BACKGROUND: Reports focused on adult heart transplant (HTx) recipients with COVID-19 suggest an increased risk of severe disease, however; it is unclear if this holds true for pediatric HTx patients, given the typically milder course of illness in children in general with COVID-19. We sought to rapidly implement a system for multi-center data collection on pediatric HTx candidates and recipients, with the aim of describing the patient population and infection related outcomes.

METHODS: The Pediatric Heart Transplant Society (PHTS) is a multi-center collaboration that seeks to improve the outcomes of children who are listed and undergo HTx. The society consists of pediatric HTx centers in North America (n = 53), UK (n = 2), and Brazil (n = 1). In response to the pandemic, PHTS developed a web-based platform to collect COVID-19 specific data on pediatric HTx candidates and recipients. Non-PHTS centers were also invited to submit data. Data fields included pre-and post-HTx patient characteristics, presumed versus documented infection, need for hospitalization (including ICU and ventilator use), treatments administered, and 30-day outcome (resolution, death, sequelae, and or unresolved).

RESULTS: Data collection was initiated on 4/30/20. As of 03/15/21 there were 225 patients [19 pre-HTx and 206 post-HTx, median age 14 years (IQR 7, 18)] reported from 41 centers. Hospitalization occurred in 42% (n = 8) of the pre-HTx and 21% (n=43) of the post-HTx patients. Among the patients listed for HTx, 21% (n = 4) required ICU and 10.5% (n = 2) were mechanically ventilated. Among post-HTx patients, 7% (n = 14) required ICU and 1% (n = 3) were mechanically ventilated. At 30 days,
Coronavirus disease (COVID-19) secondary to the SARS-CoV-2 infection was declared a pandemic by the World Health Organization on March 11, 2020. Since that time, there has been a dramatic surge of cases worldwide with increasing reports of disease in children. A number of systemic reviews have revealed that the most common presenting symptoms in children are respiratory and that the majority of children have mild symptoms with a low mortality rate.1,2,3,6 Potential risk factors for severe disease in children are not clear but those under 1 year of age may be at higher risk.7

Risk factors for a more severe course with a COVID-19 infection have been better elucidated in adults, with cardiovascular disease being a common comorbidity.8–10 However, whether heart transplantation (HTx) can be added to this category is somewhat unclear. In patients with solid organ transplant (SOT) a case series11 and a case control study12 have suggested a mild course with no increased risk compared to non-SOT patients. However, a large study in Italy that focused on adults with SOT revealed that the cumulative incidence of COVID-19 infections and 60-day mortality were almost double that of non-SOT individuals.9 Furthermore, a systematic review of SOT adult recipients with 2,772 unique patients reported that 80% of patients were hospitalized, with one-third requiring admission to an intensive care unit with an overall mortality of 18.6%.13

In children there is even less information available for both patients with SOT and more specifically those patients who have undergone heart transplantation. Goss et al. (2021) published a multi-center collaboration focusing on children with SOTs who acquired a COVID-19 infection.14 They identified 26 patients, six of whom had a HTx, none of the patients required respiratory support, a third were hospitalized and there were no deaths. Therefore, in response to the pandemic the Pediatric Heart Transplant Society launched an initiative to understand the impact of COVID-19 in heart transplant candidates and recipients. The aim of this report is to share the outcomes of these children to help further understanding of the impact of COVID-19 in this vulnerable patient population.

**Methods**

**PHTS description**

The Pediatric Heart Transplant Society (PHTS) is a multi-center collaboration whose main goal is to improve the outcomes of children who are listed and undergo HTx. The PHTS collects prospective, event driven data on patients <18 years of age at the time of transplant listing. The society consists of 56 pediatric HTx centers across North America (n = 53), UK (n = 2), and Brazil (n = 1). Institutional review board approval was obtained at each institute and patient consent to participate was left to the discretion of each institution as the registry serves as a quality improvement resource for centers. Analysis was performed at the Kirklin Institute for Research in Surgical Outcomes, located at the University of Alabama at Birmingham. The indications for listing and decision for transplant were made at the discretion of the primary medical team on the basis of individual institutional clinical practice.

**COVID-19 platform**

In response to the pandemic, PHTS developed a web-based platform to collect COVID-19 specific data in pediatric HTx candidates and recipients for PHTS enrolled patients. In addition, the system was designed to also allow for non-PHTS enrolled patient’s data to be submitted. For this analysis, the data fields included pre- and post-HTx patient characteristics, mode of diagnosis, need for hospitalization and intensive care and 30-day outcome (death, resolution, sequelae, unresolved). Data collection for non-patients or non-PHTS centers was supported by the limited HIPAA waiver granted by the US Department of Health and Human Services in response to the COVID-19 pandemic (https://www.hhs.gov/sites/default/files/hipaa-and-covid-19-limited-hipaa-waiver-bulletin-508.pdf).

**COVID-19 platform**

Definition of a COVID-19 illness included patients who: 1) were positive for SARS-CoV-2 by PCR based test and/or had symptoms of COVID-19 with a known exposure, or 2) had suspected COVID-19 illness due to symptoms but no exposure or test. To align with other infection data that is collected in the PHTS registry, only system-based involvement was collected, with no information on specific presenting symptoms. Only patients with fully completed and submitted forms to the Web-based data entry system were considered validated results and therefore included in this study. Patients with multi-system inflammatory disorder were not included in this analysis. Data collection was started on April 30, 2020 and centers were encouraged to enter patients who were diagnosed before April 30th. The end date for this analysis was March 15, 2021 (Figure 1).

**Statistical analysis**

Descriptive statistics for continuous variables were presented as mean with standard deviation or median with interquartile range.
Results

There were 225 patients with adequate data submitted for analysis of 30-day outcomes from 43 different sites within the PHTS. Of the 225 patients, 198 (88%) were previous enrolled in PHTS and 27 were patients not enrolled in PHTS but cared for at a PHTS site. Nineteen patients (8%) were HTx candidates and 206 (92%) were HTx recipients. Of the patients that were documented to be listed or transplanted during the study period, 3.5% (n=19/544) of transplant candidates and 4.7% (179/3831) of the transplanted recipients were reported to have a COVID infection. The median age of COVID-19 infection was 14 years (IQR 7, 18) with half being male (50%) (Table 1). The vast majority of patients had a positive PCR test (92%, n=208/225) with 10 patients diagnosed based on known exposure and 7 presumed due to symptoms (Table 2). The most common location of exposure to COVID-19 was in the home (n = 142, 63.1%), followed by in the community (n = 38, 17%). Thirty-one patients (14%) had an unknown exposure. Table 1 outlines medications the patients were on at the time of diagnosis of the infection. Major organ system involvement was only reported in a minority of patients including: 32% (n = 71) had fever, 27% (n =61) had respiratory involvement, 16% (n = 37) had gastrointestinal involvement, and 1% (n = 3) cardiac involvement.

The clinical course following COVID-19 infection is shown in Table 3. Following infection, 23% (n = 51/225) were admitted to hospital with a median stay of 8 days (IQR 2, 18). Intensive care was required in 8% (n = 18) with a median ICU duration of 9 days (IQR 5, 22). Advanced therapies included the need for mechanical ventilation occurred in 2% (n = 5) and inotropic therapy in 4% (n = 9) of the patients. Need for ECMO (n = 1, 0.9%) was rare.

Transplant candidates

For the 19 pre-HTx patients, the median duration of listing was 250 days (IQR 32, 452) prior to onset of COVID-19 illness. There was an equal distribution of patients with cardiomyopathy and congenital heart disease in this cohort (Table 1). The majority acquired the infection at home or in their community with a smaller proportion (15.8%) having been exposed in a hospital environment (Table 2). Hospital admission occurred in 42.1% of the pre-HTx patients (Table 3) with 21% requiring ICU admission. Two candidates (11%), required mechanical ventilation (for 22 and 32 days respectively) and both had underlying dilated cardiomyopathy. One required ECMO support after intubation.

Transplant recipients

Among 206 post-HTx patients with COVID-19, the median time after HTx was 6 years (IQR 3, 10), though 10% were <12 months from transplantation. Table 1 reviews the
clinical characteristics and demographics for these patients. Most exposures occurred in either the home or community (80%). Hospitalization occurred in 21% of the recipients, with 7% requiring ICU care. Three recipients (1.5%) required mechanical ventilation and one of these patients continued on chronic hemodialysis. Duration of mechanical ventilation ranged from 6 to 22 days. None of the patients required ECMO support.

| Table 1  | Clinical Characteristics and Demographics |
|----------|------------------------------------------|
| Overall (n = 225) | Candidates (n = 19) | Recipients (n = 206) |
| **Age at COVID (y)** | 14 (7.18) | 9 (4.16) | 14 (8.18) |
| **Race** | | | |
| White | 141 (62.7%) | 11 (57.9%) | 130 (63.1%) |
| Black | 43 (19.1%) | 3 (15.8%) | 40 (19.4%) |
| Other / Multiple | 41 (18.2%) | 5 (26.3%) | 36 (17.5%) |
| Male | 112 (49.8%) | 7 (36.8%) | 105 (51%) |
| **Diagnosis (Primary Etiology)** | | | |
| CM | 115 (51.1%) | 9 (47.4%) | 106 (51.5%) |
| CHD | 103 (45.8%) | 10 (52.6%) | 93 (45.1%) |
| Single Ventricle* | 68 (66.0%) | 8 (80.0%) | 60 (64.5%) |
| Other | 7 (3.1%) | 7 (3.4%) | 7 (3.4%) |
| **Drug Therapy at time of Infection** | | | |
| Acyclovir | 2 (0.9%) | 2 (1%) | 2 (1%) |
| Azathioprine | 13 (5.8%) | 13 (6.3%) | 13 (6.3%) |
| Basiliximab | 1 (0.4%) | 1 (0.5%) | 1 (0.5%) |
| Cyclosporine | 10 (4.4%) | 10 (4.9%) | 10 (4.9%) |
| Dapsone | 1 (0.4%) | 1 (0.5%) | 1 (0.5%) |
| Everolimus | 9 (4%) | 9 (4.4%) | 9 (4.4%) |
| Fluconazole | 1 (0.4%) | 1 (0.5%) | 1 (0.5%) |
| Ganciclovir or Valganciclovir | 16 (7.1%) | 1 (5.3%) | 15 (7.3%) |
| Immunoglobulin, IV Ig | 5 (2.2%) | 5 (2.4%) | 5 (2.4%) |
| Mycophenolate, MMF | 67 (29.8%) | 67 (32.5%) | 67 (32.5%) |
| Nystatin | 4 (1.8%) | 4 (1.9%) | 4 (1.9%) |
| Oseltamivir | 1 (0.4%) | 1 (0.5%) | 1 (0.5%) |
| Prednisone | 33 (14.7%) | 33 (16%) | 33 (16%) |
| Rituximab | 1 (0.4%) | 1 (0.5%) | 1 (0.5%) |
| Sirolimus | 45 (20%) | 45 (21.8%) | 45 (21.8%) |
| Tacrolimus | 111 (49.3%) | 111 (53.9%) | 111 (53.9%) |
| Trimethaprim-sulfamethoxazole | 18 (8%) | 18 (8.7%) | 18 (8.7%) |
| Valacyclovir | 1 (0.4%) | 1 (0.5%) | 1 (0.5%) |
| Other | 16 (7.1%) | 14 (6.8%) | 14 (6.8%) |
| ACEI | 9 (4%) | 8 (3.9%) | 8 (3.9%) |
| Hydroxychloroquine | 1 (0.4%) | 1 (0.5%) | 1 (0.5%) |

n (%) or median (IQR).

*Single Ventricle report as n (%) of CHD.

| Table 2  | Mode of Diagnosis and Location of Exposure |
|----------|------------------------------------------|
| Overall (n = 225) | Candidates (n = 19) | Recipients (n = 206) |
| **COVID Diagnosis Mode** | | | |
| Test Positive | 208 (92.4%) | 18 (94.7%) | 190 (92.2%) |
| Known Exposure | 10 (4.4%) | 1 (5.3%) | 9 (4.4%) |
| Presumed Positive | 7 (3.1%) | 7 (3.4%) | 7 (3.4%) |
| **Location of Exposure** | | | |
| Home | 142 (63.1%) | 8 (42.1%) | 134 (65%) |
| Community | 38 (16.9%) | 4 (21.1%) | 34 (16.5%) |
| Out of Hospital | 8 (3.6%) | 8 (3.9%) | 8 (3.9%) |
| In Hospital / Long Term Care Facility | 6 (2.7%) | 3 (15.8%) | 3 (1.5%) |
| Unknown | 31 (13.8%) | 4 (21.1%) | 27 (13.1%) |

n(%).
Outcomes

At 30 days, 96% of candidates and recipients had resolution of their symptoms, 3% (n = 7) had an unresolved course, and 1% (n = 2) of the patients were reported to have significant long-term sequelae (Table 4). Ongoing sequelae post 30 days included one candidate who required ongoing mechanical ventilation and one recipient with acute on chronic renal insufficiency and need for ongoing mechanical ventilation. Two recipients died after COVID-19 illness: only one was directly secondary to COVID-19 who was 61 days post re-transplantation and 13 days post COVID-19 infection diagnosis, and the other from non-adherence and rejection who was 5 years post-HTx and one-month post COVID-19 illness. There were no deaths in the candidate group. Overall mortality for the entire cohort with COVID-19 was 0.4% and for transplant recipients was 0.49%.

Discussion

In this largest cohort of pediatric HTx candidates and recipients with COVID-19 reported to date we found that the majority had quick resolution of their illness with no long-term sequelae. Relative to reporting for adult heart transplant recipients, mortality was much lower in this cohort of patients (0.5% vs. 15-30%). Rates of hospitalization (21 vs. 4.7%) and death (0.5 vs. 0.19%) were higher as compared to other children in the United States without SOT. However, the hospitalization rate was similar to reports focused on other pediatric SOT patients (21 vs. 31%) but lower than published literature on adult SOT (21 vs. 30%-78%).

Although the number of listed patients was small compared to the number of post HTx patients, our analysis suggested that these patients had a more severe degree of illness with a higher proportion of patients hospitalized and requiring ICU care including mechanical ventilation and inotropic support. Despite these patients being a sicker cohort, there was no reported mortality. This finding suggests that close and vigilant monitoring of these patients listed for HTx who acquire COVID is imperative given the potential for deterioration and that recovery from the illness is possible with supportive care.

In pediatric heart transplant the true incidence of COVID-19 infections is unknown. A recently published single center study where patients underwent COVID-19 testing prior to admission, anesthesia, office visits or for symptoms, found that 21% (n = 20/94) of their patients were diagnosed with COVID-19 based on PCR or antibody testing. In this patient population 5% of patients were admitted from home with no mortality reported. These results differ from ours due to the fact that over half (55%) of these patients were asymptomatic and undergoing routine testing, which likely underestimated the impact of disease in symptomatic patients. Our study was also not able to accurately report the true incidence of COVID-19 infections, as we are unable to ensure all symptomatic patients were included in the registry and we did not collect data on asymptomatic patients who underwent routine testing. In addition, the numbers we did provide might not have an

### Table 4 30 Day Outcomes

| COVID Infection Outcome (30d)         | Overall (n = 225) | Candidates (n = 19) | Recipients (n = 206) |
|--------------------------------------|-------------------|---------------------|----------------------|
| Resolution                           | 214 (95.5%)       | 18 (94.7%)          | 194 (95.6%)          |
| Death                                | 1 (0.4%)          | 1 (0.5%)            | 1 (0.5%)             |
| Significant Long Term Sequelae       | 2 (0.9%)          | 1 (5.3%)            | 1 (0.5%)             |
| Unresolved at 30 days                | 7 (3.1%)          | 7 (3.4%)            | 7 (3.4%)             |
| Unknown                              | 1 (0.4%)          |                     | 1 (0.49%)            |

n (%).
accurate denominator with respect to patients at risk, as there can be a delay between when a patient is listed or transplanted and when their information is entered into the web-based data system. Lastly, for the 27 patients that had COVID-19 but were not part of the registry, they were not counted in the calculation. All of these potential issues align above raise concerns for reporting bias.

While the literature for adult patients with heart transplants is limited to case reports and small case series, there is some suggestion that infection early after transplant may have an impact on outcomes.\textsuperscript{20–22} A US cohort of 28 adult heart transplant patients reported a 25% case fatality rate.\textsuperscript{15} Furthermore, in an Italian cohort of 47 patients who tested positive for SARS-CoV-2 at seven different centers, 38 were hospitalized and 14 patients died.\textsuperscript{16} These results indicate an almost doubling of the prevalence and case fatality rate when compared to the general population. Specific risk factors for mortality identified by univariate analysis included: older age, diabetes, arteriopathy, lower GFR and higher New York Heart Association classification.\textsuperscript{16}

In this PHTS cohort many patients were transplanted more than one year before contracting COVID-19. However, one-fifth of the patients were <1 year post transplant with one death in this group. This is an important group of patients to continue to monitor, given the reports of adults experiencing worse outcomes in the early phase post HTx.\textsuperscript{20–22} Whether reduction in immunosuppression is warranted in this specific group of patients is unclear.

Among both pediatric HTx candidates and recipients, the most common exposures were in the home and in the community. While we did not examine adherence to recommended public health measures undertaken by individual patients and families, these findings suggest that attention to exposures inside of the home, including behaviors of other household members, may be of importance to mitigating the risk of transmission to pediatric HTx candidates and recipients.

\textbf{Limitations}

This analysis is limited to the patients reported in the registry and therefore there is a potential for selection bias in the data. In addition to under reporting, asymptomatic cases or cases that were unknown to the heart transplant centers would not be accounted for in this data collection. Furthermore, hospitalization rates may not reflect the need for supportive care but may be inflated as a proportion of patients could have been admitted for observation only. Subsequent, analysis examining the rate of hospitalization over time as practitioners has become more familiar with the management of pediatric HTx candidates and recipients will be needed to address this potential limitation. This same limitation applies to intensive care admissions as well. The terms “required ICU admission” was the wording used in the web-based data system, instruction were given to centers to only include patients admitted specifically for COVID-19 infections, however we cannot take into account the variability in practice across centers with threshold for ICU admissions. This initial report also had a low number of patients experience certain events, therefore estimates of the median ICU and ventilator time might change as new data is added to the registry. In addition, this analysis was limited to acute presentation of COVID-19 and does not include those with M-ISC and therefore results cannot be extrapolated to this group of patients. Lastly, due to the limited number of patients and mortality events, statistical comparison between groups and risk factor analyses was not performed.

\textbf{Conclusion}

Pediatric heart transplant candidates and recipients who acquire COVID-19 are hospitalized at higher rates than have been reported for the general pediatric population but long-term sequelae and mortality remain low. Ongoing collection of data will allow for further understanding of which patients are at risk for more severe disease, potential treatment strategies and longer term complications in this unique patient population.

\textbf{Disclosure statement}

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\textbf{References}

1. Mehta SA, Rana MM, Motter JD. Incidence and outcomes of COVID-19 in kidney and liver transplant recipients with HIV: report from the National HOPE in Action Consortium. Transplantation 2021;105:216-24.
2. Irfan O, Mutalib F, Tang K, Jiang L, Lassi ZS, Bhutta Z. Clinical characteristics, treatment and outcomes of paediatric COVID-19: a systematic review and meta-analysis. Arch Dis Child 2021;106:440-8.
3. Yasuhara J, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID-19 in children: a systematic review. Pediatr Pulmonol 2020;55:2565-75.
4. Parcha V, Booker KS, Kalra R, et al. A retrospective cohort study of 12,306 pediatric COVID-19 patients in the United States. Sci Rep 2021;11:10231.
5. Hu JF. COVID-19 in children: a narrative review. Curr Pediatr Rev Published online May 26, 2021. https://doi.org/10.2174/1573396361766210526155313.
6. Chua GT, Wong JSC, Lam L, et al. Clinical characteristics and transmission of COVID-19 in children and youths during 3 waves of outbreaks in Hong Kong. JAMA Netw open 2021;4:e218824.
7. Sena GR, Lima TPF, Vidal SA. Clinical characteristics and mortality profile of COVID-19 patients aged less than 20 years old in Pernambuco - Brazil. Am J Trop Med Hyg 2021;104:1051-6.
8. Kim L, Garg S, O’Halloran A, et al. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US Coronavirus disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). Clin Infect Dis 2021;72:e206-14.
1. Trapani S, Masiero L, Puoti F, et al. Incidence and outcome of SARS-CoV-2 infection on solid organ transplantation recipients: A nationwide population-based study. Am J Transplant 2020;2:2509-21.
2. Khamis F, Memish Z, Al Bahrami M, et al. Prevalence and predictors of in-hospital mortality of patients hospitalized with COVID-19 infection. J Infect Public Health 2021;14:759-65.
3. Yi SG, Rogers AW, Saharia A. Early experience with COVID-19 and solid organ transplantation at a US high-volume transplant center. Transplantation 2020;104:2208-14.
4. Sharma P, Chen V, Fung CM, et al. COVID-19 outcomes among solid organ transplant recipients: a case-control study. Transplantation 2021;105:128-37.
5. Raja MA, Mendoza MA, Villavicencio A, et al. COVID-19 in solid organ transplant recipients: a systematic review and meta-analysis of current literature. Transplant Rev (Orlando) 2021;35:100588.
6. Goss MB, Galván NTN, Ruan W, et al. The pediatric solid organ transplant experience with COVID-19: an initial multi-center, multi-organ case series. Pediatr Transplant 2020.
7. Latif F, Farr MA, Clerkin KJ, et al. Characteristics and outcomes of recipients of heart transplant with coronavirus disease 2019. JAMA Cardiol 2020;5:1165-9.
8. 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;9:52-61.
9. Danziger-Isakov L, Blumberg EA, Manuel O, Sester M. Impact of COVID-19 in solid organ transplant recipients. Am J Transplant 2021;21:925-37.
10. Moreira A, Chorath K, Rajasekaran K, Burmeister F, Ahmed M, Moreira A. Demographic predictors of hospitalization and mortality in US children with COVID-19. Eur J Pediatr 2021;180:1659-63.
11. Bock MJ, Kuhn MA, Chinnock RE. COVID-19 diagnosis and testing in pediatric heart transplant recipients. J Hear Lung Transplant 2021;40(9):897-9.
12. Lima B, Gibson GT, Vullaganti S. COVID-19 in recent heart transplant recipients: Clinicopathologic features and early outcomes. Transpl Infect Dis 2020;22:e13382.
13. Tchana-Sato V, Ancion A, Tridetti J, et al. Clinical course and challenging management of early COVID-19 infection after heart transplantation: case report of two patients. BMC Infect Dis 2021;21:1-10.
14. Al-Darzi W, Aurora L, Michaels A, et al. Heart transplant recipients with confirmed 2019 novel coronavirus infection: The Detroit experience. Clin Transplant 2020;34:1-6.