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COVID-19 infection in a pediatric kidney transplant population: A single-center experience

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Abstract

Background: The clinical course of SARS-CoV-2 in the pediatric kidney transplant population is not well described.

Methods: We performed a retrospective cohort study of a pediatric kidney transplant population at a New York transplant center. Baseline characteristics and clinical course of patients with SARS-CoV-2 positivity (Ab or PCR) were described, and comparison between COVID-positive and COVID-negative transplant patients was performed.

Results: Twenty-two patients had COVID-19 IgG testing performed, eight of whom also had PCR testing. 23% of our cohort had evidence of COVID-19 infection. Four patients had positive IgG only, and one patient had a positive PCR. All five patients with a positive COVID test were female. Two patients had COVID-19 symptoms, which were mild. Of the symptomatic patients, one had a positive PCR at time of symptoms, while the other had a negative PCR during symptoms but subsequently had positive IgG. As compared to patients with COVID-19 negative results, those with COVID-19 positivity were significantly more likely to have a known COVID-19 exposure, and were also more likely to be female. There was no significant difference in time from transplant between the groups. Those in the COVID-positive group had higher baseline antimetabolite dose and CNI troughs, although these did not reach statistical significance.

Conclusions: Pediatric kidney transplant recipients are at risk for development of COVID-19 infection. While this population may be more at risk for SARS-CoV-2 infection due to their immunosuppressed status, their clinical course appears mild and similar to a healthy pediatric population.

KEYWORDS
COVID-19, infectious risk, pediatric kidney transplant

1 | INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pandemic has had shifting epicenters since its discovery in December 2019 in Wuhan, China. In the United States, New York City became an early hub, and now the virus continues its spread throughout the country. While the virus has had devastating effects on the elderly population,[1] data suggest that children are relatively spared.[2-5] In a report of over 70,000 COVID-19 cases from Wuhan, only 1% were diagnosed in children under 10 years of age, and another 1% in children aged 10–19.[4]

Abbreviations: Ab, antibody; MIS-C, multisystem inflammatory syndrome in children; MMF, mycophenolate mofetil; PCR, real-time polymerase chain reaction assay; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2.

TABLE 1 Demographic Information of COVID-19-Positive Transplant Recipients

Patient	Age (years)	Gender	Race/Ethnicity	Underlying Disease	Pre-Existing Comorbidities	Organ Type	Blood Type
1	14	F	Hispanic	VUR	none	DDRT	O
2	15	F	Black	IgA	HTN	LDRT	O
3	19	F	Hispanic	Takayasu	none	DDRT	O
4	17	F	Black	aHUS	HTN, BKV	DDRT	B
5	18	F	Black	Unknown	HTN	DDRT	B

Abbreviations: BKV, BK viremia; DDRT, deceased donor renal transplant; HTN, hypertension; LDRT, living donor renal transplant.

An Italian study reported that approximately 75% of pediatric cases of SARS-CoV-2 were asymptomatic or mild.[3] However, it has been noted that chronically ill children may have a more severe course of disease.[6] Within the adult population, immunocompromised individuals including solid organ transplant recipients have been shown to be at high risk.[7-11] A multicenter study with over 100 adult kidney transplant recipients showed a mortality of 32%.[9] However, little is published on pediatric transplant recipients, and it is unknown whether their course of disease is more similar to adult transplant patients or to a healthy age-matched population. Here, we report our data on COVID-19 in pediatric kidney transplant recipients in a New York transplant center.

2 | MATERIALS AND METHODS

We performed a single-center cohort study of pediatric kidney transplant recipients. From May 2017 to May 2020, we performed a total of 24 pediatric kidney transplants. Participants were patients ≤21 years at the Steven and Alexandra Cohen Children's Medical Center (CCMC), a part of Northwell Health, located on the border of Queens and Nassau counties in New York. All pediatric kidney transplant recipients who obtained blood work between 5/1/2020 and 7/15/2020 had COVID-19 antibody (Ab) testing performed as part of routine clinical care in order to help guide immunosuppressive management strategies and anticipatory guidance for patients. In addition, patients with symptoms concerning for SARS-CoV-2 infection (fever and/or respiratory symptoms) were evaluated with real-time polymerase chain reaction assay (PCR). Finally, patients who were admitted to the hospital or CCMC emergency room (ER), or who underwent any surgical procedures, obtained a COVID-19 screening PCR with or without Ab testing as part of current routine hospital protocol.

Data were collected from the enterprise electronic health record (EHR; Sunrise Clinical Manager, Allscripts). COVID-19 positivity was defined as a positive result on nasopharyngeal swab using one of several nucleic acid amplification assays utilized at Northwell Health, and/or positive serum COVID-19 IgG result.

All charts were manually reviewed for demographics, time from transplant, immunosuppressive regimen, history of known COVID-19 exposure, clinical signs and symptoms, associated laboratory values, changes in immunosuppressive management, and clinical outcome.

The study was approved by the Institutional Review Board of Northwell Health. Written informed consent was waived.

Statistical analysis was performed using STATA 12.1. Continuous variables were summarized with means and standard deviations or medians and interquartile ranges (IQR) as appropriate, while categorical variables were summarized with frequencies and percentages. Outcomes between the COVID-positive and COVID-negative groups were compared using t test, Wilcoxon rank-sum test or chi-square as appropriate.

3 | RESULTS

A total of 22 patients were included in the study. Overall, the median age of the study population was 16.5 years (IQR 14,18; range 5–21). Half of the patients were male. 40.9% were Black, 27.3% were Hispanic, and 13.6% were White. Glomerular disease accounted for 68% (15/22) of the underlying etiology of ESRD.

All 22 patients had COVID-19 Ab testing performed. Eight patients (36%) also had COVID PCR testing done. Two patients had PCR testing due to symptoms of COVID-19 (one with fever, chest tightness and one with fever, abdominal pain and muscle aches) and the remainder had testing done in conjunction with a hospital or ER admission or as part of pre-surgical testing.

A total of five patients had positive COVID-19 results on either PCR or Ab testing. One patient was positive on PCR, performed due to clinical symptoms, and the remaining four were positive only on IgG testing. Of these four, one patient had two negative COVID PCRs in the setting of fever, abdominal pain and muscle pain, however subsequent IgG testing was positive. It is likely that her PCR results were false negatives, although it is possible that she had a separate asymptomatic infection, and that her COVID-like symptoms were due to another cause.

Demographics of patients with positive COVID results are presented in Table 1. COVID-related information on these patients is presented in Table 2. The clinical course of the two patients who developed symptoms are described below.

An 18-year-old woman presented at 62 days post-transplant with symptoms of fever to a maximum of 100.6 F and chest tightness. She was sent to the ER where COVID PCR testing was found to be positive. Her vital signs on arrival to the ER were temperature of 36.6°C, heart rate of 68 bpm, blood pressure of 95/68 mmHg,

TABLE 2 COVID-19 Related Data in COVID-19-Positive Transplant Recipients

Patient	Symptoms	Time from Transplant to + test (days)	Known Exposure	Induction	IS at time of + test	CNI trough at time of COVID result (ng/ml)	Antimetabolite daily dose at time of COVID result (mg/m^2/day)	Change in Immunosuppression	Δ Creatinine (mg/dl)
1	Yes	974	Household	Basiliximab/steroid withdrawl	tacrolimus/ MMF	6.0	805	None	+0.15
2	No	989	Household	Thymoglobulin/standard steroid	tacrolimus/ MMF/ prednisone	7.9	1087	None	+0.04
3	No	633	Household	Thymoglobulin/standard steroid	tacrolimus/ MMF/ prednisone	4.7	1027	None	−0.09
4	No	576	None	Basiliximab/standard steroid	tacrolimus/ prednisone/ eculizumab	10.3	0	None	−0.22
5	Yes	62	None	Thymoglobulin/standard steroid	tacrolimus/ MMF/ prednisone	15.1	1143	MMF decreased by 50%, prednisone decreased by 50%	−0.10

Abbreviations: CNI, calcineurin inhibitor; IS, immunosuppression; MMF, mycophenolate mofetil.

TABLE 3 Comparison of COVID-Positive and COVID-Negative Transplant Recipients

	COVID Positive N=5	COVID Negative N=17	*p*
Age (years–median, IQR)	16 (11,18)	17 (15,18)	.81
Male (%)	0 (0%)	11 (64.7%)	.011
Race/ Ethnicity			
Hispanic	2 (40%)	4 (23.5%)	.56
Black	3 (60%)	6 (35.3%)	
White	0 (0%)	3 (17.7%)	
Asian	0 (0%)	3 (17.7%)	
Other	0 (0%)	1 (5.9%)	
Blood Type			
A	0 (0%)	3 (17.7%)	.21
B	2 (40%)	1 (5.9%)	
AB	0 (0%)	1 (5.9%)	
O	3 (60%)	12 (70.6%)	
BMI	23.1 (22.8, 28.1)	22.1 (17.9, 23.9)	.22
Time from Transplant (days)	636 (576, 974)	437 (359, 893)	.78
Antimetabolite Daily Dose (mg/m^2/day)	812.5 ± 472	630 ± 365	.46
CNI trough (ng/ml)	8.8 ± 1.8	5.78 ± 0.48	.18
Known Exposure	3 (60%)	1 (5.9%)	.006

Abbreviation: CNI, calcineurin inhibitor.

respiratory rate of 16 bpm, and oxygen saturation of 100% on room air. Blood work showed WBC 5.50 k/μl with lymphopenia (ALC 680 k/μl), Hgb stable at 11.7 g/dl, and mildly low platelets of 117 k/μl. Her creatinine at presentation was 1.48 mg/dl, slightly above her baseline of 1.3 mg/dl. A chest X-ray showed clear lungs with no effusion. She remained well appearing and was discharged from the ED with home O_2 monitoring and close follow-up with the transplant team. Her MMF and prednisone doses were reduced to half. She did not receive treatment considered specific for COVID at that time. Her symptoms resolved within 2 days of presentation. With 71 days of follow-up since her initial positive test, her most recent follow-up creatinine was 1.35 mg/dl and she has remained clinically stable. She did develop positive serum BK PCR during the follow-up period which responded to treatment with leflunomide and cidofovir. On subsequent COVID PCR testing, she remained positive at 27 and 32 days after initial presentation. She had a negative PCR result after 38 days. Of note, COVID-19 IgG testing performed 48 days after her initial presentation was negative.

A second patient was a 14-year-old woman who presented at 924 days post-transplant with fever, headache, muscle pain, abdominal pain, and rhinorrhea, in the setting of a COVID-positive household contact. She had two negative COVID PCRs at the

time of presentation, but subsequently was found to have positive COVID-19 IgG five weeks later, raising the possibility that the two PCRs were falsely negative. On her initial presentation, her vital signs were notable for a temperature of 38.6°C, heart rate of 113 bpm, blood pressure of 121/70 mmHg, respiratory rate of 16 bpm, and oxygen saturation of 99% on room air. Lab work showed a WBC of 13.4 k/μl with ALC of 1840 k/μl, Hgb 12.1 g/dl, and platelets of 198 k/μl. Creatinine was elevated to 1.83 mg/dl on admission, up from a baseline of 1.6 mg/dl, and improved with hydration. The patient was admitted for 1 day, and treated with IV fluids and antibiotics for possible urinary tract infection, which were stopped when urine culture returned negative. There were no changes made to her immunosuppressive regimen, as her PCR was negative and her symptoms had improved. With 96 days of follow-up from her hospital presentation, she has remained clinically stable. COVID-19 IgG was positive 50 days after her hospital presentation.

When looking at the overall cohort, as compared to patients with COVID-19 negative results, those with COVID-19 positivity were significantly more likely to have a known COVID-19 exposure, and were also more likely to be female. There was no significant difference in age, race, or blood type between the groups. Those in the COVID-positive group had higher baseline antimetabolite dose and CNI troughs, although these did not reach statistical significance. Table 3 shows comparative data between the COVID-positive and COVID-negative groups.

4 | DISCUSSION

Our results found that 18% of the tested pediatric kidney transplant recipients had detectable antibodies against COVID-19. An additional one patient had a positive COVID PCR although did not develop antibodies as of 48 days post-presentation. This may have been due to a short time since transplant and reduced immunogenic capacity. While previous case reports have shown conflicting data on Ab development in previously transplanted hosts,[12,13] our results indicate that patients on chronic immunosuppressive therapy can generate an Ab response.

Although this is a small, single-center study, our COVID prevalence is similar to that reported in May through the New York State Ab testing study, which found 11.9% seropositivity in Long Island and 19.9% in New York City in a study population of 15,000 individuals.[14] However, age-specific rates are not available, and it is possible that our population has a higher prevalence than healthy age-matched controls.

Of our patients with positive COVID testing, two out of the five had identifiable symptoms while the other three remained asymptomatic. Of the two that developed symptoms, these were mild and both patients have returned to their clinical baseline. One of the patients did not have any alteration in her immunosuppressive regimen at the time of symptoms, as her COVID PCR was negative and she quickly improved. The other symptomatic patient was managed with a 50% dose reduction in antimetabolite and prednisone doses, in line with other published reports of COVID management in kidney transplant recipients.[9] None of the patients had a clinically significant change in baseline creatinine from pre-COVID levels or have been treated for transplant rejection since the time of COVID positivity.

Our results are in contrast to those shown in adult kidney transplant recipients. A study of adult transplant recipients within our health system showed 30% mortality in a total of 10 transplant patients with COVID-positive PCR, performed due to clinical suspicion.[11] Furthermore, this study found that 50% developed AKI: one with stage 1, one with stage 2 and 3 with stage 3 AKI. A study by Pereira et al.[7] studied 90 adult organ transplant recipients in a New York center, and found that 30% had severe disease with 18% mortality. Although this study included recipients of other organs, organ type was not a significant predictor of outcome. While COVID outcomes have varied widely across locations, the TANGO Consortium, a multinational study of COVID-19 outcomes in adult transplant recipients, showed 32% mortality, similar to results reported by Nair et al.[9-11]

In contrast, the mild/ asymptomatic nature of COVID infection in our pediatric cohort was similar to reports of COVID outcomes in otherwise healthy pediatric populations,[3-6] suggesting that outcomes in transplant recipients may relate more to age than to immunocompromised status. Even within the adult transplant population, older age was associated with increased disease severity and mortality,[11] and worse outcomes were also seen in transplant patients with known co-morbidities including asthma, DM, and obesity.[15] In our cohort, no significant difference in BMI was seen between those with and without COVID.

Other COVID risk factors that have been noted in previous studies were not found to be associated with increased rate of COVID positivity in our cohort. While blood type A has been associated with increased SARS-CoV-2 severity,[16] and blood type O has been found to be protective,[17] in our cohort those who had positive COVID testing were exclusively blood types B and O. It is possible, however, that blood type played a role in the overall mild disease course in our cohort.

It is important to note that at the time of last follow-up, with a median follow-up time of 44 (IQR 28, 69) days, none of our COVID-positive patients had clinical findings suspicious for multisystem inflammatory syndrome in children (MIS-C), an entity generally occurring 3–4 weeks after an acute SARS-CoV-2 infection and defined by fever, laboratory evidence of inflammation, serious illness resulting in hospitalization, and multiorgan involvement.[18,19] It is thought that the host response and dysregulation of innate immunity can contribute to the hyperinflammatory response to COVID-19,[20,21] and that an immunosuppressed state may therefore be protective against severe disease.[22] A systematic review of MIS-C noted a majority of children responded to IVIG and corticosteroids, suggesting a role for immunomodulation,[23] however, the response to different immunosuppressed states may vary. A review by Fung and Babik[22] of COVID-19 in immunocompromised hosts noted more severe outcomes in adults with cancer and solid organ transplant recipients, however also noted that

these patients were generally managed with a reduction in immunosuppression. In contrast, patients being treated with biologic therapies had similar or occasionally improved disease outcomes as compared to the general population. The role of immunosuppression in COVID-19 outcomes has not been fully elucidated. Further studies are needed to clarify the role of the innate immune response in severe COVID-19 and MIS-C,[24] and how these differences may impact the role of immunosuppression on SARS-CoV-2 outcomes in transplant recipients.

This study has several limitations. This is a small, single-center study. COVID-19 prevalence varies with location, as do treatment and management strategies, therefore results might not be generalizable. Importantly, our study looked at a combination of PCR and IgG results, whereas the majority of studies on COVID outcomes have looked exclusively at patients with positive PCR in the setting of active disease. It is possible that there are adult transplant patients with subclinical disease who would be detected with Ab testing.

Despite these limitations, our study presents new information on COVID-19 prevalence and course in a group not previously well described. These data suggest that pediatric kidney transplant patients have asymptomatic or mild disease, and can be managed without major reductions in immunosuppression, thereby reducing the risk of subsequent transplant rejection. Further long-term studies are needed to assess for chronic or later-developing complications.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

PS, CS, EG, and LT contributed to study conception and design. JF and PS contributed to data collection. PS, CS, EM, and LT contributed to data analysis. PS, CS, AF, EG, and LC contributed to manuscript preparation.

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