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From its emergence in December 2019, coronavirus disease 2019 (COVID-19) has had a profound impact on transplant centers worldwide.¹ Although children and adolescents with solid organ transplant (SOT) are considered to be at increased risk for infections, data are scarce regarding the impact of COVID-19 in this population.² We describe the clinical and laboratory features of severe acute respiratory coronavirus-2 (SARS-CoV-2) disease in pediatric kidney and liver transplant recipients, including their postacute symptoms and serologic response.

METHODS

This retrospective study was conducted at the Schneider Children's Medical Center of Israel—a tertiary pediatric referral transplant center. The cohort included all kidney and liver transplant recipients, <20 years of age, with confirmed SARS-CoV-2 infection between June 2020 and February 2021, according to a nasopharyngeal swab–based real-time quantitative reverse transcription polymerase chain reaction (PCR) test. The study period preceded the availability of active immunization against the virus.

Follow-up of SOT recipients diagnosed with COVID-19 entailed telemedicine visits, every 3–5 days, a structured questionnaire for symptom severity and evaluation of oxygen saturation. Disease severity was defined by the National Institutes of Health criteria.³ Following resolution of the disease, an outpatient visit was conducted, which included a questionnaire on residual symptoms and a serology test for qualitative IgG antibodies against the SARS-CoV-2 “S-protein” using an indirect in-house enzyme-linked immunosorbent assay.⁴ Disease resolution was defined according to the Israeli Ministry of Health guidelines for patients with immunosuppression.⁵ Demographic, clinical and laboratory data were extracted from patients' electronic medical records between September 2020 and April 2021. The study was approved by the institutional review board.

RESULTS

Characteristics of the Study Population

During the study period, 25 (9.5%) of the 262 pediatric SOT recipients followed at our center were diagnosed with COVID-19. Fourteen (56%) were kidney transplant recipients, 10 (40%) liver recipients and 1 (4%) was a recipient of a combined liver and pancreas transplant. The mean age was 15.2 ± 4 years; 56% were males. The median time from the transplantation to a positive SARS-CoV-2 PCR was 6.9 years [interquartile range (IQR), 3.1–11.2]. The most common underlying diseases were congenital anomalies of kidneys and urinary tract and focal segmental glomerulosclerosis for the kidney transplanted patients and biliary atresia and Alagille syndrome for liver transplanted patients. Five patients had other comorbidities, 3 obesity, 3 asthma and 1 diabetes. One patient had congenital immune deficiency and hypertension. The immunosuppression regimen for the kidney and pancreas transplant recipients consisted of a triple-drug regimen: calcineurin inhibitor, prednisone and mycophenolate mofetil. Liver transplant recipients received a monotherapy regimen of calcineurin inhibitor.

COVID-19 Disease Course

Twenty-three (92%) of the patients were tested for COVID-19 due to close contact with an individual who tested positive; 18

CLINICAL OUTCOMES AND ANTIBODY RESPONSE IN COVID-19-POSITIVE PEDIATRIC SOLID ORGAN TRANSPLANT RECIPIENTS

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Abstract: We describe the clinical and laboratory manifestations and outcomes of 25 pediatric solid organ transplant recipients who tested positive for severe acute respiratory coronavirus-2. Twenty-one (84%) developed a mild disease; 22 of 23 (96%) had a positive serologic response. Two patients (8%), both kidney transplant recipients with additional comorbidities, developed a severe disease. The findings emphasize the need for close monitoring of this population.

Key Words: COVID-19, solid organ transplant recipient, immunosuppression

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TABLE 1. Clinical Characteristics of 25 Pediatric Solid Organ Transplant Recipients Infected With COVID-19

Symptom/Sign	Acute COVID-19, n (%)	Postacute COVID-19, n (%)
Symptomatic	23 (92)	3 (12)
Fever	11 (44)	-
Headache	11 (44)	0
Cough	10 (40)	0
Fatigue	9 (36)	3 (12)
Anosmia	7 (28)	0
Myalgia	7 (28)	0
Appetite or weight loss	6 (24)	0
Diarrhea	5 (20)	-
Chest pain	3 (12)	-
Acute kidney injury	2 (8)	0
Respiratory distress	2 (8)	0
Lower respiratory tract infection: pneumonia/ARDS	2 (8)	-

ARDS indicates acute respiratory distress syndrome; COVID-19, coronavirus disease 2019.

During acute COVID-19, 2 patients (8%) reported rash, 2 sore throat (8%) and 1 (4%) rhinorrhea. During the postacute COVID-19 period, 1 patient (4%) had hair loss, nightmares and mood disorder.

(78%) of them were family members. Only 2 patients (8%) were tested due to indicative symptoms. During the COVID-19 disease period, 23 (92%) patients were symptomatic, 21 (84%) had a mild disease and 2 (8%) had a severe disease. The most common symptoms were fever (44%) and headache (44%). The symptoms are summarized in Table 1. Five patients (20%) were hospitalized in a general pediatric ward, 2 of them for observation. One liver transplanted patient had concomitant recurrent pancreatitis and 2 needed inpatient medical care due to a severe COVID-19 disease.

The first patient requiring inpatient medical care was a 16-year-old kidney transplant female, 2 years after transplantation, who had Schimke immune-osseous dysplasia. She was admitted due to dehydration and prerenal acute kidney injury that resolved with intravenous fluids. While hospitalized, 12 days after her first positive test, she developed an acute respiratory distress syndrome and was treated with high-flow nasal cannula support, dexamethasone and convalescent plasma therapy. Her antimetabolite drug treatment was discontinued and cyclosporine dose was reduced. After 14 days of hospitalization, she showed significant improvement and was discharged.

The second patient requiring inpatient medical care was a 19-year-old male with intellectual disability, obesity and diabetes, who tested positive to SARS-CoV-2 9 years after a kidney transplant. He was admitted due to diarrhea and acute kidney injury. Twenty days after his diagnosis of COVID-19, he developed pleuropneumonia and was treated with fluids and dexamethasone. His antimetabolite drug treatment was discontinued without a reduction in the calcineurin inhibitor dose or level. He did not need oxygen and, therefore, opted for home treatment.

During their COVID-19 illness, none of the patients experienced an allograft rejection, needed dialysis or invasive respiratory support or died.

Postacute COVID-19 Symptoms and Serologic Response

All the patients fully recovered clinically from the COVID-19 disease; the median time for disease resolution was 27 days (IQR 21–41). Following the first positive SARS-CoV-2 PCR test, the majority (88%) had 2 documented negative tests. The mean time from the first positive to the first negative PCR test (shedding time) was 28.7 ± 11.2 days. A significantly longer shedding time

was found among kidney and pancreas transplant recipients than among liver transplant recipients (35.1 ± 9.8 versus 19.55 ± 4.74 days, $P < 0.001$).

Following resolution of the disease, at a median of 7 weeks (IQR 5–10.5) from the first positive PCR test, 22 patients (88%) were asymptomatic and 3 reported residual symptoms, mainly fatigue. The postacute symptoms are summarized in Table 1. A serologic test was taken for 23 patients (92%); 96% of those tested had a positive IgG antibody response against the SARS-CoV-2 S protein. None of the patients had multisystem inflammatory syndrome in children or recurrent COVID-19 infection during a median follow-up time of 22 weeks (IQR 12–29) from the COVID-19 diagnosis.

DISCUSSION

COVID-19 has had a profound impact on transplantation and caused reduced activity of transplant centers worldwide.¹ Pediatric SOT recipients are at increased risk for infections and severe clinical course of disease due to their immunosuppressive treatment and comorbidities.² However, a few studies described a non-severe clinical course of the SARS-CoV-2 disease among pediatric patients who were immunocompromised or recipients of SOT.^{6–8} To our knowledge, this is the first pediatric study to describe early post-COVID-19 outcomes and the serologic response of SOT recipients.

The disease incidence among our pediatric SOT patients was considerably higher than the incidence previously reported among pediatric kidney recipients.⁶ This difference may be due to the high population density and family crowding in certain Israeli cities and communities. During the acute phase of COVID-19 infection, 23 (92%) of our patients were symptomatic. This is a high percentage compared with recent data, particularly in the pediatric population.⁶ Possible explanations are that none of our patients were tested for COVID-19 as part of a screening survey, and the proportion of exposure to close family members was high. Consistent with previous studies, the majority of our patients were adolescents and had a mild disease; their symptoms were generally similar to those published for healthy children and for pediatric SOT recipients.^{6–9}

In contrast to previous studies, two patients (8%) had a severe disease that required hospital admission. Both patients were kidney transplant recipients with significant comorbidities and presented with acute kidney injury and severe lower respiratory tract infection. This suggests that pediatric kidney transplant recipients with comorbidities might have greater risk for severe COVID-19 disease and may need monitoring for kidney and respiratory function and immunosuppressive therapy reduction during the disease.

The immune system response to SARS-CoV-2 virus, in both healthy and immunosuppressed populations, is still under investigation. A mean shedding time of 14–17 days has been reported for healthy children tested by nasopharyngeal swabs.⁹ The mean shedding time of 28 ± 10.5 days in our pediatric SOT population is consistent with the strong association that was reported of persistent viral shedding (>21 days) with the immunosuppression state among hospitalized adults.¹⁰ Notably, the mean shedding time was longer among kidney and pancreas recipients than among liver-only recipients. This, as well as the presentation of severe disease in 2 kidney transplant recipients compared with none of the liver transplant recipients, may be explained by the different immunosuppressive regimens: none of the solitary liver recipients was treated with antimetabolites. Larger studies are needed to confirm this observation.

Examining the serologic response to COVID-19, we found that 96% of SOT recipients developed IgG antibodies against the S protein. This suggests a good humoral immune response

to SARS-CoV-2 virus among young SOT recipients. It is still unknown if the demonstration of serologic response against the virus correlates with protection from disease in the event of future exposure to the virus. Further research is needed to examine the effectiveness of these antibodies in neutralization-based assays, as well as their clinical protection, magnitude and durability over the course of time.

This study has several limitations. Due to its retrospective nature, PCR testing was not done at uniform time points, thus potentially influencing the shedding time. However, patients were tested frequently due to our follow-up protocol for transplant recipients. Another limitation is the relatively small sample size, which is a result of the small population of pediatric SOT recipients.

In conclusion, the majority of pediatric SOT recipients who had COVID-19 in our study developed a mild disease but mounted a positive IgG response. Nevertheless, kidney transplant recipients with additional comorbidities developed a severe disease, emphasizing the need for close monitoring in this particular population.

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ANTIBODIES TO SEASONAL CORONAVIRUSES RARELY CROSS-REACT WITH SARS-COV-2

FINDINGS FROM AN AFRICAN BIRTH COHORT

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Abstract: Antibodies to seasonal human-coronaviruses (sHCoV) may cross-protect against SARS-CoV-2. We investigated antibody responses in biobanked serum obtained before the pandemic from infants with polymerase chain reaction-confirmed sHCoV. Among 141 samples with antibodies to sHCoV, 4 (2.8%) were positive for SARS-CoV-2-S1 and 8 (5.7%) for SARS-CoV-2-S2. Antibodies to sHCoV rarely cross-react with SARS-CoV-2 antigens and are unlikely to account for mild pediatric illness.

Key Words: seasonal coronavirus, cross-protection, antibodies, child, COVID-19

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Children have been largely spared in the COVID-19 pandemic, developing predominantly asymptomatic or mild disease.¹ Globally, children constitute around 8% of infections, <2% of hospitalizations and <1% of all COVID-19 associated mortality in high and low-middle income countries (LMICs).² In South Africa, 9% of infections and <0.1% of COVID deaths occur in children or adolescents, who comprise >30% of the population.³ Although pneumonia remains a major cause of mortality and morbidity in children in LMICs, risk factors for severe pneumonia such as malnutrition, HIV or prematurity have also not emerged as risk factors for COVID-19.⁴

A key knowledge gap is why pediatric disease is relatively mild. One hypothesis is that cross-protection to SARS-CoV-2 may occur from immunity to one of the 4 seasonal coronaviruses [seasonal human-coronaviruses (sHCoVs); 229E, NL63, OC43 and HKU1], which are common and circulate seasonally worldwide.^{5–9} Recently, individuals, including children, unexposed to SARS-CoV-2, were reported to have antibodies to the S2 subunit of SARS-CoV-2 spike (S) protein from presumed prior sHCoV infection.⁷ Shared sequence conservation between sHCoVs and SARS-CoV-2 raises the possibility that immunity against sHCoV may cross-protect against SARS-CoV-2.

We recently reported the epidemiology of sHCoV infection in infants preceding the COVID-19 pandemic in an African birth cohort, the Drakenstein Child Health study (DCHS).¹⁰ By leveraging this unique dataset and matching biobank of samples, we investigated cross-reactivity of antibodies induced by PCR-confirmed sHCoV infection prior to the COVID pandemic against SARS-CoV-2.