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ORIGINAL ARTICLE

Immunocompromised Seroprevalence and Course of Illness of SARS-CoV-2 in One Pediatric Quaternary Care Center

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Background. The burden of coronavirus disease 2019 (COVID-19) is poorly understood in pediatric patients due to frequent asymptomatic and mild presentations. Additionally, the disease prevalence in pediatric immunocompromised patients remains unknown.

Methods. This cross-sectional study tested convenience samples from pediatric patients who had clinically indicated lab work collected and an immunocompromising condition, including oncologic diagnoses, solid organ transplant (SOT), bone marrow transplant, primary immunodeficiency, and rheumatologic conditions or inflammatory bowel disease on systemic immunosuppression, for the presence of antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Results. We tested sera from 485 children and observed SARS-CoV-2 seroprevalence of 1.0% (Confidence Interval [CI] 95%: 0.3%–2.4%). Two patients were positive by nasopharyngeal (NP) swab Reverse transcriptase polymerase chain reaction (RT-PCR), but only 1 seroconverted. Patients with oncologic diagnoses or SOT were most likely to be tested for COVID-19 when presenting with respiratory illness as compared with other groups.

Conclusions. Seroprevalence of antibodies to SARS-CoV-2 in immunocompromised children was similar to that of an immunocompetent pediatric population (0.6%, CI 95%: 0.3%–1.1%), suggesting an adequate antibody response. However, none of the patients who tested positive for antibodies or via NP RT-PCR had more than a mild illness course and 2 patients did not have any reported illness, suggesting that SARS-CoV-2 may not cause a worse clinical outcome in immunosuppressed children, in contrast to immunocompromised adults.

Key words. COVID-19; immunocompromised; pediatric; SARS-CoV-2; serology.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged in the winter of 2019 in Wuhan, China, and rapidly made its way around the globe causing a pandemic of coronavirus disease 2019 (COVID-19) [1]. Presentation of infection is highly variable, ranging from asymptomatic persons to respiratory and multiorgan failure, requiring mechanical ventilation, to death [2]. One population of particular concern is those who are immunosuppressed, including those who have received solid organ transplants (SOTs), bone marrow transplants (BMTs), chemotherapy, or other immunomodulators. Immunosuppression makes recipients more susceptible to infections, either through broad immunosuppression of chemotherapy [3], the suppression of T-cells [4], or tumor necrosis factor [5].

Reports on immunocompromised adults with SARS-CoV-2 infection, including SOT recipients [6], including lung [7] and kidney [8–12], and patients receiving chemotherapy [13–16] indicate an increased rate of hospitalization and mortality. Adults taking biologics for immune-mediated inflammatory diseases, however, have not had worse COVID-19 outcomes [17]. Immunosuppressed adults have been demonstrated to effectively produce antibodies to SARS-CoV-2 infection, albeit a bit delayed as compared with immunocompetent controls, allowing serological studies to be utilized to determine the incidence of infection in this population [18].

There have been limited reports of COVID-19 and pediatric immunosuppressed patients. A case report [19] and small case series [20] of pediatric heart transplant recipients and of a renal [21] and liver [22] transplant recipient demonstrated minor illness course, as did reports of children with cancer [23–25]. Additionally, the capacity for pediatric immunosuppressed persons to effectively make antibodies to this infection is not understood. To the best of our knowledge, the burden of SARS-CoV-2

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disease and outcomes in the immunosuppressed pediatric population through a serologic survey has not been evaluated.

Diagnosis of SARS-CoV-2 acute infection is best facilitated by Reverse transcriptase polymerase chain reaction (RT-PCR)-based testing of nasopharyngeal (NP) swabs. When SARS-CoV-2 began circulating in the United States in January 2020, this testing was not widely available, and while the virus easily spread across the country, the mobilization and availability of testing were limited. This led many centers to adopt an exposure and symptom-based testing approach. Because children with SARS-CoV-2 infection are often asymptomatic or only display mild symptoms, they were underrepresented in this strategy [26, 27]. Antibodies, in particular Immunoglobulin G (IgG), persist after an infection for months to years, thus serologic testing can be utilized to characterize retrospectively the burden of a disease in a population. However, there are emerging data that antibody responses to SARS-CoV-2 infection may be short-lived, with waning by 3 months, such that assessing serology in these patients may also underdetect previous infection [28].

We sought to understand the burden of SARS-CoV-2 infection in the pediatric immunocompromised population receiving care at our hospital, including recipients of SOTs and BMTs, oncology patients on active chemotherapy, patients with primary immunodeficiency, or patients taking immunomodulators for rheumatologic or inflammatory bowel disease. We also wanted to determine how the seroprevalence in the pediatric immunocompromised population differs from the total pediatric population. We utilized remnant sera from patients receiving care at the University of Pittsburgh Medical Center Children's Hospital of Pittsburgh (UPMC CHP), to surveil patients receiving care at our institution for past infection with SARS-CoV-2. We collected sera from convenience blood specimens drawn from March to July 2020. Demographic information for each patient was extracted from the electronic medical record (EMR) to determine the factors associated with SARS-CoV-2 seropositivity and to assess for reported clinical disease.

METHODS

Sampling Site

UPMC CHP is a quaternary pediatric hospital in Pittsburgh, Pennsylvania, with a large catchment area, spanning the entirety of western Pennsylvania and extending into eastern Ohio, West Virginia, western Maryland, and western New York. Additionally, our strong transplant program attracts pediatric patients from all over the world. All laboratory testing drawn at the clinical campus is processed through the UPMC clinical labs with the majority of testing done on-site.

Sample Collection

This study was approved by the Institutional Review Board at the University of Pittsburgh (IRB 20040027) for the collection of convenience samples and EMR data. Data were stored in a secure RedCap database [29].

Available data in adult patients suggested that IgG antibodies are detectable 7 to 14 days from positive NP PCR [30, 31]. Therefore, sample collection began approximately 2 weeks following the March 2020 peak of cases of COVID-19 in Allegheny county, where Pittsburgh is located. This initial peak occurred between March 25 and April 15 based on the data from the Allegheny County Department of Health (ACDH) [32]. This study is a part of a larger pediatric seroprevalence study that serially collected all pediatric remnant blood samples from UPMC Children's Hospital of Pittsburgh during 2 phases: from April 27, 2020 to May 19, 2020 and June 22, 2020 to July 4, 2020. This larger pediatric seroprevalence study was used as the non-immunocompromised patient comparison cohort, and both phases were assessed as a single group. Patients from both phases were included in this study. Only the first blood sample from each individual patient was included. Samples included were from patients aged less than 19 years old who had an underlying condition for which they were immunocompromised, including SOT, BMT, oncologic diagnosis on active chemotherapy, primary immunodeficiency, and rheumatologic condition or inflammatory bowel disease on systemic immunosuppression. Patients were excluded if they were below the age of 6 months (due to maternal antibody confounding), had a prolonged hospitalization of greater than 30 days at the time of blood collection (due to lack of community exposure), and if they were receiving treatments that would specifically interfere with antibody production or profile (i.e., intravenous or subcutaneous immunoglobulin, rituximab, or bortezomib) in the 6 months prior to sample collection. The larger pediatric seroprevalence study and this immunocompromised subpopulation shared the same collection methodology with the exception of zip code. The pediatric seroprevalence study included only zip codes in southwestern PA, while the immunocompromised seroprevalence study included all-comers.

SARS-CoV-2 Antibody Testing

Laboratory-derived SARS-CoV-2 IgG testing was manually performed via enzyme-linked immunosorbent assay utilizing the Euroimmun platform (PerkinElmer, Lübeck, Germany) by certified medical technologists. This assay was validated for use in the Clinical Laboratory Improvement Amendments-certified high complexity clinical laboratories at UPMC. The sensitivity of the assay is 98.7% and specificity 98.9% (at 14 days). Index values (IDV) are calculated by taking the ratio of the sample to calibrator per manufacturer's instructions. Each positive specimen was confirmed by additional testing on the Beckman Coulter SARS-CoV-2 IgG automated Emergency Use Authorization (EUA) assay (Brea, CA, USA). Specimens with discrepancies between the 2 tests were further assessed on the Siemens Centaur SARS-CoV-2 Total automated EUA assay (Munich, Germany).

Test-to-Illness Ratio

As part of the EMR review for each patient, if a patient had documentation of a febrile (temperature >38.0°C) or respiratory illness (cough, congestion, or shortness of breath) either through phone message or clinical encounter between January 1, 2020 and the blood sample date, they were considered to have had a prior illness that *may* have been consistent with SARS-CoV-2. We then assessed how many of these patients were tested for SARS-CoV-2 via NP RT-PCR in the context of this presentation. The *test:illness ratio* is the number of patients tested out of the number of patients with recorded illness.

Statistics

We calculated apparent seroprevalence as the proportion of confirmed reactive to total specimens. Apparent seroprevalence within selected subgroups (type of immunocompromise) was calculated as the proportion of confirmed reactive to total specimens in that subgroup. Confidence intervals were calculated with the Clopper–Pearson Exact method. Chi-square analysis was performed to compare the contingency analysis of test-to-illness ratio. All statistical tests were evaluated using a significance value of .05 and performed using GraphPad Prism (version 7.0; GraphPad) software.

RESULTS

Patient Characteristics

In total, 485 patients were included in this study. Most of the patients were oncology patients (42.7%), with a predominance of hematologic malignancy (58.0%) over solid tumor malignancy. Patients with SOTs made up 22.3% of the population and not only were predominately liver (38.9%) and kidney (31.5%) recipients, but also included recipients of heart, bowel, multivisceral, and lung transplants. Six transplant patients received multiple organs, including 1 heart/lung recipient, 1 liver/lung, 3 liver/kidney recipients, and 1 combined liver and small intestine (Table 1). Patients with inflammatory bowel disease made up 21.4% of the population, followed by patients with rheumatologic disease, BMT, and primary immunodeficiency.

The age of the patients ranged from 0.8 years to 18.9 years, with a mean of 11.0 years and a median of 11.9 years. About half of the patients were above the age of 12 (49.7%), and nearly a quarter was from the 0- to 6-year (27.8%) and 6- to 12-year (22.5%) categories. There was a slight male predominance (53.4%) and most of the patients identified as Caucasian (85.6%) (Table 1).

During the study period, 27.2% of the patients reported a febrile or respiratory illness, most of which was greater than 2 weeks prior to the blood collection utilized for the study (71.2%). In total, 15.7% of this population was tested for SARS-CoV-2 acute disease with NP RT-PCR-based testing due to presenting symptoms or in anticipation of a procedure. Only 2 patients tested positive for SARS-CoV-2 via this method (0.4% of the population and 2.6% of those tested). One of those patients was admitted for observation for a period of 6 hours, while the other patient recovered as an outpatient. Both patients who tested positive for SARS-CoV-2 had ill family members, one family tested positive for SARS-CoV-2, while the other family had a member who worked in a skilled nursing facility who was ill but was not tested. No other exposures were documented in the study cohort.

In order to understand which population was most likely to be tested for SARS-CoV-2 during acute illness, we devised the "testing-to-illness ratio" for each population, or a metric of how many patients were tested out of the total number of patients who had a presentation of respiratory or febrile illness beginning January 1, 2020 until sample date based on EMR review. Analysis of the immunocompetent patients in our companion study demonstrated that immunocompromised patients were more than 3 times as likely to be tested for SARS-CoV-2 when presenting for a respiratory or febrile illness during this time ($P < .0001$) (Table 2). This testing index was highest for the oncology population ($P < .0001$), followed by SOT ($P < .0001$). Rheumatologic patient and Inflammatory Bowel Disease (IBD) patients were not tested at a rate significantly higher than their immunocompetent counterparts. Neither BMT nor primary immunodeficiency had any patients tested (Table 1).

Of the entire cohort, 5 patients (1.0%) were found to have IgG antibodies to SARS-CoV-2 Spike protein. Two patients with positive antibodies were from the rheumatology category (systemic juvenile idiopathic arthritis and idiopathic bilateral uveitis), 2 patients with SOT (heart), and 1 patient with solid tumor malignancy (neuroblastoma). Only 1 of the patients who tested positive for SARS-CoV-2 via NP swab had detectable antibodies.

For the 5 seropositive patients, 3 were below age 5, 1 between 6 and 11 years old, and 1 above 12 years of age. All identified as Caucasian. Three patients were female and 2 male. Three patients had documented illnesses inclusive of febrile or respiratory symptoms at least 2 weeks prior to blood sample collection. As for exposures, the PCR-positive patient was exposed to an infected family member. One of the seropositive patients works at a grocery store but did not have any known exposures. Seroprevalence by category was 4.3% (Confidence Interval [CI] 95%: 0.5%–14.5%) for rheumatologic conditions, 1.9% (CI 95%: 0.2%–6.5%) for SOT, 0.5% (CI 95%: 0%–2.7%) for oncology, and 0% for BMT, primary immunodeficiency, and inflammatory bowel disease (Table 1). Seroprevalence for the total immunocompromised population was 1.0% (CI 95%: 0.3%–2.4%). Only 1 of the 5 seropositive patients was admitted to the hospital, the aforementioned SARS-CoV-2-positive patient via NP RT-PCR. None of the patients required respiratory support, intensive care support, or died.

Each of the 5 seropositive patients had test values clearly above the positive threshold of 1.1 IDV, with an average of 5.067 IDV and a range of 2.777 to 9.247 IDV. This was comparable to

Table 1. Summary Table

Immunocompromised by Type	Total (%)	Oncology (%)	SOT (%)	BMT (%)	Primary ID (%)	Rheum (%)	IBD (%)
Total patients	485						
Total oncology patients		207 (42.7)					
Hematologic malignancy		120 (58.0)					
Solid tumor malignancy		87 (42.0)					
Total solid organ transplant			108[a] (22.3)				
Heart			17 (15.7)				
Lung			3 (2.8)				
Liver			42 (38.9)				
Kidney			34 (31.5)				
Bowel			10 (9.3)				
Multivisceral			8 (7.4)				
Bone marrow transplant				15 (3.1)			
Primary immunodeficiency					4 (0.8)		
Rheumatologic disease						47 (9.7)	
Inflammatory bowel disease							104 (21.4)
Age							
Mean	10.96	9.1	10.19	8.73	10.61	12.22	15.27
Median	11.88	7.82	10.26	8.1	10.81	12.59	16.50
Range	0.79–18.96	1.09–18.94	0.79–18.79	1.01–18.63	6.9–13.9	0.84–18.96	3.55–18.94
0 to 6	135 (27.8)	86 (41.6)	33 (30.6)	6 (40.0)	0 (0)	8 (17.0)	2 (1.9)
6 to 12	109 (22.5)	46 (22.2)	27 (25.0)	6 (40.0)	2 (50.0)	13 (27.7)	15 (14.4)
12 to 18	241 (49.7)	75 (36.2)	48 (44.4)	3 (20.0)	2 (50.0)	26 (55.3)	87 (83.7)
Sex							
Male	259 (53.4)	117 (56.5)	62 (57.4)	6 (40.0)	4 (100)	20 (42.6)	49 (47.1)
Female	226 (46.6)	89 (43.0)	46 (42.6)	9 (60.0)	0 (0)	27 (57.5)	55 (52.9)
Race							
Caucasian	415 (85.6)	181 (87.4)	86 (79.6)	9 (60.0)	4 (100)	39 (83.0)	96 (92.3)
African American	47 (9.7)	16 (7.7)	14 (13.0)	5 (33.3)	0 (0)	5 (10.6)	7 (6.7)
Latinx	3 (0.6)	1 (0.5)	2 (1.9)	0 (0)	0 (0)	0 (0)	0 (0)
Asian American	10 (2.1)	4 (1.9)	3 (2.8)	0 (0)	0 (0)	2 (4.3)	1 (1.0)
Not listed	10 (2.1)	5 (2.4)	3 (2.8)	1 (6.7)	0 (0)	1 (2.1)	0 (0)
BMI (patients > 2 yo, sufficient data)	461 (95.1)	197 (95.2)	100 (92.6)	14 (93.3)	4 (100)	43 (91.5)	103 (99.0)
<25	388 (84.2)	172 (87.3)	89 (89.0)	14 (100)	4 (100)	33 (76.7)	76 (73.8)
25 to <30	40 (8.7)	10 (5.1)	9 (9.0)	0 (0)	0 (0)	6 (14.0)	15 (14.6)
30 or greater	33 (7.2)	15 (7.6)	2 (2.0)	0 (0)	0 (0)	4 (9.3)	12 (11.7)
PCR tested for SARS-CoV-2	76 (15.7)	48 (23.2)	24 (22.2)	0 (0)	0 (0)	2 (4.3)	2 (1.9)
SARS-CoV-2 PCR Positive	2 (0.4)	1 (0.5)	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)
Documented SARS-CoV-2 Exposure	2 (0.4)	1 (0.5)	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)
Patients with respiratory illness (January 2020 to Sample)	132 (27.2)	66 (31.9)	35 (32.4)	6 (40.0)	1 (25.0)	9 (19.2)	15 (14.4)
Patients with positive SARS-CoV-2 antibodies [CI 95%]	5 (1.0) [0.3–2.4]	1 (0.5) [0.0–2.7]	2 (1.9) [0.2–6.5]	0 (0)	0 (0)	2 (4.3) [0.5–14.5]	0 (0)

Abbreviations: BMI, body mass index; BMT, bone marrow transplant; IBD, Inflammatory Bowel Disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOT, solid organ transplant.
[a]1 heart/lung, 1 lung/liver, 3 liver/kidney, and 1 liver/small bowel.

Table 2. Contingency Tables for Test:Illness Ratio χ^2 Analysis

	Immunocompetent	Immunocompromised		Total		
Tested (RT-PCR)	46	76		105		
Not tested	190	56		201		
Total	236	132		306		
Contingency table summary						
	Immunocompetent	All Immunocompromised	Oncology	SOT	Rheum	IBD
Test:illness ratio	0.19	0.58	0.73	0.69	0.22	0.13
P value (vs immunocompetent)		*P* = <.0001	*P* = <.0001	*P* = <.0001	n.s.	n.s.

Abbreviations: IBD, Inflammatory Bowel Disease; SOT, solid organ transplant.

values observed in pediatric immunocompetent patients (5.177, range 1.224–8.564), but lower than adult immunocompromised and immunocompetent patients who generated immune responses >10 IDV within 20 days of symptom onset [18]. While we did not specifically investigate the waning of antibodies in this immunocompromised pediatric population over time, 1 patient was inadvertently double sampled, with a first IgG measurement of 3.06 and a value of 2.961 six weeks later.

DISCUSSION

SARS-CoV-2 infection of adult immunosuppressed patients has increased severity and mortality as compared with immunocompetent adults; however, the few reports on pediatric immunosuppressed patients infected with SARS-CoV-2 have demonstrated relatively minor disease. In this study, we sought to understand SARS-CoV-2 infection in pediatric immunosuppressed patients, including capacity for antibody formation, provider testing habits, seroprevalence, and illness course.

In our study of 485 patients, we detected antibodies to SARS-CoV-2 in 5 patients, for a seroprevalence of 1.0% (CI95%: 0.3%–2.4%). In a recent companion study of seropositivity to SARS-CoV-2 during an overlapping study period in the general pediatric population, a similar seroprevalence of 0.6% (CI 95%: 0.3%–1.1%) (G. Rapsinski, personal communication) was noted among immunocompetent children.

Interestingly, contrary to common dogma that immunosuppressed patients are at higher risk of severe disease when encountering respiratory infections, only 1 of these patients was admitted for COVID-19 during the time period of sample collection and she had only a mild respiratory illness. Previous work after the emergence of SARS-CoV-1 suggested that several coronaviruses, including SARS-CoV-1, induced signaling through the calcineurin pathway and that when cyclophilins were inhibited by cyclosporine A, coronavirus replication of all genera was blocked, leading to a potential hypothesis that children on calcineurin inhibitors could be somewhat protected from severe disease outcomes [33]. The other RT-PCR-positive SARS-CoV-2 patient, with a history of liver transplant, who did not seroconvert, also had a mild illness and did not require hospital admission. By comparison, in a recent study of immunocompromised adults at our institution, 3 of 3 SOT recipient patients who tested positive for SARS-CoV-2 infection required mechanical ventilation and ultimately succumbed to their infection. In 4 adult patients on daily inhaled fluticasone, 1 of which was also on etanercept, 2 required mechanical ventilation support [18]. Immunocompromised adult patients are more likely to be admitted and have significantly poorer outcomes than children.

Of the 2 patients who had tested positive for SARS-CoV-2 via NP RT-PCR-based testing, only 1 of them seroconverted. The patient who had a positive NP SARS-CoV-2 test, but negative serology was a teenage patient with liver transplant who tested positive for SARS-CoV-2 approximately 3 months prior to the collection of blood sample and antibody testing. It is unknown if antibodies had formed and waned or if they had never formed at all. While we have not studied the durability of SARS-CoV-2 IgG antibodies in detail, another patient with positive antibodies incidentally had 2 blood collections tested during the course of our study period, 6 weeks apart, and was robustly above the threshold of positivity each time with minor variation in the measured value.

The highest seroprevalence by immunocompromising condition was in patients in the "rheumatology" category, with a seroprevalence of 4.3% (CI 95%: 0.5%–14.5%). This could be due to a variety of factors, including type of medication (1 patient on methotrexate and 1 on adalimumab); however, none of the >100 patients with IBD, mostly on infliximab and many on methotrexate, were seropositive. It could also be due to family perceptions of degree of immunocompromise, and consequent degree of behavioral change, including strict adherence to masking and social distancing in the other categories of immunosuppression such as SOT and oncology. The sample size of the rheumatology population was also smaller than that of oncology or SOT.

There are a few limitations to this study, which is a convenience sample of immunocompromised patients, both receiving inpatient and outpatient care, and may not be representative of all immunocompromised patients. Due to the low number of infections in our area and, as a result, in each subgroup of immunocompromised patients, it may not be possible to generalize

infection rates to the entire population or to make strict comparisons of rate of infection among the groups. Additionally, because we excluded patients receiving therapies that altered the production of antibodies, we cannot comment on the antibody response of those patients to SARS-CoV-2. We are not able to interpret seroconversion rates in immunosuppressed patients, as there were only 2 patients positive for SARS-CoV-2 via NP RT-PCR. As repeat samples were not routinely collected, we are also not able to comment on the potential for antibody waning over time and how it may compare to an immunocompetent population.

Overall, in this study, we sought to understand the degree of antibody formation, provider testing habits, seroprevalence, and illness course of immunocompromised pediatric patients to SARS-CoV-2. We discovered that immunocompromised pediatric patients are capable of making an antibody response to SARS-CoV-2; however, one documented RT-PCR-positive patient did not seroconvert. Unsurprisingly, immunocompromised patients presenting with respiratory or febrile illness during this time period were 3 times as likely as the general pediatric population to be tested for SARS-CoV-2. Finally, all patients with documented exposure to SARS-CoV-2 in this study had relatively minor illnesses, a stark contrast to reported cases in immunocompromised adults.

Notes

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