groups were thought to interfere with the ability of SARS-CoV, the virus that causes SARS, to enter the host cell through ACE 2 [20]. Guillon et al [17] revealed that anti-A antibodies block interactions with cellular receptors; they therefore provide protection against SARS. Interestingly, SARS-CoV-2 has the same mechanism of cell entry, so it is possible that anti-A titers have a protective effect against COVID-19. Athough an increase susceptibility was observed in the AB blood group recipients in this study, the protective effect of anti-A antibody is not proven, because there was no observed protection in combined O and B blood group recipients when compared with AB and A blood group recipients.

Race and comorbid conditions play an important role in the susceptibility to COVID-19. Recipients who were of Asian or African descent were more likely to be positive for COVID-19. Elias et al [21] performed a prospective trial evaluating the incidence and risk factors for COVID-19 among kidney transplant recipients and similarly reported that non-White recipients were more susceptible than White recipients. However, it is unclear whether race association with susceptibility is cofounded by social status or wealth disparity. Universal health care access has been provided by the country to control the spread of infection during the pandemic [22]. Comorbidities such as diabetes mellitus, obesity, and chronic pulmonary disease, in addition to hypertensive kidney disease and DVT, were found to increase susceptibility to COVID-19 [21]. This observation emphasizes the importance of primary prevention, especially in recipients with these nonmodifiable risk factors.

The most common symptoms in our cohort were cough and fever, similar to that reported in previous studies in both the general population and post−kidney transplant recipients [23−25]. Several recipients presented with shortness of breath and

Table 2. Multivariable Analysis of Risk Factors Associated Susceptibility to COVID-19

Variable	OR	95% CI	*P* value
AB blood group	10.38	(1.77-61.07)	.01
Asian	3.71	(1.42-9.71)	.008
Hypertensive nephropathy	6.92	(1.55-30.89)	.01
Deep vein thrombosis	5.85	(0.79-43.42)	.08
Tacrolimus trough level	1.34	(1.06-1.70)	.01

CI, confidence interval; COVID-19, coronavirus disease 2019; OR, odds ratio.

Table 3. Risk Factors Associated With COVID-19 Severity

Variable	Hospital ICU admission (n = 9)	Hospital non-ICU admission (n = 25)	Isolation facility (n = 9)	*P* value
Age, (y), mean ± SD	57 ± 5	53 ± 11	45 ± 10	.03
Sex, male, n (%)	6 (67)	20 (80)	9 (100)	.2
Living donor transplant, n (%)	7 (78)	22 (88)	7 (78)	.4
Time from transplant (y), mean ± SD	8 ± 4	9 ± 6	6 ± 4	.5
Diabetes mellitus	4 (44)	16 (64)	2 (22)	.09
Hypertension	8 (89)	23 (92)	8 (89)	.9
Ischemic heart disease	2 (22)	3 (12)	0	.2
Congestive heart failure	0	1 (4)	0	.7
COPD	0	1 (4)	0	.7
Asthma	2 (22)	1 (4)	0	.1
Deep vein thrombosis	0	4 (16)	1 (11)	.4
Pulmonary embolism	0	0	0	1
Atrial fibrillation/Flutter	0	1 (4)	0	.7
Maintenance immunosuppression, n (%)				
Steroids	9 (100)	24 (96)	9 (100)	.9
Cyclosporin	2 (22)	5 (20)	2 (22)	.9
Tacrolimus	7 (78)	19 (76)	7 (78)	.9
MMF dosage >1500 mg daily	5 (56)	13 (52)	5 (56)	.6
Creatinine at baseline (μmol/L)	138 ± 72	117 ± 57	124 ± 25	.4
Flu Vaccine, n (%)	7 (78)	18 (72)	5 (56)	.6
Clinical presentation and laboratory findings at presentation				
Symptoms at presentation, n (%)				
Asymptomatic	0	6 (12)	6 (67)	.0006
Fever	8 (89)	9 (36)	1 (11)	.002
Sore throat	0	3 (12)	1 (11)	.5
Shortness of breath	4 (44)	3 (12)	0	.02
Fatigue	0	3 (12)	0	.3
Body aches	0	7 (28)	1 (11)	.1
GI symptoms	1 (11)	5 (20)	1 (11)	.6
Hypoxia, n (%)	6 (67)	3 (12)	0	.0006
WBC (10^3 per μL)	8.8 ± 5.5	5.6 ± 2.6	5.4 ± 1.5	.6
Lymphopenia, n (%)	7 (78)	11 (44)	1 (11)	.02
Hemoglobin (g/dL)	12.1 ± 1.7	13.4 ± 1.9	13.1 ± 2.1	.1
Hematocrit (%)	38 ± 6	42 ± 6	40 ± 6	.2
Platelet (10^3 per μL)	229 ± 88	216 ± 59	202 ± 66	.8
ALT (U/L)	22 ± 12	22 ± 23	18 ± 6	.6
AST (U/L)	28 ± 15	24 ± 15	18 ± 3	.3
Albumin (g/L)	29 ± 7	36 ± 6	40 ± 4	.01
LDH (mmol/L)	349 ± 156	234 ± 62	ND	.01
Ferratin (μg/L)	684 ± 366	556 ± 607	ND	.2
Lactate (mmol/L)	1.2 ± 0.5	1.4 ± 0.8	ND	.8
CRP (mg/L)	97 ± 61	44 ± 57	ND	.02
Procalcitonin (ng/mL)	1.6 ± 1.4	0.08 ± 0.06	ND	.01
CPK (U/L)	135 ± 57	150 ± 116	ND	.9
Creatinine at presentation (μmol/L)	300 ± 313	130 ± 68	139 ± 33	.2
Acute graft dysfunction, n (%)	8 (89)	6 (24)	0	.0001
CNI trough level (ng/mL):				
Tacrolimus	7.3 ± 1.4	7.9 ± 2.5	7.0 ±1.8	.7
Cyclosporin	93 ± 10	118 ± 55	111 ± 29	.8
Laboratory findings post COVID-19 infection				
Ferratin at day 7 (μg/L)	1889 ± 2621	467 ± 348	ND	.01
CRP at 7 days (mg/L)	103 ± 83	46 ± 39	ND	.06
Creatinine at day 7 (μmol/L)	235 ± 233	124 ± 52	ND	.2

Only 2 patients had tacrolimus and 2 patients had cyclosporine trough levels checked at the time of COVID-19 diagnosis; 5 patients did not have their CNI levels checked.

ALT, alanine transaminase; AST, aspartate aminotransferase; CNI, calcineurin inhibitor; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CPK, creatine phosphokinase; CRP, c-reactive protein; GI, gastrointestinal; ICU, intensive care unit; LDH, lactate dehydrogenase; MMF, mycophenolate mofetil; SD, standard deviation; WBC, white blood cell count.

Table 4. Multivariable Analysis of Risk Factors Associated With ICU Admission

Variable	OR	95% CI	*P* value
Model 1			
Age	1.07	(0.97-1.19)	.2
Diabetes mellitus	0.31	(0.05-2.19)	.2
Fever on presentation	17.16	(1.79-164.14)	.01
Model 2: Model 1 + Graft dysfunction			
Age	1.08	(0.94-1.24)	.2
Diabetes mellitus	2.91	(0.02-4.87)	.4
Fever on presentation	14.2	(1.04-194.6)	.05
Acute graft dysfunction	37.26	(2.63-527.13)	.007
Model 3: Model 2 + Lymphopenia + CRP+ Ferritin			
Age	1.09	(0.94-1.25)	.3
Diabetes mellitus	0.65	(0.03-15.73)	.8
Fever on presentation	40.3	(0.61-2685.87)	.08
Acute graft dysfunction	93.7	(2.37-3710.94)	.02
Lymphopenia	10.5	(0.54-203.4)	.1
CRP	0.99	(0.96-1.01)	.3
Ferritin	1	(0.99-1.002)	.9

CI, confidence interval; CRP, c-reactive protein; OR, odds ratio.

hypoxia, and their chest radiographs suggested that a chest infection was also a common presentation in a few studies [21,26]. Reports have suggested that lymphopenia is common after SARS-CoV-2 infection in the general population [27]. In our study, 44% of patients developed lymphopenia, and the majority developed severe forms of COVID-19, a finding similar to other reports on transplant recipients [26].

The admission rate in our study was 80%, compared with 29% in the general population. Our transplant recipient admission rate is similar to previously reported rates ranging from 78% to 91% [21,25,28]. In our study, 26% of the patients required ICU admission, and 56% developed ARDS, whereas previously published rates of ICU admission and ARDS were 50% and 50%, respectively [10,29].

Acute allograft dysfunction has been shown to be an independent predictor of COVID-19 severity. The relationship between AKI and COVID-19 mortality has been well documented [30]. Cravedi et al [8] performed a multicenter retrospective study evaluating predictors of mortality post COVID-19 in kidney transplant recipients, which revealed reduced estimated glomerular filtration rate as an independent predictor. Sran et al [31] have shown low hemoglobin, low lymphocyte, high C-reactive protein, and reduced glomerular filtration rate to be predictors of disease severity and mortality. AKI has not been evaluated in literature; the exact cause of the injury and its relationship with disease severity and mortality has therefore not been defined. Tubular injury directly induced by SARS-CoV-2 in the native kidney is a proposed mechanism because tubular cells express the ACE receptor. Autopsy studies have revealed the presence of viral particles in electron microscopy images [32,33]. Other histopathologic findings were thrombotic microangiopathy and acute tubular necrosis, which might have been associated with a systemic inflammatory response syndrome. The initial presentation of AKI may therefore be a sign of an early inflammatory response to the virus or a rapid viral replication causing direct kidney injury. Furthermore, injury in the kidney allograft was more common and critical than that in the native kidney, a disparity which might have been due to delicate hemodynamics, single allograft kidney, and potential inflammatory syndrome-mediated allograft rejection.

The optimum immunosuppression goal during the course of COVID-19 remains unclear. The innate immune system has a significant role in COVID-19 severity, as studies have shown

Table 5. Management and Outcome of Kidney Transplant Recipients with COVID-19

Variable	Hospital ICU admission (n = 9)	Hospital non-ICU admission (n = 25)	Isolation facility (n = 9)	*P* value
Management				
Hydroxychloroquine, n (%)	7 (78)	13 (52)	0	.003
Oseltamivir, n (%)	5 (56)	6 (24)	0	.03
Favipiravir, n (%)	1 (11)	4 (16)	0	.4
Lopinavir-ritonavir, n (%)	3 (33)	0	0	.002
Ribavirin, n (%)	1 (11)	0	0	.1
Tocilizumab, n (%)	5 (56)	2 (8)	0	.001
Azithromycin, n (%)	7 (78)	15 (60)	0	.002
Other antibiotics, n (%)	8 (89)	17 (68)	0	.0002
Anticoagulation, n (%)	3 (33)	6 (24)	0	.2
Discontinuation of ACEI or ARB, n (%)	7/7 (100)	1/10 (10)	0/4 (0)	.0002
Reduced or discontinued CNI, n (%)	8 (89)	8 (32)	1 (11)	.003
Reduced or discontinued MMF, n (%)	9 (100)	15 (60)	0	< .0001
Outcomes				
Creatinine at day 7 (μmol/L), mean ± SD	235 ± 233	124 ± 52	ND	.2
Creatinine at day 30 (μmol/L), mean ± SD	324 ± 357	118 ± 62	128 ± 30	.3
Peak creatinine (μmol/L), mean ± SD	322 ± 264	139 ± 66	138 ± 29	.01
ARDS, n (%)	5 (56)	0	0	< .0001
Need for RRT, n (%)	3 (33)	0	0	.002
Death, n (%)	1 (11)	0	0	.1

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARDS, acute respiratory distress syndrome; CNI, calcineurin inhibitor; COVID-19, coronavirus disease 2019; ICU, intensive care unit; MMF, mycophenolate mofetil; RRT,; SD, standard deviation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

that neutropenic patients on chemotherapy have a high risk of mortality due to immunosuppression, which may prevent an adaptive immune T-cell response against SARS-CoV-2 infection [34,35]. By contrast, immunosuppressive drugs may play a role in the prevention of immune dysregulation, cytokine storm, and acute allograft rejection [9,36]. Individualized immunosuppression management is therefore recommended. We did not observe a negative or positive effect of immunosuppression levels on COVID-19 severity. In our center, the plan was to discontinue the antimetabolite dose and subsequently lower the CNI trough target depending on disease severity.

High mortality has been recorded in kidney transplant recipients infected with COVID-19; however, studies have shown variability in these reports. The mortality rate in our study was only 2.3% among the COVID-19−positive recipients and 3% among hospitalized recipients, as compared with a reported 10% to 30% among kidney transplant recipients [21,24,26,37]. This low mortality rate is comparable with the mortality rate of approximately 2% in the general population but higher than our local reported mortality rate of 0.28% [7,38]. Favà et al [26] observed a 26.9% mortality rate among Spanish kidney transplant recipients, and death was more prevalent in older recipients, with those who died having an average age of 71 years, compared with those who survived with an average age of 55 years. The mean age in our cohort was 52.4 years, which may have contributed to the observed low mortality rate in our recipients. Recent studies by Caillard et al [28] and Chavarot et al [5] have suggested that the incidences of severe COVID-19 were comparable between transplant recipients and nontransplant recipients when matched for age and comorbidities. Although Chavarot et al [5] showed similar mortality in transplant recipients and nontransplant recipients (37.1% vs 29%, $P = .9$), Caillard et al [39] showed a significant difference (17.9% vs 11.4%, $P = .38$). These studies have suggested that age and comorbidities have a more a significant role compared with having a transplant allograft or immunosuppression with respect to COVID-19 severity and mortality. Furthermore, high mortality rates were observed in Italy and Spain, areas with high infection rates that a hospital system that was not overwhelmed the health system. Similar to what was found in our cohort, Lum et al [40] reported a low mortality rate of 9.8% among 41 kidney transplant recipients with COVID-19, with a mean age of 48 years, and an underwhelmed hospital system. The mean age of transplant recipients in this study was 52 years, and the available hospital and ICU beds were not filled during the studied COVID-19 wave. Hence, our observed low mortality rate is likely owing to the young age of the recipients, low comorbidity burden, and prompt and equal access to health care facilities with highly specialized ICUs. However, the difference in severity and outcome of kidney transplant in recipients with COVID-19 between centers and countries will require further analyses using larger cohorts and registries.

Our study was limited by its retrospective nature, limited number of COVID-19 cases among patients, absence of pathologic data of kidney allograft injury, and small sample size, which prevented the addition of further variables to maintain statistical model stability.

In conclusion, management of kidney allograft recipients during the COVID-19 pandemic requires personalized care. Higher tacrolimus targets may be associated with COVID-19 development; thus, further studies to evaluate the effect of tacrolimus levels on the incidence of COVID-19 are warranted. We suggest that recipients with acute allograft dysfunction diagnosed with COVID-19 should consider seeking out a higher level of care. Acute kidney injury during the COVID-19 course may be a sign of severe disease. Prognostication of COVID-19 severity in kidney transplant recipients is crucial for early recognition of critical illness and may ensure early intervention.

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