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The pediatric solid organ transplant experience with COVID-19: An initial multi-center, multi-organ case series

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Abstract

The clinical course of COVID-19 in pediatric solid organ transplant recipients remains ambiguous. Though preliminary experiences with adult transplant recipients have been published, literature centered on the pediatric population is limited. We herein report a multi-center, multi-organ cohort analysis of COVID-19-positive transplant recipients ≤ 18 years at time of transplant. Data were collected via institutions' respective electronic medical record systems. Local review boards approved this cross-institutional study. Among 5 transplant centers, 26 patients (62% male) were reviewed with a median age of 8 years. Six were heart recipients, 8 kidney, 10 liver, and 2 lung. Presenting symptoms included cough (n = 12 (46%)), fever (n = 9 (35%)), dry/sore throat (n = 3 (12%)), rhinorrhea (n = 3 (12%)), anosmia (n = 2 (8%)), chest

Abbreviations: AA, African American; ACR, acute cellular rejection; ATG, anti-thymocyte globulin; BMI, body mass index; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; CXR, chest X-ray; ECMO, extracorporeal membrane oxygenation; FDA, Food and Drug Administration; GBS, group B streptococcus; HCQ, hydroxychloroquine; Hct, hematocrit; Hgb, hemoglobin; HTN, hypertension; MMF, mycophenolate mofetil; NP, nasopharyngeal; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TAC, tacrolimus; USA, United States; UTI, urinary tract infection; WBC, white blood cell; Wnl, within normal limits.

pain (n = 2 (8%)), diarrhea (n = 2 (8%)), dyspnea (n = 1 (4%)), and headache (n = 1 (4%)). Six patients (23%) were asymptomatic. No patient required supplemental oxygen, intubation, or ECMO. Eight patients (31%) were hospitalized at time of diagnosis, 3 of whom were already admitted for unrelated problems. Post-transplant immunosuppression was reduced for only 2 patients (8%). All symptomatic patients recovered within 7 days. Our multi-institutional experience suggests the prognoses of pediatric transplant recipients infected with COVID-19 may mirror those of immunocompetent children, with infrequent hospitalization and minimal treatment, if any, required.

KEYWORDS
pediatric transplantation, viral infection

1 | INTRODUCTION

The COVID-19 pandemic caused by SARS-CoV-2 continues to evolve with surges in many states across the USA. While emphasis has been appropriately placed on social distancing, mask wearing, and hand hygiene, the population at large, including transplant patients, remains susceptible to infection. Many drugs that fight rejection and prolong life in organ recipients function through attenuated T-cell activation and proliferation,[1] rendering patients more susceptible to viral infection. Thus, COVID-19 is postulated to cause disproportionate harm to transplant patients. There are currently no approved COVID-19 treatments, though the US FDA has granted emergency use authorizations for the antiviral remdesivir and the now-revoked antimalarials HCQ sulfate and chloroquine phosphate. As data on effective therapies for COVID-19 are limited, with management predominantly consisting of supportive care for patients not enrolled in clinical trials, insight into the clinical course of COVID-19 in transplant recipients is critical, particularly in children.

Many adult centers[2-4] have suggested that transplant recipients are at particular risk for an arduous clinical course given their immunocompromised state, though highly associated comorbidities exist as confounders and appear to play a significant role in COVID-19 outcomes for the transplant subpopulation.[5] In contrast, others[6,7] have reported similar clinical manifestations and mortality in transplant recipients relative to the general population. It has also been suggested that immunosuppression may confer a clinical advantage by potentially mitigating immune-mediated lung injury and acute respiratory distress syndrome in late severe SARS-CoV-2 infection.[8] This hypothesis may be more applicable to the pediatric population as children usually receive more immunosuppression per kilogram compared to adults.

As the transplant community seeks clarity regarding management and outcomes of recipients testing positive for COVID-19, experiences with adult patients currently comprise a vast majority of the literature. The few pediatric publications that do exist are limited to single case reports.[9,10] In view of the age-dependent risk discrepancy observed in the general population,[11] age may become an influential factor for treatment selection, modification of immunosuppression, and clinical prognosis upon post-transplant SARS-CoV-2 infection. Herein we report a multi-center, multi-organ cohort analysis focused on young transplant recipients and their clinical characteristics, management, and outcomes.

2 | MATERIALS AND METHODS

All solid organ transplant recipients ≤ 18 years at time of transplant with a positive test for COVID-19 between April 1, 2020, and July 20, 2020, from 5 centers (Texas Children's Hospital, Children's Hospital Los Angeles, Miami Transplant Institute, University of Colorado, and University of Texas Health Science Center at San Antonio) were included in this cohort analysis. COVID-19 positivity was determined via NP swab SARS-CoV-2 real-time RT-PCR (Hologic Aptima SARS-CoV-2 RT-PCR assay). IgM and IgG total SARS-CoV-2 antibodies were detected by the Ortho Clinical Diagnostics VITROS® Immunodiagnostics Products Anti-SARS-CoV-2 Test. Data were collected via institutions' respective electronic medical record systems and were reviewed for patient characteristics, history of recent exposure, timing of presentation, symptomatology, laboratory values, immunosuppression management, antiviral treatment strategies, and clinical outcomes. Local review boards approved this cross-institutional study.

3 | RESULTS

During the COVID-19 pandemic between April 1, 2020, and July 20, 2020, 5 pediatric transplant centers in the USA identified 6 heart, 8 kidney, 10 liver, and 2 lung transplant recipients that were found to be COVID-19-positive post-transplant. Eight of 26 patients (31%) were hospitalized, 3 of whom were already admitted for unrelated problems. All patients with COVID-19 symptoms at the time of diagnosis recovered before manuscript submission, with full resolution

of symptoms within a median of 3 days. No patient experienced progressive deterioration or death.

3.1 | Demographics

Overall, patient demographics are summarized in Table 1. Sixteen of 26 patients (62%) were male. The median age of COVID-19-positive transplant recipients at time of transplant was 8 years (range 5 months-18 years). Nineteen of 26 (73%) were Hispanic, 5 (19%) were Caucasian, and 2 patients (8%) were AA. Seventeen of 26 patients (65%) were blood type O, while 8 (31%) were type A and 1 patient (4%) was of the AB blood group. BMI ranged between 17.4 and 38.8 kg/m^2 with 9 of 26 (35%) <20 kg/m^2, 11 (42%) between 20 and 30 kg/m^2, and 6 (23%) >30 kg/m^2. Eight of 26 patients (31%) had undergone kidney transplantation, 10 (38%) underwent liver transplantation, 6 (23%) were heart transplant recipients, and 2 (8%) were lung recipients. Twenty-five of 26 patients (96%) underwent transplantation with a deceased donor whole organ allograft, while a single affected kidney transplant recipient underwent living donor transplantation. The median time from transplant to initial positive COVID-19 test was 1246 days (range 12-6574 days). One patient (No. 8) tested COVID-19-positive during the index transplant hospitalization and developed cough. This 18-year-old patient had received induction immunosuppressive therapy with 3 daily doses of rabbit ATG. Thirteen of 26 patients (50%) were suspected to have had COVID-19 exposure from a family member, while 11 (42%) had community-acquired infection. Two patients (8%) were exposed by a healthcare provider.

3.2 | Presentation and clinical course

The 26 COVID-19-positive transplant recipients had variable clinical presentations (Table 1). The most common documented symptom was cough (n = 12 (46%)) followed by fever (n = 9 (35%)), dry/sore throat (n = 3 (12%)), rhinorrhea (n = 3 (12%)), anosmia (n = 2 (8%)), chest pain (n = 2 (8%)), diarrhea (n = 2 (8%)), and dyspnea and headache in 1 patient each (4%). Six patients (23%) did not have any symptoms (4 kidney, 1 liver, and 1 lung recipients).

Eight of the affected patients (31%) were hospitalized at the time of COVID-19 diagnosis; however, 3 patients (Nos. 3/7/8) were already admitted for unrelated problems. The remaining 5 patients (19%) were hospitalized for a median time of 3 days, with presenting symptoms including a combination of fever (n = 3), cough (n = 2), chest pain (n = 1), diarrhea (n = 1), and rhinorrhea (n = 1). Eight of 26 patients (31%) were evaluated by CXR or CT of the chest, and only patients 8 (kidney recipient) and 15 (liver recipient) had multifocal pulmonary infiltrates consistent with COVID-19. Six patients (23%) had a decreased WBC count (<4000 per μL of blood), and 4 (15%) had low Hgb (<13.5 g/dL for males, <12.0 g/dL for females) and Hct (<41% for males, <36% for females) (1 patient had both a decreased WBC count and low Hgb and Hct); however, none of the patients presented with laboratory evidence of hepatitis or other biochemical abnormalities. There were no observed or quantified differences in severity of clinical course or treatment dependent on blood type.

Twelve of 26 patients (46%) had inflammatory biomarkers measured. Of the 12, 7 (58%) had elevation of CRP (>1.0 mg/L) and/or ferritin (>300 ng/mL for males, >150 ng/mL for females). In addition, 5 patients (42%) had elevation of fibrinogen (>400 mg/dL) and/or D-dimer (>0.5 mg/L). A smaller subset of 4 patients (15%) had serum troponin levels measured, and all were WnI (<0.4 ng/mL). Age among our pediatric cohort did not appear to influence clinical severity.

Follow-up COVID-19 NP swab testing was available in 10 of 26 patients (38%) with 5 of 10 testing negative (median time of 13 days after initial positive test) and the other 5 remaining positive (median time of 15 days after initial positive test). Only 1 patient (No. 18) was tested for the presence of SARS-CoV-2 antibodies, which detected IgG-specific antibodies, while IgM antibodies were negative indicating previous and not active infection.

3.3 | Treatment/immunosuppression

Of the 26 affected patients, none required supplemental oxygen or intubation (it should be noted that No. 3 is chronically ventilatory dependent—Table 1). One patient (No. 13) with paralysis and neurogenic bladder had a concomitant UTI with GBS, which was treated with 10 days of intravenous cefazolin. The majority of patients (25/26) received TAC -based immunosuppression; one received sirolimus. One liver transplant patient (No. 15), who presented with cough and patchy infiltrates on CXR, was hospitalized and had reduction in immunosuppression with oral sirolimus held and TAC decreased to trough level of 4-6 ng/mL from previous 6-8 ng/mL. Symptoms resolved in approximately 48 hours, and the patient was discharged home on pre-admission immunosuppression doses. One kidney transplant patient (No. 8), who contracted COVID-19 during the index transplant hospitalization and developed cough, had reduction in immunosuppression with MMF decreased to 270 mg/m^2/dose from previous 360 mg/m^2/dose and TAC decreased to trough level 8-10 ng/mL from previous 10-12 ng/mL. The cough resolved within 72 hours, but the patient remained hospitalized for other reasons. Seven days after reduction in immunosuppression, serum creatinine increased to 2 mg/dL and kidney transplant biopsy revealed moderate ACR, necessitating high-dose steroid therapy and an increase in maintenance immunosuppression. Immunosuppressive regimens were not adjusted in 24 of 26 COVID-19-positive post-transplant patients.

4 | DISCUSSION

As the morbidity and mortality associated with COVID-19 continue to impact the world, particularly in the USA, SARS-CoV-2 infection among solid organ transplant recipients is inevitable. Due to immunosuppressive treatment,[1] elevated risk of co-infections

TABLE 1 Demographics and clinical presentation of pediatric solid organ transplant recipients with SARS-CoV-2 infection

Pt	Sex	Tx age (years)	Ethnicity	Blood type	BMI	Organ	Donor type	Pertinent medical problems post-transplant
1	M	0.4	Hispanic	O+	20.2	Heart	Deceased	Shone's syndrome
2	M	4	White	O+	20.7	Heart	Deceased	Atherosclerotic disease, CVA, GERD, asthma
3	M	0.8	Hispanic	A+	21.8	Heart	Deceased	Cardiomyopathy, AKI, seizures
4	M	0.5	Hispanic	O+	17.4	Heart	Deceased	Prematurity, chromosome 15q duplication, asthma
5	M	17	White	A+	25.1	Heart	Deceased	CVA, kidney disease
6	F	13	Hispanic	A+	30.7	Heart	Deceased	Restrictive cardiomyopathy, pulmonary HTN
7	F	10	Hispanic	O+	33.1	Kidney	Living	Reflux nephropathy, DM, asthma, CVA, pancreatitis, migraines, hyponatremia
8	F	18	Hispanic	A+	22.2	Kidney	Deceased	Loss first transplant acute rejection, chronic peritoneal dialysis, ADHD, seizure disorder, bx reveals mod ACR
9	F	15	Hispanic	AB+	38.8	Kidney	Deceased	HTN, pulmonary edema, mild tricuspid and pulmonary regurgitation
10	M	17	Hispanic	A+	32.5	Kidney	Deceased	Sarcoidosis, UTIs
11	M	13	AA	O+	21.4	Kidney	Deceased	IgA nephropathy, HTN, DM, hypothyroidism
12	M	12	Hispanic	O+	29.3	Kidney	Deceased	Cystic dysplasia, HTN
13	M	14	AA	O+	19.8	Kidney	Deceased	ACR/AMR, paralysis, neurogenic bladder
14	M	6	Hispanic	O+	20.8	Kidney	Deceased	CMV, C diff, hepatoblastoma
15	M	13	Hispanic	O+	33.3	Liver	Deceased, Whole	Hepatic adenomatosis, insulin resistance
16	F	8	White	O−	25.5	Liver	Deceased, Whole	Biliary atresia, failed Kasai
17	F	1.1	White	A+	24.4	Liver	Deceased, Whole	Hepatoblastoma, HTN, CKD
18	F	0.6	Hispanic	O+	19.4	Liver	Deceased, Whole	Failure to thrive
19	F	13	Hispanic	O+	33.5	Liver	Deceased, Whole	Ellis-van Creveld syndrome, HTN, asthma, hypothyroidism
20	M	1.9	White	O+	19.1	Liver	Deceased, Whole	Hepatoblastoma, adrenal insufficiency, RTA, chemo-induced anemia/thrombocytopenia
21	F	3	Hispanic	O+	17.7	Liver	Deceased, Whole	None
22	M	1.8	Hispanic	A+	17.8	Liver	Deceased, Whole	Seizure disorder, chronic lung disease, asthma, global development delay
23	F	4	Hispanic	O+	19.5	Liver	Deceased, Whole	None
24	M	0.8	Hispanic	A+	18.8	Liver	Deceased, Whole	Adrenal insufficiency, DM
25	M	8	Hispanic	O+	19.9	Lung	Deceased	CF, chronic sinusitis, DIOS, osteoporosis
26	M	9	Hispanic	O−	23.5	Lung	Deceased	Bone marrow tx, seizures, HTN, asthma

Time from Tx to Infection (days)	Presenting symptoms	Exposure	Hospitalized	CXR/CT findings
6129	Anosmia	Family member	No	N/O
1182	Cough, rhinorrhea	Family member	No	N/O
1874	Fever	Family member	Yes (trach care)	N/O
410	Fever	Family member	Yes	Yes (normal)
1114	Cough, fever	Family member	No	N/O
2879	Cough, dry throat	Community-acquired	No	N/O
4868	Anosmia, cough, fever, rhinorrhea	Community-acquired	Yes (migraine/ hyponatremia)	N/O
12	Cough	Family member	Yes (post-transplant)	Yes (multifocal infiltrates)
1256	Cough, fever	Hospital exposure	No	Yes (normal)
436	None	Family member	No	N/O

(Continues)

TABLE 1 (Continued)

Time from Tx to Infection (days)	Presenting symptoms	Exposure	Hospitalized	CXR/CT findings
2677	Diarrhea	Community-acquired	No	Yes (normal)
2542	None	Community-acquired	No	N/O
1882	None	Community-acquired	No	N/O
119	None	Home health RN	No	Yes (normal)
1236	Chest pain, cough	Community-acquired	Yes	Yes (multifocal infiltrates)
784	Cough, dyspnea, sore throat	Community-acquired	No	N/O
4444	Cough, diarrhea, fever	Family member	Yes	Yes (normal)
1910	Fever	Community-acquired	Yes	N/O
958	Cough	Family member	No	N/O
1138	Cough	Family member	No	N/O
560	Fever	Community-acquired	No	N/O
814	Rhinorrhea	Community-acquired	Yes	N/O
1659	None	Family member	No	N/O
6574	Chest pain, fever, headache	Family member	No	N/O
3127	None	Community-acquired	No	Yes (normal)
933	Cough, sore throat	Family member	No	N/O

Basic labs	Inflammation/ Hypercoagulable evaluation	New O_2 therapy	Maintenance immunosuppression	Immunosuppression change	COVID-19 therapy
N/O	N/O	No	TAC, Rapa, Pred	No	No
Wnl	N/O	No	TAC, Rapa	No	No
Wnl	N/O	No	TAC, MMF	No	No
Wnl	Inc CRP, D-dimer	No	TAC, MMF	No	No
Dec WBC	N/O	No	Rapa, Pred, cyclosporine	No	No
Wnl	N/O	No	TAC, azathioprine	No	No
Wnl	Inc CRP, fibrinogen, D-dimer	No	TAC, azathioprine	No	Enoxaparin sulfate
Dec WBC, Hgb, Hct	Inc CRP, ferritin, fibrinogen, D-dimer	No	TAC, MMF, ATG	Yes (reduction)	No
Dec Hgb, Hct	Inc CRP, fibrinogen, D-dimer	No	TAC, MMF	No	No
Wnl	Wnl	No	TAC, Pred	No	No
N/O	N/O	No	TAC, MMF, Pred	No	No
Dec WBC	N/O	No	TAC, MMF	No	No
Dec Hgb, Hct	Inc ferritin	No	TAC, MMF, Pred	No	No
N/O	N/O	No	TAC, MMF, Pred	No	No
Dec WBC	Inc CRP, fibrinogen, D-dimer	No	TAC, Rapa	Yes (reduction)	Azm
Wnl	N/O	No	TAC	No	No
Wnl	Wnl	No	TAC, MMF, Pred	No	Azm, HCQ
Wnl	Inc CRP	No	TAC, MMF	No	Azm
Wnl	N/O	No	TAC	No	Azm
Dec WBC	N/O	No	TAC	No	No

(Continues)

TABLE 1 (Continued)

Basic labs	Inflammation/ Hypercoagulable evaluation	New O_2 therapy	Maintenance immunosuppression	Immunosuppression change	COVID-19 therapy
Wnl	N/O	No	TAC	No	No
Dec Hgb, Hct	Wnl	No	TAC, Pred	No	No
Wnl	N/O	No	TAC, Rapa, Pred	No	No
Dec WBC	Wnl	No	TAC, Pred	No	No
Wnl	Wnl	No	TAC, MMF, Pred	No	No
Wnl	N/O	No	TAC, MMF, Pred	No	No
Bacterial co-infection		**Antimicrobial agents**		**Disposition**	
No		No		Home	
No		No		Home	
No		Levofloxacin, nitrofurantoin		Home	
No		Ceftriaxone		Home	
No		No		Home	
No		No		Home	
No		Ceftriaxone, linezolid		Home	
No		No		Hospital (unrelated)	
No		No		Home	
No		No		Home	
No		No		Home	
No		No		Home	
Yes (GBS UTI)		No		Home	
No		No		Home	
No		Azm, ceftriaxone		Home	
No		No		Home	
No		Azm		Home	
No		Azm		Home	
No		Azm		Home	
No		No		Home	
No		No		Home	
No		No		Home	
No		No		Home	
No		No		Home	
No		Azm ppx		Home	
No		None		Home	

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AKI, acute kidney injury; AMR, antibody-mediated rejection; Azm, azithromycin; CF, cystic fibrosis; CKD, chronic kidney disease; CMV, cytomegalovirus; CVA, cerebrovascular accident; DIOS, distal intestinal obstructive syndrome; DM, diabetes mellitus; ESRD, end-stage renal disease; GERD, gastroesophageal reflux disease; N/O, not obtained; PIGN, post-infectious glomerulonephritis; Ppx, prophylaxis; Pred, prednisone; Rapa, rapamune/sirolimus; RN, registered nurse; RTA, renal tubular acidosis.

during the early post-transplant period,[12] and highly associated comorbidities linked to poor outcomes,[5,13,14] transplant recipients are expected to be particularly susceptible to infection and a severe clinical course in the event of SARS-CoV-2 exposure. Some transplant-specific studies report significant complications and mortality,[2-4] while other analyses demonstrate similar symptomatology and mortality rates relative to the general population.[6,7]

To date, the bulk of the literature examining COVID-19 following transplant is adult-focused, with pediatric reports limited to single patient experiences.[9,10] Mirroring the majority experience of infected children in the general population[15,16] and report of a single pediatric heart transplant recipient,[9] our multi-center pediatric transplant cohort experienced mild symptoms or lack thereof. The underpinning of milder symptomatology in children remains obscure but is likely multifactorial. Suggested reasons include a maturing

immune system primed to combat novel pathogens, decreased prevalence of comorbidities established as risk factors for severe disease, frequent infections with the common cold coronaviruses potentially providing protection, healthier respiratory tracts, and a difference in the distribution and functioning of viral receptors.

Though the virus manifested in various ways within our cohort, with cough being the most frequent presentation, complete resolution of symptoms occurred within a week for each patient. None of our liver recipients, nor other solid organs, experienced the described complication of COVID-19-induced hepatitis in an infant early after liver transplant[10] or multisystem inflammatory syndrome in children (MIS-C).[17] As a hyperinflammatory response has been associated with complications and the multi-organ involvement with COVID-19,[18] inflammatory biomarkers in chronically immunosuppressed patients are of particular interest. In our cohort, initial inflammatory biomarkers were not uniformly checked, though CRP, ferritin, fibrinogen, D-dimer, and troponin were measured in certain patients (Table 1). 58% of the measured cohort had elevation of CRP and/or ferritin, while 42% had elevation of fibrinogen and/or D-dimer. All troponin levels were Wnl. As our patients presented with mild symptoms and most recovered within days, and less than half had evaluation of serum inflammatory biomarkers, we are unable to determine the meaning and role of assessment of inflammatory biomarkers in pediatric transplant patients. More data, including serial monitoring as opposed to single measurements, are needed to assess potential predictive value.

Comorbidities associated with a severe COVID-19 clinical phenotype among adult transplant recipients, for example, HTN, obesity, and diabetes,[14] are less prevalent in the pediatric population. This may explain in part our cohort's mild symptoms at presentation and rapid recovery, without any patient requiring supplemental oxygen, intubation, or ECMO. That being said, 6 of our 26 patients (23%) were obese (BMI > 30 kg/m^2) but did not experience more severe manifestations. In addition, our cohort's relatively small patient pool and ubiquitous mild symptomatology precluded firm conclusions with respect to the described disparities in clinical course severity dependent on blood type. Nonetheless, a majority of our cohort was type O (17/26 (65%)), for which a protective effect has been attributed given its unexplained link with a milder disease phenotype.[19] It is also important to note that immunosuppression was reduced in only 2 of 26 patients (8%), with resolution of symptoms within 72 hours, suggesting that adjustment of maintenance immunosuppression may not be necessary. In fact, our experience suggests caution should be exercised when reducing immunosuppression, particularly if symptoms are mild, as renal allograft biopsy of patient No. 8 revealed moderate ACR after initially decreasing MMF and TAC.

We highlight the mild COVID-19 clinical course of 26 immunosuppressed pediatric transplant recipients across 5 institutions including California, Florida, and Texas, unfortunate COVID-19 hotspots in the USA. Our cohort suggests immunosuppression alteration may not be necessary for a complete and rapid recovery in the immediate post-infection period. Furthermore, minimal supportive therapy may be required, if symptoms remain mild. It will be critical to learn from and share our experience through the post-COVID-19 diagnosis and recovery period, with a focus on antibody kinetics and risk for re-infection, as we seek to understand the potential long-term effects of COVID-19 infection in immunosuppressed pediatric transplant patients.

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CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose as described by Pediatric Transplantation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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