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ORIGINAL ARTICLE

COVID-19 in pediatric kidney transplantation: a follow-up report of the Improving Renal Outcomes Collaborative

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Abstract

Background We report follow-up data from an ongoing prospective cohort study of COVID-19 in pediatric kidney transplantation through the Improving Renal Outcomes Collaborative (IROC).

Methods Patient-level data from the IROC registry were combined with testing, indication, and outcomes data collected to describe the epidemiology of COVID testing, treatment, and clinical outcomes; determine the incidence of a positive COVID-19 test; describe rates of COVID-19 testing; and assess for clinical predictors of a positive COVID-19 test.

Results From September 2020 to February 2021, 21 centers that care for 2690 patients submitted data from 648 COVID-19 tests on 465 patients. Most patients required supportive care only and were treated as outpatients, 16% experienced inpatient care, and 5% experienced intensive care. Allograft complications were rare, with acute kidney injury most common (7%). There was 1 case of respiratory failure and 1 death attributed to COVID-19. Twelve centers that care for 1730 patients submitted complete testing data on 351 patients. The incidence of COVID-19 among patients at these centers was 4%, whereas the incidence among tested patients was 19%. Risk factors to predict a positive COVID-19 test included age > 12 years, symptoms consistent with COVID-19, and close contact with a confirmed case of COVID-19.

Conclusions Despite the increase in testing and positive tests over this study period, the incidence of allograft loss or death related to COVID-19 remained extremely low, with allograft loss or death each occurring in < 1% of COVID-19-positive patients and in less than < 0.1% of all transplant patients within the IROC cohort.

Keywords COVID-19 · Improving Renal Outcomes Collaborative · Kidney transplant

Abbreviations

COVID-19	Coronavirus disease 2019
SOT	Solid organ transplant
IROC	Improving Renal Outcomes Collaborative
KT	Kidney transplant
AUC	Area under the curve
IQR	Interquartile range
ICU	Intensive care unit
MIS-C	Multisystem inflammatory syndrome in children
ARDS	Acute respiratory distress syndrome
CI	Confidence interval
OR	Odds ratio

Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic has presented unprecedented challenges in providing care to pediatric solid organ transplant (SOT) recipients. For multiple reasons, our understanding of the effects of COVID-19 on the clinical status and outcomes for children has lagged behind those of adults. This is especially true

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for immunocompromised children with SOT. Early data for pediatric SOT recipients with COVID-19 have suggested that children with SOT are at relatively low risk for adverse allograft and/or patient outcomes following infection with COVID-19 [1–4]. The Improving Renal Outcomes Collaborative (IROC) previously reported outcomes data for nearly 300 pediatric kidney transplant (KT) patients with testing for COVID-19 between March 2020 and August 2020 and calculated the incidence of COVID-19 to be 4% with no reported deaths or allograft failures [5]. Since our first report, we have continued to collect COVID-19 testing data for pediatric kidney transplant recipients including the natural history of COVID-19 infection, transplant-associated risk factors, as well as allograft and patient outcomes.

The objectives of this follow-up study were to (1) describe the epidemiology of COVID-19 testing, treatment strategies, and short-term clinical outcomes from September 2020 through February 2021; (2) report the incidence of COVID-19 among pediatric KT patients in participating centers during this same time period; (3) compare rates of COVID-19 testing and positivity between the early COVID-19 pandemic (phase 1: March 23, 2020–September 3, 2020) and later period (phase 2: September 4, 2020–February 28, 2021); and (4) evaluate for clinical predictors of a positive COVID-19 test and clinical outcomes.

Methods

IROC is a multicenter learning health network founded in 2016 [6]. At present, there are 36 IROC centers that collectively represent over 50% of all pediatric kidney transplants performed annually in the USA. The parent IROC study has been approved by the Institutional Review Board (IRB) at Cincinnati Children's Hospital Medical Center (CCHMC) under a master reliance agreement that has also been approved at each participating center. Under this agreement, CCHMC serves as the IRB of record for IROC activities and approved this COVID-19 study. All patient data used in this study, including age, sex, etiology of kidney failure, transplant date, immunosuppression regimen, and other medications, were obtained through the central IROC patient registry. Racial and ethnic data are incomplete within the IROC registry and as such were not included in this study. Patient-level data from the IROC registry was linked with a separate Research Electronic Data Capture [7] (REDCap) data collection tool that was created to track COVID-19 testing, indication for testing, symptoms, and patient/allograft outcomes. The details of the IROC patient registry, REDCap COVID-19 data collection tool, and data linkage have been previously described [5], but briefly, clinical data for patients at each IROC center are uploaded into a central IROC data registry. These data include patient demographics, clinic visit data, laboratory data, medications, hospitalization-related data, biopsy data, and rejection events/outcomes. The current study evaluated COVID-19 data from September 4, 2020, to February 28, 2021. As with our initial study, data entry was a voluntary process. Centers were asked to submit COVID-19 testing data regardless of whether the patient was tested at their facility or outside of their facility. Secure identifiers were used to link the IROC registry and the REDCap data collection tool. Testing data could be entered for multiple assessments on the same patient with date of testing used to determine unique tests. Individual centers were contacted to provide follow-up for missing data from either the IROC registry or the REDCap data collection tool after the data was collated prior to analysis.

Aims and statistical analysis

Aim 1 was to describe the epidemiology of COVID testing, treatment, and clinical outcomes in IROC centers. Patient characteristics, including COVID-19 symptoms and other clinical indications for testing, were summarized for the overall cohort and in subgroups that tested positive or negative for COVID-19. Patient-level data was used for analysis. If multiple tests were entered for a patient, a positive result was used, when available. If there were multiple negative tests for a patient, the most recent negative test was included for analysis. Frequencies and percentages were reported for categorical variables; median, quartiles, minimum, and maximum for continuous variables. Wilcoxon rank-sum tests were used for comparing continuous variables between groups. Chi-square test or Fisher's exact test (when more than 20% of the table cells have expected frequencies less than 5) was done for associations between the categorical variables and the group variable. Short-term outcomes data were collected to differentiate between allograft outcomes (possible outcomes include no allograft-related complications, T cell-mediated rejection, antibody-mediated rejection, mixed rejection, acute kidney injury, transplant failure) and patient outcomes from COVID-19 (possible outcomes included self-limited disease, acute respiratory failure, and death).

Aim 2 was to determine the incidence of a positive COVID-19 test using a subgroup of COVID-19 testing data from centers that confirmed entry of testing data from all COVID-19 tested patients from September 4, 2020, to February 28, 2021. First, we determined the overall incidence of COVID-19 positivity among all patients followed by these centers (# of patients with at least 1 positive COVID test/# of patients with at least one clinic visit during the study period). Second, we determined the incidence for all patients tested from these centers (# of patients with at least 1 positive COVID test/# of patients with at least 1 test during the study period).

Aim 3 was to describe rates of COVID-19 testing and positivity across the first phase (March 23, 2020–September 3, 2020) and second phase of data collection (September 4, 2020–February 28, 2021). All COVID-19 testing data submitted during both phases are included in this analysis. We describe data at monthly intervals and compared additional subgroups of those aged ≤ 12 years and > 12 years. This age cutoff was selected to separate the cohort into younger children and adolescents.

Aim 4 was to assess for clinical predictors of a positive COVID-19 test using patient-level data from phase 2 of this study (September 4, 2020–February 28, 2021) as described in aim 1. To build a prediction model for a positive COVID-19 test result, a two-stage stepwise model selection procedure was used. Candidate predictors from patient clinical characteristics or COVID-related characteristics identified in Table 1 or 2 that reached significance level of $P < 0.1$ were used. The first stage of selection was done within each candidate pool (clinical characteristics and COVID-related characteristics) separately. Then the selected variables were put together for the second stage of stepwise selection. The significance level for a predictor to stay in the model was $P < 0.05$. The performance of the selected models from each stage was compared using AUC (area under the curve), sensitivity, specificity, and the average misclassification rate from ten-fold cross-validation. Two hundred simulations were done for the cross-validation.

SAS 9.4 (SAS Institute, Inc.) and R 4.0.2 were used for data analysis and visualization of data. R package pROC v1.16.2 was used for ROC-AUC analysis. Statistical significance is claimed if a P value was < 0.05.

Results

Patient enrollment

From September 4, 2020, to February 28, 2021, there were 648 tests performed for 465 patients. Figure 1 displays the locations of the participating IROC centers that participated in this study. Figure 2 describes the patient enrollment in the study. At the time of this study, there were 3390 patients enrolled in the IROC registry from 30 centers. Of these, 21 centers that care for a total of 2690 patients entered COVID-19 testing data using the REDCap data collection tool. These data were used for analysis of COVID-19 testing, clinical descriptions, and outcomes. Twelve centers confirmed that all COVID-19 testing data were submitted for kidney transplant patients tested for COVID-19. From these 12 centers, 351 patients were included in the COVID-19 incidence analysis for aim 2.

Epidemiology of COVID-19 testing, clinical description, and outcomes

Patient characteristics and demographics are detailed in Table 1. COVID-19 testing indications and symptoms are detailed in Table 2. All centers reported using SARS-CoV-2 PCR for testing. There were 109 (23%) patients that tested positive out of 465 patients tested. Patients with a positive test tended to be older [median age (interquartile range—IQR) 16.9 years (12.7–19.3) vs. 14.7 years (9.4–18.1), $P = 0.003$]. Not surprisingly, patients with a positive test were more likely to have symptoms consistent with COVID-19 (70.6% vs. 26.4%, $P < 0.001$) and have a known close contact with a confirmed case (39.4% vs. 7.3%, $P < 0.001$). Thirty-two of the 109 (29%) positive patients had no symptoms at the time of testing. The most common symptoms at the time of testing were fever (36%), cough (33%), rhinorrhea (26%), vomiting (13%), diarrhea (10%), and shortness of breath (8%). Nine patients (8%) with a positive test reported loss of taste or smell while none of the patients with a negative test reported loss of taste or smell. Table 3 displays the clinical symptoms for COVID-19-positive patients at the time of testing between both phases of the study. Table 4 displays the interventions and treatments, highest level of care required, and outcomes for patients with a positive test between the first and second phases of this study. Overall, there were no differences between the treatments received, level of care required, outcome of the illness for the patient, and outcome of the allograft between the two phases. During phase 2, 5.5% of patients with COVID-19 had their immunosuppression reduced compared to 16.7% in phase 1 ($P = 0.08$). With respect to allograft outcomes in phase 2, 97 (89%) patients experienced no transplant complications, 2 (2%) experienced antibody-mediated rejection, 1 (1%) experienced mixed rejection, 8 (7%) experienced acute kidney injury that did not require dialysis, and 1 (1%) experienced loss of allograft. For patient outcomes from COVID-19 in phase 2, 107 (98%) had self-limited disease, 1 (1%) had acute respiratory failure, and 1 (1%) died from complications of COVID-19.

One allograft loss was thought to be related to COVID-19 infection. This young adult patient presented for transplant biopsy in fall 2020 for elevated creatinine and found to be positive for COVID-19 with mild symptoms. Pathology showed a new immune-complex glomerulonephritis without evidence of acute rejection. Following the finding of idiopathic immune complex glomerulonephritis, the patient received an empiric 4-week course of oral steroids with no appreciable response in kidney function. The allograft function precipitously deteriorated over several months with persistent glomerulonephritis, evolving crescents, and worsening microscopic hematuria and proteinuria. The patient

Table 1 Patient characteristics and demographic information

	Positive ($N=109$)	Negative ($N=356$)	Overall ($N=465$)	P-value
Age at test (years)				0.0026
N	109	356	465	
Min–max	1.4–23.8	2.0–26.2	1.4–26.2	
Median (Q1, Q3)	16.9 (12.7, 19.3)	14.7 (9.4, 18.1)	15.0 (9.8, 18.5)	
Age group				0.0038
≤ 12 years	23 (21.1%)	128 (36.0%)	151 (32.5%)	
> 12 years	86 (78.9%)	228 (64.0%)	314 (67.5%)	
Years from kidney transplant to test date				0.8618
N	102	343	445	
Min–max	0.0–17.4	0.0–20.2	0.0–20.2	
Median (Q1, Q3)	3.4 (1.5, 6.1)	3.3 (1.3, 7.0)	3.3 (1.3, 6.6)	
Missing	7	13	20	
Sex				0.4868
Male	63 (57.8%)	219 (61.5%)	282 (60.6%)	
Female	46 (42.2%)	137 (38.5%)	183 (39.4%)	
Primary diagnosis of kidney				0.1806
CAKUT[a]	37 (35.9%)	109 (32.2%)	146 (33.0%)	
Ciliopathy	6 (5.8%)	9 (2.7%)	15 (3.4%)	
Glomerulonephritis	22 (21.4%)	59 (17.4%)	81 (18.3%)	
Infarct injury	1 (1.0%)	8 (2.4%)	9 (2.0%)	
Nephrotic syndrome/FSGS[b]	3 (2.9%)	13 (3.8%)	16 (3.6%)	
PKD[c]	1 (1.0%)	21 (6.2%)	22 (5.0%)	
Other	33 (32.0%)	120 (35.4%)	153 (34.6%)	
Missing	6	17	23	
Donor type				0.9716
Deceased	56 (54.9%)	189 (55.1%)	245 (55.1%)	
Living	46 (45.1%)	154 (44.9%)	200 (44.9%)	
Missing	7	13	20	
Immunosuppression regimen				
Antimetabolite	77 (70.6%)	237 (66.6%)	314 (67.5%)	0.4273
Belatacept	2 (1.8%)	4 (1.1%)	6 (1.3%)	0.6285
Calcineurin inhibitor	71 (65.1%)	231 (35.1%)	302 (64.9%)	0.9618
mTOR inhibitor	9 (8.3%)	30 (8.4%)	39 (8.4%)	0.9553
Steroid	51 (46.8%)	148 (41.6%)	199 (42.8%)	0.3355
Missing	32 (29.4%)	108 (30.3%)	140 (30.1%)	0.8454
Patient on any antihypertensive agents				0.6989
Yes	62 (56.9%)	195 (54.8%)	257 (55.3%)	
Patient on ACE inhibitor				0.5962
Yes	10 (9.2%)	39 (11%)	49 (10.5%)	

Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables

[a]Congenital anomalies of kidney and urinary tract

[b]Focal segmental glomerulosclerosis

[c]Polycystic kidney disease

required transition to dialysis within 6 months of testing positive for COVID-19.

Three weeks after a positive COVID-19 test, one adolescent patient developed progressive respiratory failure despite therapy with antibiotics and bronchodilators. Intensive care treatment included high flow nasal cannula, dexamethasone, and remdesivir followed by a transition to intravenous immunoglobulin and anakinra to treat multisystem inflammatory syndrome in children (MIS-C) when COVID-19 antibodies resulted positive. Echocardiography discovered coronary

Table 2 Clinical descriptions for patients tested for COVID-19 and symptoms at testing

	Positive ($N=109$)	Negative ($N=356$)	Overall ($N=465$)	P-value
Risk factors for testing				
Symptoms consistent with COVID-19	77 (70.6%)	94 (26.4%)	171 (36.8%)	<0.0001
Close contact with a confirmed case of COVID-19	43 (39.4%)	26 (7.3%)	69 (14.8%)	<0.0001
Close contact with a person under investigation	2 (1.8%)	6 (1.7%)	8 (1.7%)	1.0000
Patient screened by hospital policy	17 (15.6%)	234 (65.7%)	251 (54.0%)	<0.0001
Symptoms at time of testing				
None (patient had exposure/other testing indication)	32 (29.4%)	241 (67.7%)	273 (58.7%)	<0.0001
Fever	39 (35.8%)	58 (16.3%)	97 (20.9%)	<0.0001
Cough	36 (33.0%)	29 (8.1%)	65 (14.0%)	<0.0001
Rhinorrhea	28 (25.7%)	21 (5.9%)	49 (10.5%)	<0.0001
Vomiting	14 (12.8%)	16 (4.5%)	30 (6.5%)	0.0019
Diarrhea	11 (10.1%)	13 (3.7%)	24 (5.2%)	0.0078
Shortness of breath	9 (8.3%)	5 (1.4%)	14 (3.0%)	0.0011
Loss of smell or taste	9 (8.3%)	0	9 (1.9%)	<0.0001

Chi-square test or Fisher's exact test for categorical variables

Fig. 1 Map of participating IROC centers for the COVID-19 study

artery dilation that prompted anticoagulation. Kidney function remained stable throughout the acute illness.

One death was attributed to COVID-19 infection. This adolescent patient was on tacrolimus and sirolimus due to a history of multiple rejection episodes and was considered at increased risk due to multiple comorbidities including obesity, diabetes, and obstructive sleep apnea. The patient tested positive on admission with a history of cough for 1 day, developed acute respiratory distress syndrome (ARDS), and required intubation on the day of admission. This patient was treated with hydrocortisone, broad spectrum antibiotics, and remdesivir while immunosuppression

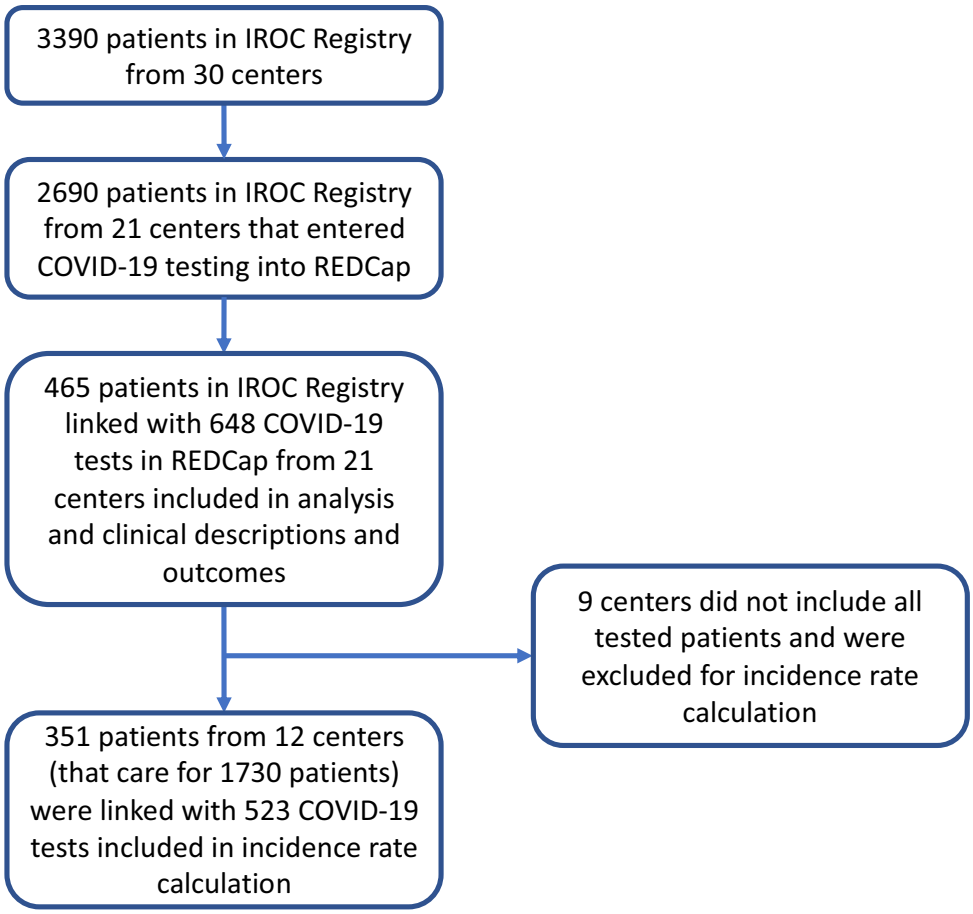

Fig. 2 Flow diagram to show enrollment in phase 2 (September 2020–February 2021) of the study

was held. The patient's respiratory status deteriorated, and the patient expired within 48 h of admission.

Incidence of COVID-19

We estimated the incidence of a positive COVID-19 test between September 2020 and February 2021 and used the data submitted from IROC centers that confirmed submitting all data on patients tested for COVID-19. Twelve centers that care for 1730 total patients submitted testing data on 351 patients. The overall incidence of COVID-19 among all patients receiving care at these centers was 4% (67/1730). The incidence of COVID-19 among tested patients at these centers was 19% (67/351).

Testing across phase 1 and phase 2

There were 1105 tests submitted for 683 patients between March 2020 and February 2021 from 25 IROC centers. Figure 3 is a bar chart describing the total number of tests reported during that period with the percent of tests that were positive. Rates of testing increased in August 2020 and remained relatively steady through February 2021. Starting in August 2020, testing remained above 100 tests performed per month and the percent positive rate across all IROC centers ranged from 8 to 25%. December 2020 and January 2021 had the highest percent positive rates, with 25% and 23% positive tests, respectively. Figure 4 displays the percentage of positive tests with the cohort split into age ≤ 12 years and age > 12 years over the same period. Except for August 2020, patients age > 12 years had more positive tests compared to those age ≤ 12 years over the study period.

Clinical predictors of a positive COVID-19 test and clinical outcomes

We utilized a two-stage stepwise model selection procedure to evaluate clinical characteristics predictive of a positive COVID-19 test. The first stage selected age group from the clinical characteristic pool, and COVID symptoms and close contact with confirmed case from the COVID-related characteristic pool. The final model with the best predicting performance based on AUC and cross-validation misclassification rate included the following clinical characteristics: (1) presence of symptoms consistent with COVID-19, (2) close contact with a confirmed case of COVID-19, and (3) patient age > 12 years. This model had good predictive performance with a sensitivity of 77%, specificity of 77%, and an AUC of

Table 3 Symptoms of COVID-19-positive patients between phases of study

	Phase 1 March 23, 2020–September 3, 2020 (***N*** = 24)	Phase 2 September 4, 2020–February 28, 2021 (***N*** = 109)	Overall (*N* = 133)	*P*-value
None (patient had exposure/other testing indication)	9 (37.5%)	32 (29.4%)	41 (30.8%)	0.4342
Fever	7 (29.2%)	39 (35.8%)	46 (34.6%)	0.5375
Cough	8 (33.3%)	36 (33.0%)	44 (33.1%)	0.9770
Rhinorrhea	2 (8.3%)	28 (25.7%)	30 (22.6%)	0.1027
Vomiting	4 (16.7%)	14 (12.8%)	18 (13.5%)	0.7412
Diarrhea	3 (12.5%)	11 (10.1%)	14 (10.5%)	0.7174
Shortness of breath	2 (8.3%)	9 (8.3%)	11 (8.3%)	1.0000
Loss of smell or taste	0	9 (8.3%)	9 (6.8%)	0.3627

Chi-square test or Fisher's exact test for categorical variables

Table 4 Treatments and outcomes for COVID-19-positive patients between phases of study

	Phase 1 March 23, 2020–September 3, 2020 (*N* = 24)	Phase 2 September 4, 2020–February 28, 2021 (*N* = 109)	Overall (*N* = 133)	*P*-value
Treatment of patient				
Supportive care only	19 (79.2%)	98 (89.9%)	117 (88.0%)	0.1665
Reduction of immunosuppression	4 (16.7%)	6 (5.5%)	10 (7.5%)	0.0809
Highest level of care required				0.2808
Outpatient	16 (66.7%)	87 (79.8%)	103 (77.4%)	
Inpatient, non-ICU[a]	6 (25.0%)	17 (15.6%)	23 (17.3%)	
ICU	2 (8.3%)	5 (4.6%)	7 (5.3%)	
Outcome of transplant				0.3409
No allograft-related complications	20 (83.3%)	97 (89.0%)	117 (88.0%)	
T cell-mediated rejection (TCMR)	1 (4.2%)		1 (0.8%)	
Antibody-mediated rejection (AMR)	1 (4.2%)	2 (1.8%)	3 (2.3%)	
Mixed TCMR/AMR		1 (0.9%)	1 (0.8%)	
Acute kidney injury	2 (8.3%)	8 (7.3%)	10 (7.5%)	
Transplant failure		1 (0.9%)	1 (0.8%)	
Outcome of illness				1.000
Self-limited disease	24 (100%)	107 (98.2%)	131 (98.5%)	
Acute respiratory failure		1 (0.9%)	1 (0.8%)	
Death		1 (0.9%)	1 (0.8%)	

Chi-square test or Fisher's exact test for categorical variables

[a]Intensive care unit

0.815 (95% CI 0.768–0.863). The average misclassification rate of tenfold cross-validation from 200 simulations is 27.5%. The adjusted odds ratios for predictors are detailed in Table 5 and the receiver operator characteristic (ROC) curve for the model is displayed within Fig. 5. The selected predictors all showed significant association with COVID-19 test results in univariate analysis (Tables 1 and 2) and remained significant in the multivariable model and showed the following factors can increase the odds of having a positive test [adjusted OR (95% CI) provided for each]: (1) patients with close contact with a confirmed case of COVID-19 [9.0 (4.8–17.1); $P < 0.0001$]; (2) patients with symptoms consistent with COVID-19 [6.6 (3.9–11.2); $P < 0.0001$]; and (3) patients > 12 years of age [1.9 (1.1–3.4); $P = 0.03$].

Given the rarity of events for patient-level outcome of illness other than "self-limited disease" or for allograft-level outcome of transplant other than "no transplant complications," we did not have adequate power to predict other outcomes based on clinical characteristics.

Discussion

This follow-up study of COVID-19 in pediatric kidney transplant patients in the USA details the testing indications, symptoms present at the time of testing, and clinical outcomes for both patients and allografts. Compared to the first report, this follow-up study captured COVID-19 testing and patient data at a time when many children had returned to in-person instruction at school and during the largest COVID-19 surge in the USA at the time [8], although it should be noted that it is unclear how many of the children in our study had returned to school. Despite the increased number and proportion of COVID-19-positive patients in this follow-up study compared to the first report (23% vs. 9%), the clinical outcomes were generally favorable and consistent with reported outcomes for their non-immunosuppressed peers [9–12]. In this study, the incidence of allograft loss or death related to COVID-19 remained extremely low, with allograft loss or death each occurring in < 1% of COVID-19-positive patients and in less than < 0.1% of all transplant patients within the IROC cohort. These estimates are likely even lower since it is likely that many patients in the cohort with COVID-19 were not tested given how common asymptomatic infection is in children [13]. Similar findings have been reported by other cohorts of immunosuppressed children (both SOT and non-SOT patients) [1–3]; however, to our knowledge this is the largest cohort of pediatric kidney transplant patients with documented clinical indications for testing and outcomes for patients with a positive COVID-19 test.

Patients with a positive test were more likely to be older (age > 12 years) in this cohort, which is consistent with the general pediatric COVID-19 data [14]. While symptoms and the clinical outcomes between immunosuppressed and non-immunosuppressed children and adolescents appear similar across multiple studies, 29% of the COVID-19-positive patients in this study were asymptomatic at the time of testing and were tested for another indication (e.g., pre-procedure testing or routine testing for hospital admission)—consistent with other reports of kidney transplant patients [15]. It has been reported that up to 20% of non-immunosuppressed children with COVID-19 may be asymptomatic [13]. While these children are not showing clinical symptoms, this represents a significant number of infected individuals that may facilitate spread of the disease either in the healthcare setting or in the general community. Therefore, despite the generally favorable outcomes for pediatric kidney transplant recipients with COVID-19 disease, it remains important to follow all public health mitigation strategies, especially pre- and post-transplant vaccination of eligible patients, in order to decrease the negative impact of this disease at the individual and population level.

Kidney failure and pediatric kidney transplantation are uncommon, and the number of transplants performed at any single center is limited. Multi-site collaboration is required to produce generalizable data in a timely manner. One of the strengths of this study centered around the use of existing infrastructure in the Improving Renal Outcomes Collaborative to facilitate a rapid, time-sensitive

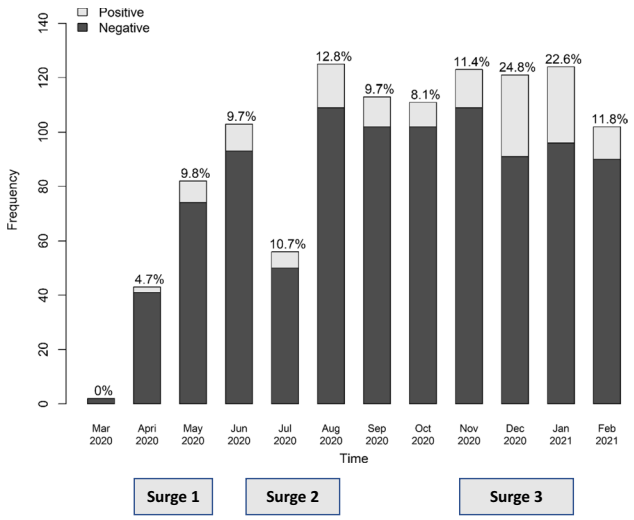

Fig. 3 Bar graph for COVID-19 testing and percent of positive tests by month. Surge 1: April 4 (male 53.9, female 55.3)–May 2 (male 55.7, female 57.6); surge 2: June 27 (male 86.4, female 92.3)–August 1 (male 88.0, female 95.7); surge 3: November 14 (male 276.8, female 301.4)–January 16 (male 329.9, female 348.6). Surge data reported are incident cases per 100,000 population, nationwide [8]

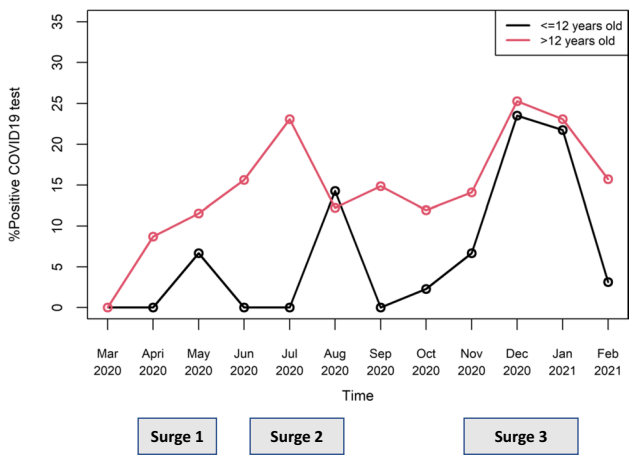

Fig. 4 Line graph for percent positive COVID-19 tests by month by age ≤ 12 years and age > 12 years. Surge 1: April 4 (male 53.9, female 55.3)–May 2 (male 55.7, female 57.6); surge 2: June 27 (male 86.4, female 92.3)–August 1 (male 88.0, female 95.7); surge 3: November 14 (male 276.8, female 301.4)–January 16 (male 329.9, female 348.6). Surge data reported are incident cases per 100,000 population, nationwide [8]

Table 5 Adjusted odds ratios for the individual components of the model predicting a positive COVID-19 test

Clinical predictor	Odds ratio (95% CI)	*P*-value
Patient age > 12 years	1.9 (1.07–3.4)	0.0298
Patient with symptoms consistent with COVID-19	6.64 (3.94–11.21)	< 0.0001
Patient with a close contact with a confirmed case of COVID-19	9.04 (4.79–17.07)	< 0.0001

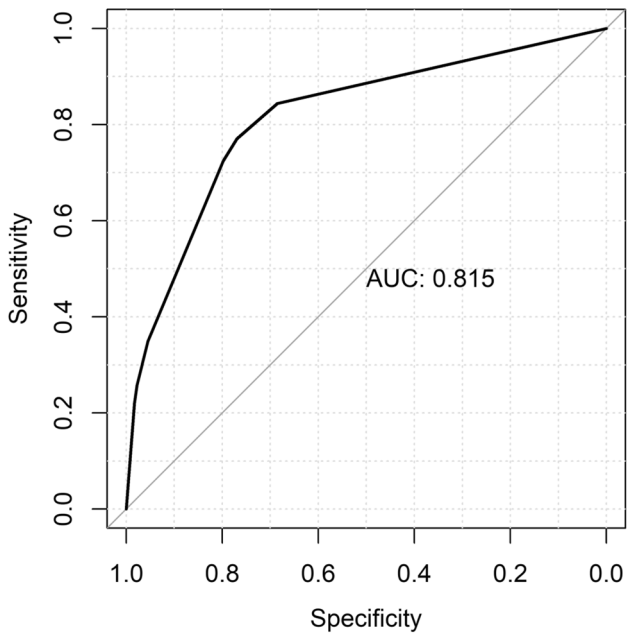

Fig. 5 Receiver operator characteristic curve showing the predictive performance of the model to assess for clinical predictors of a positive COVID-19 test using testing and outcomes data. This model used the following predictors: (1) presence of symptoms consistent with COVID-19, (2) close contact with a confirmed case of COVID-19, and (3) patient age (≤ 12 years or > 12 years). AUC 0.815 (95% CI 0.768–0.863), sensitivity 0.77, specificity 0.77

mechanism for data capture during the ongoing COVID-19 global pandemic. Furthermore, and in contrast to all other published data, the IROC registry provides a mechanism for longitudinal assessment of pediatric kidney transplant recipients. This has allowed us to critically evaluate changing rates of COVID-19 positivity and track meaningful patient- and graft-specific outcomes. Lastly, the investment in understanding the impact of COVID-19 on our pediatric KT patients has served as an opportunity to educate both medical personnel and parent/family partners within IROC amidst a quickly evolving global pandemic. Our collaborating centers continue to regularly share clinical experiences and outcomes for children affected by COVID-19. The high level of engagement specific to the COVID-19 pandemic has allowed us to mobilize participating centers to enter COVID-19 data in an accurate and complete manner that allows for a comprehensive understanding of the impact of COVID-19 on our pediatric patients.

Despite these strengths, our study has some limitations, including those common to registry-based studies. This study focuses on COVID-19 testing from September 2020 to February 2021, which occurred prior to the emergence of new variants as the predominant SARS-CoV-2 strains (e.g., the delta and omicron variants), which may limit generalizability to the current state of the pandemic [16]. Both reporting periods were also prior to the announcement in the USA by the Food and Drug Administration of the Pfizer vaccine emergency use authorization expanding to include children as young as 5 years old [17]; however, a small proportion of KT patients aged 16 and up may have received vaccination prior to the end of phase 2. The COVID-19 testing data collected using a REDCap data collection tool was provided on a voluntary basis; therefore, we were only able to consider submitted data for analysis. Not all participating centers submitted all tested kidney transplant patients (in most cases, omitting negative test results) and there was no surveillance testing occurring as part of this study. For our analysis on incidence data, we only utilized the data from centers that confirmed they entered all testing data (positive and negative) for the transplant patients at their center. For the analysis of demographic information, testing indications, clinical outcomes, and testing over time, we chose to include all reported patients from all centers, thus caution should be taken as these data likely underestimate the rate of testing and may overestimate the rate of positivity. This, however, does not devalue the utility of this data when analyzing the positive cases only with regard to symptoms and outcomes as well as the incidence rates calculated using only centers that submitted all tested patients. Unfortunately, race and ethnicity data are incomplete in the IROC registry, which precludes analysis of racial/ethnic disparities in incidence and outcomes—however, this is being addressed within the registry. Lastly, standardized criteria on which patients to test for COVID-19 do not exist; thus, testing is not uniform across the transplant centers that submitted testing data.

The findings of this follow-up report continue to show that through February 2021, children with a kidney

transplant have fared overall very well with COVID-19 and have outcomes comparable to their non-immunosuppressed peers despite the continued global spread of the SARS-CoV-2 virus and an increase in the number and proportion of COVID-19-positive patients. We will continue prospectively collecting COVID-19 data within this population to evaluate whether emerging variants impact rates of testing, case positivity, symptoms, and outcomes in pediatric kidney transplant patients. This cohort can also serve as a historical control to compare the impact of vaccination and novel therapeutics on incidence, symptoms, and clinical outcomes in this population of immunosuppressed children.

Supplementary Information The online version contains a graphical abstract available at https://doi.org/10.1007/s00467-022-05570-w.

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Author contribution Varnell, Harshman, Danziger-Isakov, Seifert, and Hooper conceptualized and designed the study. Varnell, Harshman, Smith, Liu, Danziger-Isakov, Seifert, and Hooper were involved in the analysis and interpretation of the data. Varnell and Harshman drafted the article. Varnell, Harshman, Liu, Smith, Al-Akash, Barletta, Brakeman, Chaudhuri, Fadakar, Galea, Garro, Gluck, Kershaw, Matossian, Patel, Peterson, Pruette, Ranabothu, Rodig, VanSickle, Singer, Weng, Danziger-Isakov, Seifert, and Hooper were involved with the critical revision of the article. Liu provided statistical expertise. Varnell, Harshman, Al-Akash, Barletta, Brakeman, Chaudhuri, Fadakar, Galea, Garro, Gluck, Kershaw, Matossian, Patel, Peterson, Pruette, Ranabothu, Rodig, VanSickle, Singer, Weng, and Seifert were involved in the data collection and assembly.

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Declarations

Conflict of interest The authors of this manuscript have conflicts of interest to disclose: G.B.—consultant: Alnylam; P.B.—advisory boards: CareDX and Horizon Therapeutics USA, Inc.; J.V.—speaker agreement: Alexion; L.D.—consultant: Merck and Takeda; grant support for contracted clinical research paid to institution: Astellas, Ansun, BioPharma, Merck, Takeda, and Viracor; D.H.—consultant: Hive Networks, Magnolia Innovation, Bioporto, Kaneka, and Alnylam. The other authors declare no competing interests.

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