BRIEF COMMUNICATION

COVID-19 infection in pediatric solid organ transplant patients

Neha Bansal[1] [iD]　|　Nadia Ovchinsky[2]　|　Marc Foca[3]　|　Jacqueline M. Lamour[1]　|　Debora Kogan-Liberman[2]　|　Daphne T. Hsu[1]　|　Kimberly Beddows[1] [iD]　|　Lincy Abraham[1]　|　Maura Coburn[4]　|　Ryan Cunningham[2]　|　Trang Nguyen[2]　|　Nicole Hayde[4]

[1]Division of Pediatric Cardiology, Children's Hospital at Montefiore, Bronx, New York, USA

[2]Division of Pediatric Gastroenterology, Hepatology, and Nutrition Children's Hospital at Montefiore, Bronx, New York, USA

[3]Division of Pediatric Infectious Diseases, Children's Hospital at Montefiore, Bronx, New York, USA

[4]Division of Pediatric Nephrology, Children's Hospital at Montefiore, Bronx, New York, USA

Correspondence
Neha Bansal, Division of Pediatric Cardiology, Children's Hospital at Montefiore, 3415 Bainbridge Ave- R1, 10467 Bronx, NY, USA.
Email: nbansal@montefiore.org

Abstract

Background: Adult SOT recipients with COVID-19 have higher mortality rates when compared to general population. There is paucity of data on outcomes in pediatric SOT recipients.

Methods: This is a cross-sectional study investigating the prevalence of COVID-19 infection and outcomes in pediatric SOT (heart, liver, and kidney) recipients. We extracted demographic and clinical characteristics and COVID-19 testing (PCR or [Ab] test) results from medical records. Clinical characteristics were compared between patients who were positive for COVID-19 (PCR or Ab) and those who did not, using Mann-Whitney, Student's t test, or chi-square test. p value <.05 was statistically significant.

Results: A total of 108 SOT recipients with a median age of 13.1 (8.4, 17.8) years and median 4.2 (2.7, 7.9) years from transplant were checked for COVID-19 via a PCR or Ab test. A positive PCR was confirmed in 10 patients (9.3%), while 12 patients (11.1%) were positive for COVID-19 Ab. The patients who tested positive in our cohort were 9/50 (18%) heart, 6/68 (8.8%) kidney, and 7/50 (14%) liver transplant recipients. There were no differences in the clinical characteristics between patients with and without COVID-19 infection. All patients were either asymptomatic (50%) or had self-limiting symptoms. No changes were made to the immunosuppressive regimen. Only one patient was hospitalized and none had an oxygen requirement.

Conclusions: In our cohort of pediatric SOT recipients, COVID-19 infection was asymptomatic or mild. This data may aid clinicians in counseling patients and families in this increased-risk population.

KEYWORDS
COVID 19, solid organ transplant

1 | INTRODUCTION

NYC was a major initial epicenter for COVID-19 infection in the United States and, in the borough of Bronx, where our hospital is located, there was a higher prevalence of infection compared to other NYC boroughs.[1] The clinical manifestations of COVID-19 are typically mild in children.[2-4] A review by the Chinese CDC indicated that only 1% of the cases (416/72 134) were in children younger than 10 years of age with no mortality in this population.[5]

In general, immunocompromised patients are more susceptible to viral infections than immunocompetent individuals.[6] This knowledge led to the concern that SOT recipients on immunosuppressive medications may be at a higher risk for infection, morbidity and mortality from COVID-19. The reports in adult SOT, particularly kidney transplant recipients, indicate a significantly increased morbidity and mortality when compared to the general population.[7,8] Initial reports in pediatric kidney transplant recipients indicate a decreased risk for infection and less severe disease when compared to their adult counterparts.[9] The main objective of this study was to determine the prevalence of COVID-19 infection and the clinical outcomes in pediatric SOT (heart, liver, and kidney) recipients at our center.

2 | METHODS

After approval from the institutional review board with a waiver of consent, we conducted a cross-sectional study at our institution from April 2020 to December 2020 as testing became readily available in April 2020. While COVID-19 PCR testing was done on symptomatic or for pre-procedural testing, all other patients were tested once for the presence COVID-19 Ab during their routine clinical follow-up starting April 2020. All patients were screened for COVID-19 exposure and symptoms during their clinical care using a standardized series of questions based on US CDC symptom checklist.[10] We extracted the demographic and clinical data of the study population from the electronic medical record. Variables of interest included organ transplanted, date of transplant, age at transplant, immunosuppression regimen, current height in centimeters, current weight in kilograms, and the presence of comorbidities (hypertension, diabetes, chronic lung disease, and history of malignancy). Trough tacrolimus levels for the 6 months prior to COVID-19 Ab testing were also extracted from the EMR, and the mean trough levels were calculated. There was no standard protocol decided whether or not children should go to daycare or school, but was based on the comfort and resource availability of the individual families. It should be noted that for most of the study period, most schools in the NYC metro area did not have in person classes.

SOT recipients were tested for SARS CoV-2 using a real-time reverse transcriptase PCR assay obtained from a nasopharyngeal swab, if they exhibited symptoms concerning for infection or prior to any scheduled surgical procedures. All patients were tested for the presence of COVID-19 Ab once during a routine clinic visit, regardless of symptoms or known COVID-19 exposure. The Ab testing was performed using the ELISA IgM and IgG test by Viracor laboratory. A unit value of <9.0 indicated there was no detectable IgG Ab present and Immune Status Ratio value of <1.0 indicated there was no detectable IgM Ab present. Data provided by the company indicate that the specificity of this test is 100% for both IgM and IgG.[11] Positive infection was defined as either a positive COVID-19 PCR or Ab test.

2.1 | Statistical analysis

Descriptive data for patients were expressed as median (interquartile range), mean/median (standard deviation) and frequency (%) as appropriate. Mann-Whitney or Student's *t* test (continuous variables) and chi-square tests (categorical variables) were used to compare clinical characteristics between pediatric SOT recipients who were COVID-19 positive (PCR or Ab positive) and those who were negative. We compared clinical characteristics between the 2 groups using SPSS software. A *p* value <.05 was considered statistically significant.

3 | RESULTS

At our center, a total of 50 heart transplant, 50 liver, and 68 kidney transplant patients are followed. Of the 168 SOT patients, 108 (64.3%) were seen at our clinic site during the study period and were tested for COVID-19 via a PCR or Ab test. The other SOT recipients were being followed via telemedicine and off-site laboratory testing due to personal concerns of becoming infected with COVID-19. Twenty-two of the 108 patients (20.4%) tested positive for COVID-19 either via PCR or Ab test. The demographics of the patients, stratified by organ, are shown in Table 1. The patients who tested positive in our cohort were 9/50 (18%) heart, 6/68 (8.8%) kidney, and 7/50 (14%) liver transplant recipients. A positive COVID-19 PCR from a respiratory specimen was confirmed in 10 patients. Of these 10 patients, 4 also had positive Ab testing average 2 months from the positive PCR. The remaining 12 patients tested positive only via Ab testing.

The median age of our study population was 13.1 (8.4, 17.8), (range 0.6–26) years. The median time after transplantation was 4.2 (2.7, 7.9) years. The time from transplantation ranged from 0.2 to 19 years. There were 10 (9%) patients ≤1 year from transplantation, of which 3 had COVID-19. Seven (32%) of the 22 COVID-19 positive transplant recipients were suspected to have had COVID-19 exposure from a family member based on the questionnaire. Eleven (50%) of 22 COVID-19 positive patients were asymptomatic. The other patients had self-limiting symptoms which included fever (*n* = 5), nasal congestion or cough (*n* = 6), malaise or headache (*n* = 3), abdominal pain or diarrhea (*n* = 5), and anosmia or ageusia (*n* = 2). Only 1 patient required hospitalization. He was a 12-month-old male with history of biliary atresia who was 3 months post liver transplant, presented with fever, congestion, and cough and was admitted for concerns of

TABLE 1 Patient demographics

Median (IQR)/Mean ±SD/n (%)	Heart (n = 42)	Kidney (n = 44)	Liver (n = 21)
Median age (years)	13.6 (8.5, 17.3)	15.4 (9.9, 18.5)	8.1 (3.9, 13.9)
Median time since transplant (years)	4.7 (2.6, 9.2)	4.3 (2.7, 9.5)	3.5 (2, 6.5)
Sex (Male)	23 (54.7%)	36 (81.8%)	14 (63.6%)
Height (cm)	152 (127, 169)	150 (129.5, 164.5)	129.5 (104.5, 160)
Weight (Kg)	47.8 (31.5, 68.2)	50.9 (32.9, 66.9)	28.3 (17.4, 45.1)
BMI (kg/m^2)	19.5 (16.5, 23.5)	20.6 (18.7, 26.8)	17.4 (16.1, 21.9)
Vitamin D levels (ng/mL)	30.3 ± 10.7	33.9 ± 11.3	29.3 ± 7.7
Aspirin	38/42 (90.5%)	2/44 (4.5%)	1/21 (4.8%)
Symptoms	5/42 (11.9%)	0/44	4/21 (19%)
Total COVID-19 positive (PCR or Ab)	9/42 (21.4%)	6/44 (13.6%)	7/21 (33.3%)
COVID-19 PCR positive	5/42 (11.9%)	0/44	5/21 (23.8%)
COVID-19 Ab positive			
IgG	4/42 (9.5%)	4/44 (9%)	2/21 (9.5%)
IgM	3/42 (7.1%)	4/44 (9%)	0/21
Immunosuppression			
Tacrolimus	42/42 (100%)	44/44 (100%)	20/21 (95%)
Cyclosporine	0	0	1 (4.7%)
Mycophenolate Mofetil	23 (54.7%)	43 (9.8%)	5 (23.8)
mTOR inhibitors	6 (14.2%)	0	0
Azathioprine	4 (9.5%)	0	2 (9.5%)
Steroids	3 (7.1%)	33 (75%)	4 (19%)
Calcineurin Inhibitor monotherapy	6/42 (14.2%)	0/44	13/21 (59%)
Mean tacrolimus levels (ng/dL)	5.2 ± 1.3	5.4 ± 1.04	6.6 ± 2.6

TABLE 2 Comparison of clinical characteristics between COVID-19 positive and negative patients

Mean ±SD/n (%)	COVID-19 positive[a] (n = 22)	COVID-19 negative (n = 85)	p value
Age (years)	7.3 ± 6.6	10.6 ± 5.9	.8
Time since transplant (years)	5.1 ± 4.3	8.5 ± 12.5	.4
Height (cm)	115.4 ± 45.9	136.5 ± 27.8	.6
Weight (Kg)	23.4 ± 26.8	37.9 ± 26.9	.45
BMI (kg/m^2)	16.8 ± 6.3	19.9 ± 4.9	.3
Gender (Male)	13/22	50/85	.9
Mean tacrolimus trough levels (ng/dL)	4.4 ± 2.4	4.1 ± 1.3	.7
Steroids	8/22 (36%)	35/85 (38%)	.7
Comorbidities	8/22 (36.3%)	29/85 (82.8%)	.8
Hypertension	3 (13.6%)	20 (23.5%)	
Diabetes	0	5 (5.9%)	
Obesity	4 (18%)	5 (5.9%)	
History of malignancy	0	3 (3.5%)	
Chronic lung disease	3 (9%)	1 (1.1%)	
Vitamin D levels (ng/mL)	22.7 ± 10.5	33.3 ± 10.8	.7

[a]Positive PCR or Ab testing.

sepsis. He did not require supplemental oxygen and was discharged 48 h post improvement in his clinical profile and negative blood cultures. No patients in our cohort developed MIS-C. In addition, no one required escalation of care (oxygen support, intubation, or [ECMO] utilization) and there were no deaths. None of our patients received COVID-19 specific therapy (remdesivir or convalescent plasma). All patients who were positive for COVID-19 via PCR followed quarantine recommendations and were closely monitored via telemedicine visits until complete recovery.

All heart transplant patients were on aspirin for coronary artery vasculopathy prevention. In addition, 2 kidney transplant patients and 1 liver transplant patient were on aspirin. One kidney transplant patient had underlying coagulopathy, and another had a history of a cerebrovascular event. The liver transplant patient had portal vein stenosis treated with a stent. None of the pediatric SOT recipients who tested positive for COVID-19 were on anticoagulants at the time of diagnosis, and no anticoagulants were initiated after diagnosis. All transplant recipients received routine immunosuppressive medications, and no changes were made to their regimen after the diagnosis of COVID-19. All but one patient was on a tacrolimus-based regimen with levels in the expected range. The majority of kidney transplant patients (75%) were also on steroids. The heart transplant recipients were on a steroid avoidance regimen with 7.1% on steroids. The majority (59%) of the liver transplant patients and 14.2% of heart transplant recipients were on monotherapy with tacrolimus. There was no change in allograft function. The vitamin D levels were within the normal range for most of the patient.

The cohort was stratified into two groups, those who tested positive for COVID-19 via either PCR or Ab and those who tested negative (Table 2). COVID-19 positive patients were an average age of 7.2 years at the time of COVID-19 diagnosis and were an average 5.1 years post-transplant. The median time from transplant in COVID-19 positive patients was 3.2 (2.1, 10.2) years. None of the variables analyzed were statistically significant. In our cohort, 8/22 (36%) patients who tested positive had comorbidities including hypertension, obesity, and chronic lung disease compared to 29/85 (34%) patients with similar comorbidities who tested negative for COVID-19 ($p = .8$).

4 | DISCUSSION

In agreement with other published studies in the pediatric transplant population, our cohort of pediatric heart, kidney, and liver transplant recipients had COVID-19 outcomes similar to those published in literature for immunocompetent children.[2,3] Although pediatric SOT recipients were initially considered at higher risk for COVID-19 due to their life-long immunosuppression, their outcomes, as demonstrated by this study, are in contrast with published data from adult SOT recipients who had worse disease progression and high mortality rates.[8,12,13]

In a large registry study from the UK, 597 (1.3%) of the 46 789 SOT recipients developed COVID-19 with a mortality of 25.8%.[14]

In addition, a study of 47 heart transplant recipients showed that compared to the general population, the prevalence (18 vs. 7 cases per 1000) and mortality rate (29.7% vs. 15.4%) in heart transplant recipients were doubled.[12] This study was limited by the small sample size. Kidney transplant recipients have been shown to have more rapid clinical progression than the general population.[7] The adult kidney transplant cohort at our center had an overall mortality of 20.5%, but it was significantly increased (37.8%) in the patients who required hospitalization.[15]

The findings of our study support other, small pediatric studies and case reports of COVID-19 in pediatric SOT recipients suggesting that this population may have risks and complications of infection similar to immunocompetent children.[16,17] A multi-center study of pediatric SOT recipients (heart, liver, kidney, lung) had 26 PCR positive patients (median time post-transplant was 3.4 years) among 5 centers who were tested for symptoms.[18] Of these, 8/26 patients required hospitalization (no patients required supplemental oxygen or intubation). Similar to our study, there were no deaths and all patients recovered completely. They concluded that COVID-19 in pediatric SOT patients mimicked pediatric immunocompetent children. However, in contrast to our study, they did not perform COVID-19 Ab testing on asymptomatic children. Given that 50% of our patients were asymptomatic, we would not have known of their COVID-19 infection had the antibodies not been tested. Using the IROC database (2732 patients, 281 were tested), Varnell et al. found that 24 (8.5%) patients who tested positive, of which 15 (63%) were symptomatic.[9] In the cohort, the median time after transplant was 2.9 years.[9] Similar to their study, this study also showed that 50% of the patients were asymptomatic and tested positive on Ab testing during a routine clinic visit.

Due to the higher mortality rates in adult transplant recipients when compared to the general population, providers may adapt aggressive approaches in SOT recipients with COVID-19, including discontinuation of immunosuppressive agents. This may result in the formation of donor specific antibodies and rejection, ultimately decreasing graft survival. Unlike adult recipients, we did not modify or discontinue immunosuppression in COVID-19 patients[19] and none of our patients had rejection or graft dysfunction. While most of our heart transplant patients were on aspirin as part of the protection against coronary artery vasculopathy, unlike adult studies and in keeping with other pediatric studies, we did not start anticoagulation medications on our patients.[19]

Independent risk factors for COVID-19 infection included hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular disease, and cerebrovascular disease were.[20] In adult transplant recipients, comorbidities like hypertension, obesity, and diabetes are associated with a severe COVID-19 clinical phenotype.[21] These comorbidities are less prevalent in the pediatric population. In addition, given that the greatest odds of acquiring COVID-19 are seen with older age, more favorable outcomes in our population may be due to their young age, which may mitigate other risk factors.[22] In our cohort, 37 patients (34%) had comorbidities including hypertension, diabetes, and obesity. However, these patients did not have a significant disadvantage in developing symptomatic disease due to their comorbidities, possibly due to their younger age.

There are design limitations to our study. It is a retrospective, single-center study of pediatric SOT recipients with a small sample size. In addition, it is not powered to show a difference between patients who tested positive for COVID-19 and those who tested negative. Therefore, clinically significant differences may not be detected. The median time from transplant was 4 years with only 9% <1 year from transplant. However, this is similar to other pediatric studies where median time from transplant was >2 years. Transplant recipients are generally at greatest risk of infection in the first-year post-transplant.[23] During COVID-19, the rates of transplantation decreased significantly nationwide, including at our center.[24] This may explain why only 9% of patients were ≤1 year from transplantation. Our data may, therefore, not fully capture the risk of COVID-19 infection that recently transplanted pediatric recipients may face. It is important to note that New York State implemented more rigorous masking, social distancing, school closures, and other public health measures were mandated when compared to other states. This may have impacted the findings in our cohort. Although our goal was to test all patients who were followed at our institution, some were not included in the study, primarily due to having routine laboratory testing done at a location not affiliated with our hospital. Finally, given the recent results of immunogenicity of the COVID-19 vaccine in adult SOT, we recognize that Ab testing may not be reliable in pediatric SOT recipients and may not be sufficient surrogate for a prior infection, especially when performed at only one point in time.[25] It is important to note that while no cross-reactivity with IgM antibodies to Influenza A, Influenza B, and Respiratory Syncytial Virus was observed, false positive results due to cross-reactivity with antibodies to other coronaviruses can occur.[11] This may limit the interpretation of the Ab test result.

5 | CONCLUSION

Despite the uncertainty and lack of evidence regarding the optimal management of COVID-19 in transplant recipients, especially in the pediatric age group, these data add to the literature showing that pediatric SOT recipients with COVID-19 are mostly asymptomatic and the few recipients who develop symptoms recover well with no significant complications. Thus, the majority of pediatric SOT recipients can be adequately monitored in the home environment. Immunosuppression alteration may not be always necessary for a complete and rapid recovery. The results of this study may help the provider to triage these patients while reassuring the patient and family about the risks with COVID-19 in these patients.

CONFLICT OF INTEREST
None.

AUTHOR CONTRIBUTION
Neha Bansal[1], MD, involved in conceptualization, data collection, data analysis, and writing—original draft. Nadia Ovchinsky[2], MD, Marc Foca[3], MD, Jacqueline M. Lamour, MD[1], Debora Kogan-Liberman[2], MD, and Daphne T. Hsu[1], MD, involved in conceptualization, writing—critical review of manuscript. Kimberly Beddows[1], CPNP, Lincy Abraham[1], CPNP, Maura Coburn[4], CPNP, Ryan Cunningham[2], CPNP, and Trang Nguyen[2], CPNP, involved in data collection and writing—critical review of manuscript. Nicole Hayde[4], MD, involved in conceptualization, writing—critical review of manuscript, and supervision.

ORCID
Neha Bansal https://orcid.org/0000-0001-7026-3058
Kimberly Beddows https://orcid.org/0000-0002-2563-0477

REFERENCES
1. New York City, Department of Health. 2020. Last accessed June 6, 2021.
2. Lu X, Zhang L, Du H, et al. SARS-CoV-2 infection in children. *N Engl J Med*. 2020;382:1663-1665.
3. Zachariah P, Johnson CL, Halabi KC, et al. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a children's hospital in New York City, New York. *JAMA Pediatr*. 2020;174:e202430.
4. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr*. 2020;109:1088-1095.
5. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. *JAMA*. 2020;323(13):1239-1242.
6. Green M, Michaels MG. Infections in pediatric solid organ transplant recipients. *J Peds Infect Dis Soc*. 2012;1(2):144-151.
7. Akalin E, Azzi Y, Bartash R, et al. Covid-19 and kidney transplantation. *N Engl J Med*. 2020;382:2475-2477.
8. Yi SG, Rogers AW, Saharia A, et al. Early experience with COVID-19 and solid organ transplantation at a US high-volume transplant center. *Transplantation*. 2020;104(11):2208-2214.
9. Varnell C Jr, Harshman LA, Smith L, et al. COVID-19 in pediatric kidney transplantation: the improving renal outcomes collaborative. *Am J Transplant*. 2021;21(8):2740-2748.
10. Prevention CDC. Symptoms of COVID-19. Last Accessed June 1, 2021.
11. Viracor- Eurofins Clinical Diagnostics. https://www.viracor-eurofins.com/test-menu/403607p-antibody-testing-for-coronavirus-covid-19-sars-cov-2-igg-and-igm/. Accessed March 6, 2021.
12. Bottio T, Bagozzi L, Fiocco A, et al. COVID-19 in heart transplant recipients: a multicenter analysis of the Northern Italian outbreak. *JACC Heart Fail*. 2021;9(1):52-61.
13. Columbia University Kidney Transplant Program. Early description of coronavirus 2019 disease in kidney transplant recipients in New York. *J Am Soc Nephrol*. 2020;31(6):1150-1156.
14. Ravanan R, Callaghan CJ, Mumford L, et al. SARS-CoV-2 infection and early mortality of waitlisted and solid organ transplant recipients in England: a national cohort study. *Am J Transplant*. 2020;20(11):3008-3018.
15. Azzi Y, Parides M, Alani O, et al. COVID-19 infection in kidney transplant recipients at the epicenter of pandemics. *Kidney Int*. 2020;98(6):1559-1567.
16. Bush R, Johns F, Acharya R, Upadhyay K. Mild COVID-19 in a pediatric renal transplant recipient. *Am J Transplant*. 2020;20(10):2942-2945.
17. Heinz N, Griesemer A, Kinney J, et al. A case of an infant with SARS-CoV-2 hepatitis early after liver transplantation. *Pediatr Transplant*. 2020;24(8):e13778.

18. Goss MB, Galvan NTN, Ruan W, et al. The pediatric solid organ transplant experience with COVID-19: an initial multi-center, multi-organ case series. *Pediatr Transplant*. 2021;25(3):e13868.

19. Akdur A, Karakaya E, Ayvazoglu Soy EH, et al. Coronavirus disease (COVID-19) in kidney and liver transplant patients: a single-center experience. *Exp Clin Transplant*. 2020;18(3):270-274.

20. Wang B, Li R, Lu Z, et al. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging (Albany NY)*. 2020;12(7):6049-6057.

21. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. *JAMA*. 2020;323(20):2052-2059.

22. Rosenthal N, Cao Z, Gundrum J, et al. Risk factors associated with in-hospital mortality in a US national sample of patients with COVID-19. *JAMA Netw Open*. 2020;3(12):e2029058.

23. Singh N, Limaye AP. Infections in solid-organ transplant recipients. *Mandell, Douglas, and Bennett's Princ Pract Infect Dis*. 2015:3440-3452.

24. Charnaya O, Chiang TP, Wang R, et al. Effects of COVID-19 pandemic on pediatric kidney transplant in the United States. *Pediatr Nephrol*. 2021;36(1):143-151.

25. Boyarsky BJ, Werbel WA, Avery RK, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. *JAMA*. 2021;325(17):1784-1786.