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Coronavirus Disease 2019 in Kidney Transplant Recipients: Single-Center Experience and Case-Control Study

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ABSTRACT

Background. Kidney transplant recipients (KTR) are considered high-risk for morbidity and mortality from coronavirus disease 2019 (COVID-19). However, some studies did not show worse outcomes compared to non-transplant patients and there is little data about immunosuppressant drug levels and secondary infections in KTR with COVID-19. Herein, we describe our single-center experience with COVID-19 in KTR.

Methods. We captured KTR diagnosed with COVID-19 between March 1, 2020 and May 18, 2020. After exclusion of KTR on hemodialysis and off immunosuppression, we compared the clinical course of COVID-19 between hospitalized KTR and non-transplant patients, matched by age and sex (controls).

Results. Eleven KTR were hospitalized and matched with 44 controls. One KTR and 4 controls died (case fatality rate: 9.1%). There were no significant differences in length of stay or clinical outcomes between KTR and controls. Tacrolimus or sirolimus levels were >10 ng/mL in 6 out of 9 KTR (67%). Bacterial infections were more frequent in KTR (36.3%), compared with controls (6.8%, $P = .02$).

Conclusions. In our small case series, unlike earlier reports from the pandemic epicenters, the clinical outcomes of KTR with COVID-19 were comparable to those of non-transplant patients. Calcineurin or mammalian target of rapamycin inhibitor (mTOR) levels were high. Bacterial infections were more common in KTR, compared with controls.

CORONAVIRUS disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has created the worst pandemic since the 1918 Spanish flu. Since its first appearance in December 2019 in China, there have now been over 15 million cases of COVID-19 worldwide and over 600,000 deaths [1]. Despite the ongoing surge of COVID-19 cases, leading to widespread epidemiologic and clinical investigations throughout the world [2], our understanding of outcomes in high-risk populations is still incomplete.

Organ transplant recipients (OTR) are considered high-risk for morbidity and mortality from COVID-19, due to the unique combination of immunosuppression (IS) and other chronic illnesses [3–5]. Case fatality rates (CFR) vary significantly in different case series, anywhere from significantly higher than the general population (30%-64%) [4,6–11] to much lower, comparable to the CFR of non-immunosuppressed individuals [12–14]. Notably, in many

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studies, few patients were still hospitalized at the time of data analysis; therefore, the CFR may be underestimated [4,5,7,10,12,13].

To our knowledge, only one case-control study of COVID-19 in OTR has been published to date, which found similar CFR between OTR and consecutive non-transplant patients (controls), despite more comorbidities in OTR [15]. In this study, we describe our institutional COVID-19 preparedness, and analyze baseline characteristics, clinical course, outcomes, and therapeutic interventions in kidney transplant recipients (KTR) with COVID-19, compared with age- and sex-matched non-transplant patients (controls), all of whom were either discharged home or died.

METHODS

COVID-19 Preparedness

The first case of COVID-19 was diagnosed in RI on March 1, 2020. The Division of Infectious Diseases (ID) created 2 dedicated COVID-19 inpatient services, one for each teaching hospital affiliated with Brown University in Providence, RI (The Miriam Hospital and Rhode Island Hospital). Admitted patients with COVID-19 were evaluated by ID, either in person or remotely. Starting on March 19, 2020, our first-line treatment for COVID-19 was remdesivir, through enrollment in a clinical trial, or under emergency use authorization after May 15, 2020. Starting on April 15, 2020, convalescent plasma was also offered as adjunct or alternative (for patients who did not meet criteria for remdesivir) treatment. Most patients admitted to the intensive care unit were empirically treated with broad-spectrum antibiotics. Overall, providers at both institutions had a low threshold for empirical anticoagulation, based on D-dimer level and clinical suspicion for any thrombotic event.

Unlike other centers [3,4,6,9,10,14–20] use of hydroxychloroquine in OTR and cancer patients was discouraged from early on at our centers, given its potential of added IS and side effects. This approach was the result of our early participation in studies showing no benefit from hydroxychloroquine [21,22], and timely review of emerging data, including concerns about validity of the seminal report that suggested the drug may be an effective treatment for COVID-19 [23]. Most of our transplant patients receive low-dose prednisone; high-dose corticosteroids were not widely used for COVID-19 alone, although short courses were given in a small number of patients [24].

Starting on March 15, 2020, living donor kidney transplants were suspended; deceased donor kidney offers were assessed on a case-by-case basis, prioritizing recipients who would benefit the most. Listed transplant candidates with significant comorbidities, and those who would likely need induction IS with antithymocyte globulin, were made temporarily unavailable. KTR with negative SARS-CoV-2 polymerase chain reaction (PCR) were hospitalized in a different building than patients with positive SARS-CoV-2 PCR. Throughout the study period, outpatient clinic visits and inpatient consultations were done remotely through telehealth, with very few exceptions.

Our approach to outpatient KTR with positive SARS-CoV-2 PCR or person under investigation evolved with medical knowledge and availability of testing kits, personal protective equipment, and promising treatments for COVID-19. Asymptomatic KTR with positive SARS-CoV-2 PCR, or those with only mild, upper respiratory symptoms, were initially advised to isolate and rest at home, with daily follow-up phone calls from the transplant team. Patients with diarrhea were advised to have routine bloodwork, including tacrolimus or sirolimus trough levels. Those with shortness of breath at rest or exertion, persistent high fever (>101°F), or self-reported deterioration in any way, were advised to present to the nearest emergency room or electively admitted to the hospital. Once testing and personal protective equipment became widely available, KTR with mild or moderate symptoms were also offered testing at the closest testing center, sometimes in addition to vital sign measurement and clinical assessment in a RI Department of Health respiratory clinic. With early reports of remdesivir efficacy [25,26], and of some KTR in the pandemic epicenters dying at home [4], we started recommending admission to the hospital for almost all symptomatic KTR and other immunosuppressed patients with COVID-19.

COVID-19-related phone calls and incidents were brought to the attention of a transplant nephrologist (GB, CC, RG, BM) or surgeon (AJO, PM), and the Director of Transplant ID (DF), who provided additional recommendations, as needed. Adjustments in IS were evaluated on a case-by-case basis; as a rule, the antimetabolite was discontinued or its dose was reduced in KTR with COVID-19 at the time of diagnosis, and resumed once their symptoms had improved or resolved, depending on severity of illness, the net state of IS, and risk for rejection.

Study Population

We captured KTR who were diagnosed with COVID-19 during the study period (March 1, 2020-May 18, 2020). KTR on hemodialysis and off IS were excluded from the analysis, as they are no longer classic hosts on immunosuppressive medications. KTR on IS who were admitted to the hospital were matched by age and sex with non-transplant patients, admitted during the same period to The Miriam Hospital or Rhode Island Hospital (controls). Given a relatively uneven distribution of cases due to the significant surge in April, each KTR was matched with 3-5 controls of the same sex and age (±2 years), prioritizing when feasible those admitted to the hospital within 2 weeks, in order to adjust for potential evolution of medical knowledge and institutional standards of care. We only included KTR and controls who either died or were discharged at the time of data analysis.

We extracted the following features from electronic medical records, which were then compared between hospitalized KTR on IS and controls:

1. Demographics: age, sex, time from transplant, IS, race, and ethnicity
2. Key comorbidities, defined by chart review of past medical history unless otherwise indicated: chronic cardiac disease (coronary artery disease or congestive heart failure), chronic pulmonary disease (asthma, chronic obstructive pulmonary disease, and other conditions), chronic kidney disease (defined as baseline estimated glomerular filtration rate of <60 mL/min by the Diet Modification for Renal Disease formula), liver cirrhosis, and diabetes
3. Clinical course of COVID-19: mortality, length of stay (for all patients and after exclusion of those who died), highest oxygen (O_2) requirements; mortality in KTR was compared to that for all inpatients from the ID COVID-19 master list, and for all patients with positive SARS-CoV-2 PCR in RI [27]. Therapeutic interventions: adjustments in IS, remdesivir, hydroxychloroquine, convalescent plasma, and tocilizumab

Table 1. Characteristics of KTR Still on IS With COVID-19

Age (y)	Sex	Tx (mo)	Conv. Plasma/RDV	IL-6_{max} (pg/mL)	Toci	HCQ	Infx	Abx	LOS (d)	Worst O_2	Ordinal Scale	Tacro/Sirolimus Trough (ng/mL) Baseline	Highest
Hospitalized													
61	F	25	–/–	1377.84	–	+	+ (VAP)	+	10	DE	1	11.6	19.9
65	F	99	–/–	–	–	–	+ (urosepsis)	+	2	MV	2	17.1	17.1
65	F	31	+/-	20.05	–	–	+ (diverticulitis)	+	8	RA	5	2.3*	6.2
68	F	37	–/+	–	–	–	–	+	11	RA	5	7.8	7.8
36	M	1	+/+	157.53	–	–	–	+	15	HF	3	8.8	22.2
43	M	56	–/–	–	–	–	–	+	8	LF	4	3.9	9.2
44	M	59	–/+	2243.02	+	–	–	+	13	LF	4	7.8	17.3
34	F	41	–/–	–	–	–	–	+	6	LF	4	–	–
35	F	20	+/+	303.61	+	–	+ (urosepsis)	+	24	MV	2	17.1	17.6
55	M	37	+/-	1487.81	+	–	–	–	7	HF	3	11.3	11.3
58	F	195	–/–	–	–	–	–	+	1	RA	5	–	–
Outpatients													
54	F	120	–/–	–	–	–	–	–	0	RA	5	–	–
50	M	203	–/–	–	–	–	–	–	0	RA	5	–	–

Ordinal (modified National Institute of Health/World Health Organization) scale: 1, dead (DE); 2, mechanical ventilation (MV); 3, high-flow O_2 (HF); 4, low-flow O_2 (LF); 5, room air (RA).

Abx, broad spectrum antibacterials; COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine (± azithromycin); Infx, (bacterial) infection; IS, immunosuppression; KTR, kidney transplant recipients; LOS, length of stay; RDV, remdesivir; Toci, tocilizumab; Tx, transplant (mo prior to COVID-19 diagnosis); VAP, ventilator-associated pneumonia.

*First dose held until the trough level was back.

For O_2 requirements, we modified the National Institutes of Health/World Health Organization ordinal scale used in clinical trials [25,26]: (1) dead, (2) mechanical ventilation, (3) high-flow O_2 (>6 Lt/min) or noninvasive ventilation such as BiPAP, (4) low-flow O_2, (5) room air.

4. Patient charts were independently reviewed by 2 clinical abstractors (AH, DF). The study was approved by the Lifespan Institutional Review Board.

Statistical Analyses

Data are presented as n (%) for categorical variables, or median (range) for continuous variables. Categorical variables were compared with χ^2 or Fisher exact test. For those with >2 categories (eg, race), *P*-values refer to 2x2 comparisons (corresponding row vs all others combined). The results were not different for 2x3 comparisons by χ^2 test. Continuous variables were compared with Mann-Whitney *U*-criterion. Given the small number of cases, and especially deaths, we did not perform multivariate analyses. Two-tailed *P*-values of <.05 were considered significant, whereas those between 0.05 and 0.1 were also noted as trends.

RESULTS

Study Cohort

During the study period, we identified 16 KTR with COVID-19. Three KTR off IS, who were excluded from further analyses, survived, and 2 of them were hospitalized. Median age of KTR on IS was 54 (range, 34-65) years; 5 of 13 KTR on IS (38.4%) were men. Median time from transplant was 41 months (range, 1-203). Two KTR on IS, both transplanted >10 years ago, were managed as outpatients (Table 1). Nine KTR of 13 on IS (69.2%) were white, 3 (23%) were black, 5 (38.4%) were Hispanic. Eleven KTR were hospitalized (84.6%) and matched with 44 controls. There were no significant differences in race or ethnicity between hospitalized KTR on IS and controls (Table 2).

Comorbidities

As expected, more hospitalized KTR on IS had chronic kidney disease (81.8%), compared to age- and sex-matched controls (9.1%, $P < .001$). However, no KTR had history of chronic lung disease, as opposed to 29.5% of controls ($P = .049$). More KTR had history of hypertension (90.9%) and chronic cardiac disease (36.3%), compared to controls (59.1% and 11.4%, $P = .075$ and .067, respectively). Seven patients in the control group (15.9%) were active smokers, as opposed to no KTR, but this difference was not statistically significant (Table 2). Liver cirrhosis was uncommon (only 3 patients, all in the control group).

Clinical Course

One KTR on IS died [CFR 6.25%; 7.6% (1/13) in KTR on IS; 9.1% (1/11) in hospitalized KTR on IS]. Four controls died [CFR: 9.1% (4/44); state CFR: 5.6% (988/17,711); inpatient CFR: 15.4% (117/759), $P > .1$ for all comparisons to KTR]. In all cases, death was secondary to respiratory insufficiency and multi-organ failure. The 1 kidney transplant recipient returned to renal replacement therapy, specifically continuous venovenous hemofiltration, prior to her death. There were no significant differences in length of stay or worst O_2 status between hospitalized KTR and controls. Among hospitalized patients, bacterial infections were significantly more frequent in KTR (36.3%), compared to controls (6.8%, $P = .02$) (Table 2). Two KTR had urinary tract infection/graft pyelonephritis, and both presented with urosepsis; 1 of the 2 who had a prolonged intensive care unit stay and received tocilizumab developed

Table 2. Comparison Between Hospitalized KTR on IS with COVID-19 and Controls

	KTR (n=11)	Controls (n=44)	*P*-value
Demographics			
Age (y)	55 (34-68)	55 (33-68)	.974
Men	4 (36.3)	17 (38.6)	.835
Race: White	7 (63.6)	32 (72.7)	.712
Black	3 (27.2)	9 (20.4)	.689
Other	1 (9.1)	3 (6.8)	.712
Ethnicity: Hispanic	5 (45.5)	16 (36.3)	.731
Comorbidities			
Hypertension	10 (90.9)	26 (59.1)	.075
Chronic cardiac disease	4 (36.3)	5 (11.4)	.067
Chronic pulmonary disease	0 (0)	13 (29.5)	.049*
Chronic kidney disease	9 (81.8)	4 (9.1)	<.001*
Diabetes	7 (63.6)	19 (43.2)	.315
Smoker: Never	9 (81.8)	35 (79.5)	.866
Former	2 (18.2)	2 (4.5)	.174
Active	0 (0)	7 (15.9)	.323
Outcomes			
Mortality	1 (9.1)	4 (9.1)	.557
LOS (d)	8 (1-24)	9 (1-44)	.825
LOS (d) among survivors	7.5 (1-24)	8.5 (1-44)	.836
Worst O_2 status (ordinal scale)	4 (1-5)	4 (1-5)	.991
Bacterial infection	4 (36.3)	3 (6.8)	.023*
Treatment			
Convalescent plasma	4 (30.7)	0 (0)	.001*
Remdesivir	4 (30.7)	12 (27.2)	.823
Tocilizumab	3 (27.2)	0 (0)	.006*
Hydroxychloroquine	1 (9.1)	7 (15.9)	.924
Broad spectrum antibacterials	10 (90.9)	27 (61.3)	.080

Data are presented as n (%) or median (range).
COVID-19, coronavirus disease 2019; IS, immunosuppression; KTR, kidney transplant recipient; LOS, length of stay.
*Significant *P*-values (<.05).

graft pyelonephritis with bacteremia from extended spectrum β-lactamase producing *E. coli* after discharge, and was readmitted to the hospital. Both patients were cured of their urinary tract infections. One additional KTR had *Pseudomonas* and *Stenotrophomonas* growth from tracheal aspirate with concern for ventilator-associated pneumonia and died; 1 KTR presented with COVID-19, diarrhea, and acute uncomplicated diverticulitis, which resolved completely with antibiotics (Table 1).

Therapeutic interventions

IS was reduced in 11 of 13 (84.6%) KT, in all 11 who were hospitalized, most often by discontinuation of the antimetabolite (azathioprine or mycophenolate). Goal tacrolimus or sirolimus trough levels were 4-6 ng/mL, except for 1 patient who had KT <1 month prior to COVID-19. In 1 patient with diarrhea, the first dose of tacrolimus was empirically held, before obtaining a trough level. It should be noted that, despite lowering the trough goal, tacrolimus or sirolimus levels were >10 ng/mL in 4 of 9 (44.4%) KTR with available levels on admission and 6 of 9 KTR (67%) at any point during the hospital stay (Table 1).

Four hospitalized KTR (30.7%) received remdesivir, 4 convalescent plasma, 3 (23%) tocilizumab. Notably, interleukin 6 (IL-6) levels were extremely high, >1000 pg/mL (normal: <5) in 3 of 6 KTR (50%) with IL-6 levels measured during their hospital stay. Only 1 KTR, who did not qualify for enrollment in the remdesivir clinical trial (the only treatment trial available at the time) and subsequently died, was started on azithromycin and hydroxychloroquine; the latter was discontinued after 4 of 5 planned days of treatment because of leukopenia and concern for arrhythmia, both of which were likely multifactorial, as this patient was hypothermic, intubated, on vasopressors, and receiving continuous venovenous hemofiltration.

The differences in the proportions of patients treated with remdesivir or hydroxychloroquine between KTR and controls were not statistically significant. KTR received more broad spectrum antibiotics (90.9% vs 61.3%, $P = .08$), convalescent plasma (30.7 vs 0%, $P = .001$) or tocilizumab (27.2% vs 0%, $P = .006$), compared to controls (Table 2).

DISCUSSION

To our knowledge, this is the second case-control study evaluating OTR with COVID-19, and the only one to exclusively study KTR. Furthermore, we investigated immunosuppressive drug levels, and rates of bacterial coinfections in KTR with COVID-19.

Our CFR was lower than most previous reports, and we found comparable outcomes between KTR and matched controls in mortality, O_2 requirements, and length of stay, in agreement with another case-control study [15]. There may be several reasons for these observations: first, although our hospitals experienced some strain in terms of resources, RI was less stretched than the pandemic epicenters in the United States [4,9,15,28], Europe [9–11], or Iran [3]. Our center had enough time to adopt a structured, intensive and evidence-based approach to the management of KTR with COVID-19, including low thresholds for hospital admission and close follow-up of all outpatients. Second, no KTR with COVID-19 in our study had underlying chronic pulmonary disease, unlike other series [15,20].

Third, OTR, one of the highest-risk groups for infectious complications, are often followed closer by ID specialists, and may be started on anti-effective treatment earlier than non-transplant patients. Such approaches may account for better outcomes reported by some investigators in OTR with serious infections other than COVID-19, including sepsis, compared with matched non-transplant patients [29,30]. Some also argue that IS may have a protective role against the detrimental inflammatory cascade [29,30]. Nevertheless, our finding of a higher risk of infectious complications in KTR with COVID-19, compared with non-transplant controls, does not support a net beneficial effect from IS on the course of SARS-CoV-2 infection.

It should be noted that very few of our patients received hydroxychloroquine, compared with the vast majority of previous case series [3,4,6,9,10,14–20]. Instead, most of our KTR received remdesivir or convalescent plasma (Tables 1 and 2). This high enrollment in clinical trials may have also contributed to improved outcomes, given emerging literature on the efficacy of these treatments [25,26,31–33], as opposed to hydroxychloroquine, which likely has no role in the treatment of COVID-19 [16–18,21,22,34–36].

We found higher rates of bacterial coinfections and antibiotic use in KTR compared with controls (Table 2). Antibiotic administration in critically ill patients is often empirical, even more so in the setting of a pandemic [37]. Nonetheless, in our study, there was significant evidence of more severe, proven bacterial infections in KTR compared with controls. This increased rate could be due to baseline IS with higher than usual tacrolimus or sirolimus levels (Table 1), possibly in addition to immune dysregulation from SARS-CoV-2; the latter could make immunocompromised patients even more susceptible to bacterial infections. Further studies are needed to confirm our findings, which could dictate important management decisions such as earlier empirical use of antibiotics. Also, these observations possibly justify the decision to decrease IS as tolerated in hospitalized OTR with COVID-19, as well as symptomatic outpatients. This has been the practice at our hospitals, and most, if not all, transplant centers [3–5,7,12–15,19,20,38,39] so far.

Tacrolimus or sirolimus levels were elevated in most KTR with COVID-19 at some point during their hospital stay, despite lower trough goals. This could be secondary to diarrhea, but also hepatic dysfunction in COVID-19 [40], resulting in decreased glycoprotein-P and Cytochrome P450 (CYP)-enzyme mediated clearance [41,42], respectively. With this knowledge, some clinicians may choose to preemptively aim for lower than usual doses of calcineurin or mammalian target of rapamycin inhibitors in KTR with SARS-CoV-2 infection, in order to achieve the desired trough levels, given the risk for bacterial coinfections and the potential severity of COVID-19 itself.

High levels of IL-6 were noted in most KTR in our study (Table 1), in agreement with previous case series [43–46]. High IL-6 levels (>0.5 pg/mL) seem to be common in patients with COVID-19. Moreover, some KTR in our study and one previous report [4] had "extreme" IL-6 levels (>1000 pg/mL), which have been mainly described during the cytokine storm of chimeric antigen receptor T-cell immunotherapies, the only indication for which tocilizumab is FDA-approved [47].

At our center, tocilizumab has so far only been used in KTR. All 3 KTR who received it survived; 1 subsequently developed graft pyelonephritis and extended spectrum β-lactamase bacteremia (Table 1). In recent observational studies, tocilizumab was shown to improve outcomes in patients with severe COVID-19 [39,48–51], including OTR [52]. However, in one retrospective study of ventilated patients, the rate of coinfections in patients who received tocilizumab was significantly higher compared to the standard of care, but use of tocilizumab was still associated with improved survival [49]. Pending more definitive results from randomized controlled trials, we usually reserve use of tocilizumab for KTR with convincing symptoms or signs of (impending) cytokine storm, such as high fever and rapid respiratory deterioration later in the course of COVID-19, and in the absence of high clinical suspicion for secondary viral, bacterial, or fungal infections.

Our treatment protocols did not include administration of corticosteroids. The use of dexamethasone recently showed a significant association with decreased mortality in patients with COVID-19 requiring supplemental O_2 [53,54]. However, this strategy has not been validated in patients who are already immunosuppressed, especially those receiving low-dose corticosteroids. In a recent study of patients with cancer, administration of corticosteroids was associated with a nonsignificant increase in 30 day mortality, but the number of patients receiving corticosteroids was small; the vast majority received other treatments as well, and confounding by indication made these results inconclusive [22]. The potential effect of corticosteroids on the infection risk in immunocompromised individuals with COVID-19 remains unknown.

Our study has limitations: it is a single-center study with small, although comparable to that of other case-series [11,19,37,52,55], sample size. Therefore, our findings need to be validated by larger cohort studies, prospective registries and randomized controlled clinical trials. Second, we did not compare presenting symptoms, signs, routine laboratory results, or imaging between KTR and non-transplant recipients with COVID-19. Lastly, we matched cases to controls, rather than perform multivariate analyses in a large cohort of consecutive patients, which could potentially mask important associations [56].

CONCLUSIONS

In summary, unlike early reports from the pandemic epicenters, the clinical course and outcomes of KTR with COVID-19 in our small case series were comparable to those of age- and sex-matched non-transplant patients, with low CFR. Calcineurin or mammalian target of rapamycin inhibitor levels were high, likely due to COVID-19-related intestinal and hepatic dysfunction. Bacterial infections were more frequent in KTR. Extremely high IL-6 levels were common in KTR with COVID-19. The role of adjustments in IS and potential benefits from empirical antibiotics or investigational treatments remain to be elucidated.

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