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Spectrum of Coronavirus Disease 2019 Outcomes in Kidney Transplant Recipients: A Single-Center Experience

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ABSTRACT

Purpose. We reviewed the clinical experience of kidney transplant recipients diagnosed with severe acute respiratory syndrome coronavirus 2 infection in order to understand the impact of the current coronavirus disease 2019 (COVID-19) pandemic infection on transplant recipients. Given that early reports from heavily affected areas demonstrated a very high mortality rate amongst kidney transplant recipients, ranging between 30% and 40%, we sought to evaluate outcomes at a center with a high burden of cases but not experiencing acute crisis due to COVID-19.

Procedures. In this single center retrospective observational study, medical records of all kidney transplant recipients at the UCLA Medical Center were reviewed for a diagnosis of COVID-19 by polymerase chain reaction, followed by chart review to determine kidney transplant characteristics and clinical course.

Main findings. A total of 41 kidney transplant recipients were identified with COVID-19 positive polymerase chain reaction. Recipients had been transplanted for a median of 47 months before diagnosis. The large proportion of infected individuals were minorities (Hispanic 65.9%, black 14.6%), on prednisone, tacrolimus, and mycophenolate mofetil (95.1%, 87.8%, and 87.8%, respectively), and had excellent allograft function (median 1.25 mg/dL). The most common presenting symptoms were fever, dyspnea, or cough. Most patients were hospitalized (63.4%); mortality was 9.8% and occurred only in patients in the intensive care unit. The most common treatment was reduction or removal of antimetabolite (77.8%). Approximately 26.9% presented with AKI.

Conclusions. COVID-19 infection in kidney transplant recipients results in a higher rate of hospitalization and mortality than in the general population. In an area with a high number of infections, the mortality rate was lower compared with earlier reports from areas experiencing early surge and strain on the medical system. Minorities were disproportionately affected. Future studies are needed to determine optimal approach to treatment and management of immunosuppression in kidney transplant recipients with COVID-19 infection.

SEVERE acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus first isolated in December 2019, and is the virus causing the current coronavirus disease 2019 (COVID-19) pandemic [1], with over 20,00,000 confirmed cases worldwide [2]. This public health

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crisis has caused significant mortality around the world including the United States, where over 5,000,000 cases have been reported [2].

Early reports from COVID-19 hot spots indicated a high rate of mortality amongst kidney transplant recipients, ranging from 24% to 30% [3–7]. These early reports focused primarily on hospitalized patients, many of whom required intensive care unit (ICU) care and/or required intubation for respiratory failure, in areas acutely impacted by COVID-19. Follow-up in most studies was <1 month.

We sought to understand the impact of COVID-19 in a geographic area with a high number of infections that had not reached a critical point of significantly straining the medical system, including analysis of patients cared for in both the inpatient and outpatient setting, including management of patients via telemedicine. Patients received a range of interventions for COVID-19. Herein we describe the experience of transplant recipients from a large transplant center.

METHODS

Patient cases were identified by review of the electronic medical record under a retrospective research study approved by the UCLA Institutional Review Board. As previously reported [8], patients at increased risk for rejection received induction with antithymocyte globulin and others received basiliximab. Patients received maintenance immunosuppression with tacrolimus, mycophenolate mofetil, and prednisone following a standardized protocol.

COVID-19 testing was performed via nasopharyngeal swab for polymerase chain reaction (PCR). Inpatient testing was performed at the UCLA Clinical Microbiology Laboratory based on the Food and Drug Administration–approved Centers for Disease Control and Prevention COVID-19 PCR test, with limit of detection <500 copies/mL. Outpatient testing was performed via the commercially available Quest SARS-CoV-2 rRT-PCR test.

RESULTS

Demographics of Transplant Recipients With COVID-19

A total of 41 kidney transplant recipients with COVID-19 were identified by medical record from March 1, 2020 to July 31, 2020 (see Table 1). The average age was 48.5 years and 53.7% were male. Cause of end-stage renal disease was varied amongst the population, with the most common cause being diabetes mellitus in 24.4% of patients. A total of 27 were Hispanic (65.9%) and 7 were black (14.6%). Hypertension was the most common comorbidity (53.7%), and 29.3% had diabetes mellitus at the time of diagnosis.

The majority of patients received a deceased donor kidney transplant (63.4%). Antithymocyte globulin was used for induction in 46.3% of cases. The induction regimen was unknown in 5 cases. The most common immunosuppression regimen was a combination of prednisone, tacrolimus, and mycophenolate mofetil (75.6%). Thirty-nine were on prednisone (95.1%), 36 on tacrolimus (87.8%), and 36 on mycophenolate mofetil (87.8%). Allograft function was excellent for most patients, with an average creatinine of 1.24 mg/dL at time of diagnosis. Three had a creatinine >2 mg/dL.

The median time from transplant to COVID-19 infection was 47 months (range, 0.5-223 months) and follow-up time after initial COVID-19 diagnosis was 1.5 months (0-5 months).

Clinical Course of Transplant Recipients With COVID-19

The most common presenting symptoms were fever (58.5%) and dyspnea with cough (29.3%) (Table 2). There were also several patients with atypical presentations including diarrhea (14.6%) or body aches (7.3%) without respiratory symptoms.

Fifteen patients were managed through at home telehealth after their diagnosis and recovered (36.9%). Laboratory testing when needed was performed primarily through use of home health services. Of the 26 patients requiring hospitalization (63.4%), 9 patients required elevation of care to the ICU (34.6% of hospitalized patients), and 8 were intubated for respiratory failure. Four patients died of COVID-19 in the hospital for an overall mortality of 9.8%; all were in the ICU and intubated. The remainder have been discharged home and are alive and well as of this publication. One patient died 2 months after COVID-19 infection from unrelated causes. This mortality rate for hospitalized kidney transplant recipients at our center is similar to that observed in nontransplant recipients hospitalized during this time period, where a mortality rate of 9.0% was observed, although the median age of these patients was older (mean age 61 years) than the kidney transplant recipients who required hospitalization (mean age 53 years).

The most common management strategy was reduction or discontinuation of antimetabolite. Thirty-six patients were on mycophenolate at the time of diagnosis, and 28 underwent reduction or elimination of this medication (77.8%). Of those who recovered, the antimetabolite was restarted 2 days after resolution of symptoms. All critically ill patients had both calcineurin inhibitor and mycophenolate held, although prednisone was continued. Several patients also received attempted anti-COVID-19 therapy including hydroxychloroquine (19.5%), followed by convalescent plasma (17.1%), remdesivir (17.1%), and leronlimab (4.9%). Lymphopenia was common, and the majority of patients demonstrated increased markers of inflammation (Table 2).

Renal Outcomes

Acute kidney injury (AKI) was common amongst transplant recipients with COVID-19 (26.9%). AKI was severe enough to require renal replacement therapy in 4 patients (9.8% of total) but most patients recovered to their prior baseline function. The only 2 patients with long-term allograft impact were a patient with a serum creatinine of 3.3 mg/dL at time of diagnosis who required and remains on dialysis, and another patient who developed AKI who is in the recovery phase. To date, no episodes of

Table 1. Demographic and Clinical Characteristics of Kidney Transplant Recipients Diagnosed With COVID-19

Demographics	
Age	
Mean 48.5 y	
Sex	
M	22/41 (53.7%)
F	19/41 (46.3%)
Cause of ESRD	
DM	10/41 (24.4%)
GN	8/41 (19.5%)
HTN	4/41 (9.8%)
Congenital	4/41 (9.8%)
PKD	3/41 (7.3%)
Unknown	7/41 (17.1%)
Other	5/41 (12.2%)
Race	
Hispanic	27/41 (65.9%)
Caucasian	7/41 (17.1%)
Black	6/41 (14.6%)
Asian	1/41 (2.4%)
Comorbidities	
HTN	22/41 (53.7%)
DM	12/41 (29.3%)
Chronic infection	6/41 (14.6%)
Kidney Transplant Information	
Type	
Deceased donor	26/41 (63.4%)
Living donor	15/41 (36.6%)
Induction	
ATG	19/41 (46.3%)
Basiliximab	17/41 (41.5%)
Unknown	5/41 (12.2%)
Maintenance immunosuppression	
Prednisone	39/41 (95.1%)
Tacrolimus	36/41 (87.8%)
Mycophenolate	36/41 (87.8%)
Cyclosporine	2/41 (4.9%)
AZA	1/41 (2.4%)
Belatacept	3/41 (7.3%)
Eculizumab	2/41 (4.9%)
Kidney function	
Median Creatinine, mg/dL (range)	1.24 mg/dL (0.56-3.3 mg/dL)
Time from transplant to diagnosis of COVID-19	
Median in mo (range)	47 mo (0.5-223 mo)
Mean	59.6 mo
Follow-up time after diagnosis of COVID-19	
Median in mo. (range)	1.5 mo (0-5 mo)
Mean	2.1 mo

Abbreviations: ATG, antithymocyte globulin; AZA, azathioprine; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; ESRD, end-stage renal disease; GN, glomuerulonephritis; HTN, hypertension; PKD, polycystic kidney disease.

acute rejection after recovery from COVID-19 have been reported.

DISCUSSION

The current COVID-19 pandemic has resulted in one of the largest public health crises of the century. Early surges resulted in significant strain on the medical systems in Italy [9], Spain [10], and New York City [11]. Reports from these areas demonstrated significant mortality among hospitalized kidney transplant recipients, many of whom were elderly [5].

Los Angeles, California is a large metropolitan area that has had a high number of COVID-19 cases, with over 200,000 cases (https://covid19.ca.gov). However, the medical system was arguably less overwhelmed than other metropolitan areas, likely due to early stay at home orders. We examined the course of 41 patients transplanted at

Table 2. Clinical Course of COVID-19 Infection in Kidney Transplant Recipients

COVID-19 Course	
Presenting symptoms	
Fever	24/41 (58.5%)
SOB/cough	12/41 (29.3%)
Diarrhea	6/41 (14.6%)
Sore throat	3/41 (7.3%)
Muscle aches	3/41 (7.3%)
Lost taste	1/41 (2.4%)
Asymptomatic	1/41 (2.4%)
Time from transplant to diagnosis of COVID-19	
Median in mo (range)	47 mo (0.5-223 mo)
Mean	59.6 mo
Management	
Reduction antimetabolite	28/36 (77.8%)
Convalescent plasma	7/41 (17.1%)
Pulse steroids	4/41 (9.8%)
Plaquenil	8/41 (19.5%)
Remdesivir	7/41 (17.1%)
Leronlimab	2/41 (4.9%)
Tocilizumab	2/41 (4.9%)
Hospitalization	
Managed at home	15/41 (36.9%)
Hospitalized	26/41 (63.4%)
ICU	9/26 (34.6%)
Intubated	8/26 (19.5%)
Death due to COVID-19	4/41 (9.8%)
Renal outcomes	
AKI at presentation	11/41 (26.9%)
Need for RRT	4/41 (9.8%)
Impaired function at followup	2/41 (4.9%)
Measure of lymphopenia*	
Median absolute lymphocyte count (range)	0.7 (0.07-2.15) x10^3/μL
Measures of inflammation*	
Median IL-6 (range)	20.3 (0-21.6) pg/mL
Median ferritin (range)	1510 (199-5657) ng/mL
Median D-dimer (range)	1308 (729-7846) ng/mL
Follow-up time after diagnosis of COVID-19	
Median in mo (range)	1.5 mo (0-5 mo)
Mean	2.1 mo

Abbreviations: AKI, acute kidney injury; COVID-19, coronavirus disease 2019; IL-6, interleukin 6; RRT, renal replacement therapy; SOB, shortness of breath.
*Laboratory values were only measured for patients requiring inpatient admission.

UCLA Medical Center who were found to have COVID-19. Forty were cared for in the greater Los Angeles area. The one remaining patient developed COVID-19 in another state and expired.

Our study showed a much younger population with an average age of 48.5 years at the time of diagnosis compared with previous reports of both kidney transplant recipients and patients from the general population [6,12]. Infection occurred as early as 2 weeks post kidney transplant and at median of 47 months post transplant. As has also been seen in the general population [13], in our patients, minorities were disproportionately affected by COVID-19 in our series—Hispanics accounted for 65.9% of the documented COVID-19 cases. Historically, Hispanics account for approximately 50% of our transplant volume [14]. Blacks make up approximately 17% of our transplant volume and represented 14.6% of documented COVID-19 infections. Disproportionate infection of minorities has been seen within the general population of the greater Los Angeles area [15].

Despite a younger population being infected 63.4% required hospitalization for symptoms. This number would be as high as 75.6% if emergency room visits were included in patients who did not require admission and were managed at home. The overall mortality rate was 9.8% at a median of 1.5 months, much lower than previously reported by other centers, and similar to the mortality rate for nontransplant recipients at our center. However, ICU mortality was 44.4%. This observed difference in overall mortality from prior studies may be in part due to younger age of our population, reporting in an area not under surge, and fewer patients with ICU status [6].

Another issue in transplantation that remains unclear is the optimal choice of therapy and the role of reduction of immunosuppression [16]. The majority of our patients who were admitted did have immunosuppression reduced, primarily by having mycophenolate held. A range of treatment approaches were utilized including remdesivir, convalescent plasma, tocilizumab, and leronlimab. Of note, patients on chronic immunosuppression nonetheless demonstrated high levels of inflammatory markers (Table 2). Given what is known about the pathophysiology of COVID-19 infection, in terms of increased mortality in older adults [17], and signals of T cell exhaustion [18], hyperinflammation [19], and immune dysregulation [20], it will be important to understand the immune response of transplant recipients receiving immunosuppression in order to tailor immunomodulating therapies.

Kidney impairment was common, but was reversible in most patients. At the time of follow-up only 1 of the surviving 36 patients was on dialysis. This patient had marked impaired allograft function at the time of infection and was already relisted for a second transplant. Another was only 1-week post discharge with resolving AKI. The remaining 34 patients (94.4%) had renal function similar to their baseline before infection. These results were reassuring compared with other reports of the impact of COVID-19 on kidney function in renal transplant recipients [4].

The primary limitation of this study is that it is a single-center study, which is limited by documentation of COVID-19 infection. Not all laboratory data was available at the time of diagnosis and not all patients were treated at a single center. We had 1 patient with missing treatment data. However, we have attempted to balance these limitations with increased follow-up time after patient diagnosis. We also included only documented cases of COVID-19; no suspected cases were included.

CONCLUSION

COVID-19 infection in kidney transplant recipients results in a high rate of hospitalization. Mortality among transplant recipients is higher than previously reported in the general population, but may be lower than previously reported.

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