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Is cardiorespiratory disease associated with increased susceptibility of SARS-CoV-2 in children?

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Abstract

Background: There are limited data in pediatric populations evaluating whether chronic cardiorespiratory conditions are associated with increased risk of coronavirus disease 2019 (COVID-19). We aimed to compare the rates of chronic cardiac and respiratory disease in children testing positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2[+]) compared with those testing negative (SARS-CoV-2[−]) at our institution.

Method: Prospective cohort with nested case–control study of all children tested by polymerase chain reaction (PCR) for SARS-CoV-2 by nasopharyngeal/oropharyngeal sampling between March and October 2020. Children were identified prospectively via laboratory notification with age and sex-matching of SARS-CoV-2[+] to SARS-CoV-2[−] (1:2). Clinical data were extracted from the electronic medical record.

Results: In total, 179 SARS-CoV-2[+] children (44% females, median age 3.5 years, range: 0.1–19.0 years) were matched to 391 SARS-CoV-2[−] children (42% female, median age 3.7 years, range: 0.1–18.3 years). The commonest comorbidities showed similar frequencies in the SARS-CoV-2[+] and [−] groups: asthma ($n = 9$, 5% vs. $n = 17$, 4.4%, $p = 0.71$), congenital heart disease ($n = 6$, 3.4% vs. $n = 7$, 1.8%, $p = 0.25$) and obstructive sleep apnoea ($n = 4$, 2.2% vs. $n = 10$, 2.3%, $p = 0.82$). In the SARS-CoV-2[+] group, the prevalence of symptomatic disease was similar among children with and without cardiorespiratory comorbidities ($n = 12$, 75% vs. $n = 103$, 57%, $p = 0.35$). A high proportion of children hospitalized with SARS-CoV-2 infection had cardiac comorbidities (23.8%).

Conclusions: In this single site data set, rates of pre-existing cardiorespiratory disease were similar in SARS-CoV-2[+] and SARS-CoV-2[−] children. Rates of symptomatic infection were similar between children with and without cardiorespiratory comorbidity. High rates of comorbid cardiac disease were observed among

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hospitalized children with COVID-19 warranting further research to inform vaccine prioritization.

KEYWORDS

asthma, cardiac, child, COVID-19, pediatric lung disease, SARS-CoV-2

1 | INTRODUCTION

There are limited data in pediatric populations evaluating whether chronic cardiac or respiratory conditions, such as congenital heart disease (CHD) and asthma, are associated with increased susceptibility to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. Understanding the comorbidity profiles of children with COVID-19 is important to inform public health measures and vaccine prioritization. Adult data indicate that asthma and cystic fibrosis (CF) may not affect susceptibility to or outcomes from coronavirus disease 2019 (COVID-19).[1–4] The aims of this study were to evaluate the prevalence of asthma and other cardiorespiratory diseases in a pediatric cohort attending a major tertiary pediatric facility (The Royal Children's Hospital [RCH] Melbourne, Australia) for SARS-CoV-2 testing. Our specific objectives were to (1) determine whether children with cardiac or respiratory comorbidities were more likely to test positive for SARS-CoV-2 than those without, and (2) if children with these pre-existing comorbidities experienced a higher rate of symptomatic infection than those without comorbidities.

2 | METHODS

This prospective cohort, within a nested case-control study, included all children consecutively tested with reverse-transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 from nasopharyngeal/oropharyngeal samples collected at RCH between February 1 and October 31, 2020. SARS-CoV-2 positive (SARS-CoV-2[+]) children were age and sex-matched to consecutively tested SARS-CoV-2 negative (SARS-CoV-2[−]) controls at a ratio of 1:2. Negative controls used for matching were chosen using the following sequential criteria; (1) nearest chronological swab, (2) closest age match, and (3) gender match. Symptom data and past medical history were obtained via a questionnaire completed by the child's guardian and verified against the participant's electronic medical record. Cardiac disease was defined as any previously diagnosed CHD ranging from septal defects to cyanotic CHD. Respiratory disease was defined as previously diagnosed asthma, obstructive sleep apnoea (OSA), bronchopulmonary dysplasia (BPD), CF, primary ciliary dyskinesia (PCD), interstitial lung disease (ILD), bronchiectasis or neuromuscular weakness. This study received ethics approval from the RCH Human Research Ethics Committee (HREC #37024 and #63013).

Descriptive statistics were used to summarize the cohort characteristics. Median and inter-quartile ranges were reported as data were non-normally distributed. Statistical analysis was performed using Stata Version 16.0 (Stata Corporation). Pearson's χ^2 test was used for comparison of categorical variables of more than 10 positive events, while Fisher's exact test was used for categorical variables that consisted of less than 10 positive events.

3 | RESULTS

In the study period, 26,819 upper respiratory tract swabs were performed at RCH, of which 179 (0.68%) were SARS-CoV-2[+] (44% females, median age 3.5 years). They were matched to 391 SARS-CoV-2[−] children (42% females, median age 3.7 years). Of the children with PCR-confirmed SARS-CoV-2 infection, 16/179 (8.9%) had a previously documented cardiorespiratory comorbidity. Samples from the SARS-CoV-2[+] and SARS-CoV-2[−] cohorts were obtained from outpatient services (87.6% vs. 81.7%) and inpatient services (12.4% vs. 18.3%) (Table 1).

Overall, SARS-CoV-2[+] children were no more likely than SARS-CoV-2[−] children to report a history of any cardiac or respiratory disease (Figure 1). Similar rates of asthma (5.0% vs. 4.4%; $p = 0.718$), CHD (3.4% vs. 1.8%; $p = 0.154$), and OSA (2.2% vs. 2.3%; $p = 1.0$)

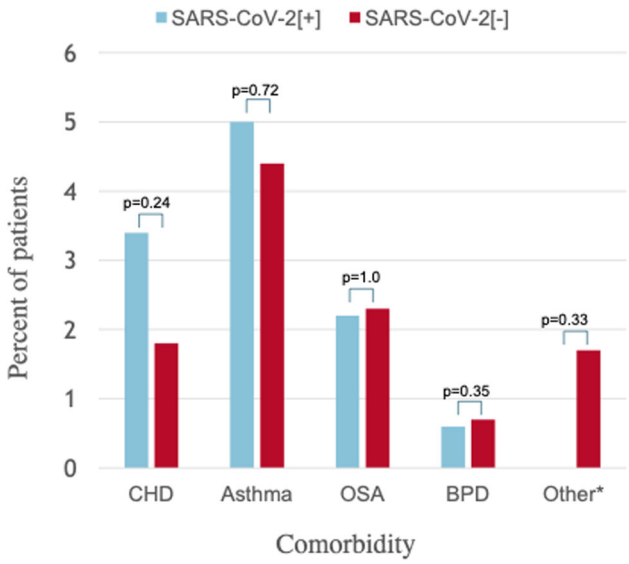

FIGURE 1 Comparison of prevalence of cardiac and respiratory comorbidities between SARS-CoV-2 positive and SARS-CoV-2 negative children R1. tiff. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2 [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Study population characteristics

Variable	SARS-CoV-2[+]	SARS-CoV-2[−]	*p* value
Subjects	179	391	
Male	100 (55.9%)	226 (57.8%)	0.67
Age–years (range)	3.5 (0.1, 19.0)	3.7 (0.1, 18.3)	0.76
Location of testing			
Outpatient clinic	160 (89.4%)	318 (81.4%)	0.02
In-hospital care	19 (10.6%)	73 (18.6%)	0.02

Note: Data presented as *n*, *n* (%) and median (range).

were observed between groups. No patient with BPD, CF PCD, ILD, bronchiectasis, or neuromuscular weakness presented with SARS-CoV-2 infection. Among the SARS-CoV-2[+] group with a current diagnosis of asthma, two children ($n = 2/179$; 1.1%) were receiving inhaled corticosteroid therapy at the time of sampling, compared with three ($n = 3/391$, 0.8%;) with asthma receiving therapy in the SARS-CoV-2[−] group. In total, 115 of 179 (64.2%) of SARS-CoV-2[+] children reported symptoms compared with 226 of 391 (57.8%) in the SARS-CoV-2[−] group. $p = 0.879$) (Table 2).

Approximately one in ten ($n = 21/179$; 11.7%) SARS-CoV-2[+] children were subsequently hospitalized as a result of their infection, with six (28.6%) having a history of any cardiac and/or respiratory disease (four had CHD requiring previous surgical intervention, one had atrial septal defect that did not require surgical intervention as well as asthma, and one had asthma as their only comorbidity). Two of these children were admitted for deteriorating respiratory symptoms and four were admitted for observation. No cases of surgically corrected CHD were reported among the SARS-CoV-2[−] group.

Most hospitalized children had mild respiratory symptoms and were admitted for observation, feeding support or for reasons unrelated to SARS-CoV-2 infection. Three had severe disease requiring respiratory intervention; one had severe COVID-19 (with comorbid complex CHD), one had pediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) and one a Kawasaki's disease like presentation temporally associated with SARS-CoV-2.

4 | DISCUSSION

In this single-center prospective cohort study with nested case–control, similar rates of cardiac and respiratory disease were observed in children infected with SARS-CoV-2 compared with those uninfected. In addition, those with a history of cardiac or respiratory disease were no more likely, than those without, to present with symptomatic infection. Our findings support those of other studies indicating that children with SARS-CoV-2 infection overwhelmingly experience mild symptoms and many are asymptomatic.[5–8]

Interestingly, we also observed a high proportion of hospitalized children with SARS-CoV-2[+] infection had a history of cardiac disease (23.8%). Recent data suggest that pre-existing cardiac disease in children is associated with hospitalization, intensive care unit (ICU) admission, and mechanical ventilation.[9–11] A systematic review by Williams et al. showed high rates of cardiac disease ($n = 11/48$; 23%) in hospitalized children and adolescents with COVID-19 requiring mechanical ventilation.[10] Furthermore, the authors also reported that cardiac disease requiring prior surgical intervention was associated with more severe forms of SARS-CoV-2 infection and higher rates of hospitalization. Cardiac disease was also shown to be associated with ICU admission in a recent European multicentre study.[11] In contrast, while asthma was relatively common in the SARS-CoV-2[+] cohort, two (9.5%) children who were hospitalized with COVID-19 reported a history of asthma, though both had mild disease. A recent large cross-sectional study by Kompaniyets et al. evaluated for an association between underlying medical conditions and COVID-19 severity in 43,465 children across 800 hospitals in the United States.[12] Cardiac and congenital circulatory abnormalities were identified as

TABLE 2 Comorbidities and symptoms

Variable	SARS-CoV-2[+]	SARS-CoV-2[−]	*p* value
Asthma	9 (5%)	17 (4.4%)	0.72
Cardiac disease	6 (3.4%)	7 (1.8%)	0.24
Obstructive sleep apnoea	4 (2.2%)	9 (2.3%)	1.0
Bronchopulmonary dysplasia	1 (0.6%)	2 (0.8%)	1.0
Cystic fibrosis	0	2 (0.5%)	1.0
Bronchiectasis	0	1 (0.3%)	1.0
Primary ciliary dyskinesia	0	1 (0.3%)	1.0
Interstitial lung disease	0	1 (0.3%)	1.0
Symptomatic	115 (64.2%)	226 (57.8%)	0.37
Fever	48 (26.8%)	97(24.8%)	0.61
Cough	67 (37.4%)	122 (31.2%)	0.14
Runny nose	53 (30.6%)	152 (38.9%)	**0.03**
Shortness of breath	2 (1.1%)	23 (5.9%)	**0.01**
Sore throat	19 (10.6%)	50 (12.8%)	0.46
Fatigue	19 (10.6%)	22 (5.6%)	0.03
Headache	13 (7.3%)	16 (4.9%)	0.11
Muscle ache and pain	4 (2.2%)	7 (1.8%)	0.74
Vomiting	12 (6.7%)	34 (8.7%)	0.42
Diarrhea	11 (6.2%)	8 (2%)	**0.01**
Abdominal pain	6 (3.4%)	19 (4.9%)	0.42
Poor appetite	7 (3.9%)	39 (9.9%)	**0.01**
Loss of taste	2 (1.1%)	1 (0.026%)	0.23
Loss of smell	1 (0.6%)	3 (0.76%)	1.0

Note: Data presented as *n*, *n* (%) and median (range). Bold values indicate statistical significance ($p \leq 0.05$).

being strong risk factors for hospitalization and development of severe COVID-19 illness. The authors also reported asthma as being the most frequent diagnosed condition and associated with an increased risk of hospitalization. However, in hospitalized children under 12 years of age, asthma was not associated with a heightened risk of severe COVID-19 illness. In a separate multicentre study which surveyed and analyzed responses from 174 pediatric centers, Moeller et al.[13] also demonstrated low rates of severe COVID-19 illness in asthmatic patients hospitalized with SARS-CoV-2. Interestingly, despite being a tertiary care center, we observed a lower prevalence of asthma in our study cohort in comparison to the reported prevalence of asthma in Australia (4.8% vs. 11%).[14] While limited numbers in the present study preclude a definitive conclusion, available literature indicates that childhood asthma is unlikely to be associated with increased COVID-19 severity.

Matching controls of age and sex were used to address potential confounding factors. Another potential confounder that was not accounted for in this study was patient ethnicity. Published after our data collection, Sze et al. reported findings of a systematic review investigating the relationship between ethnicity and clinical outcomes in those infected by SARS-CoV-2. The authors reviewed outcomes reported in 50 international studies, collectively comprising a total of 18,728, 893 patients from a wide variety of ethnic backgrounds. Findings from this meta-analysis indicated that those of Black and Asian ethnicity were at a higher risk of SARS-CoV-2 infection.[15]

While symptom profiles of SARS-CoV-2[+] and SARS-CoV-2[−] groups were similar, SARS-CoV-2[−] children were more likely, than SARS-CoV-2[+] children, to report a "runny nose," shortness of breath and/or reduced appetite. In contrast, SARS-CoV-2[+] children more commonly reported diarrhea than the SARS-CoV-2[−] group (6.2% vs. 2%; $p = 0.011$). Rates of cough were similar between groups and in those with and without cardiorespiratory disease (data not shown). Due to the inherent difficulty in differentiating different causes of wheeze in children (e.g., viral associated wheeze vs. preschool asthma) we decided not to include this in the list of respiratory illnesses. We chose instead to include doctor-diagnosed, parent-reported asthma. We acknowledge that reporting bias may have impacted on these numbers.

This study has several strengths. First, testing was performed in a single pediatric hospital where health-care workers and laboratory staff adhere to strict guidelines of sample collection and processing. Second, compared with community-based settings, there was likely to be a higher proportion of children with pre-existing comorbidities, as hospital-based testing clinics generally attract patients of the hospital. Third, age and sex-matching in a 2:1 ratio removed these factors as potential confounders. There are several limitations that warrant mention. While simultaneously a strength, parents of children with pre-existing comorbidities may have preferentially presented to the RCH over their local testing center, potentially introducing selection bias. Also, as this was a single-center study conducted in a region of low COVID-19 prevalence, our sample size is small in comparison to international studies. We acknowledge that due to this our data set could have potentially been affected by sample bias and type II error. However, our small sample size is likely balanced by the high level of case ascertainment in Australia. Moreover, while current data investigating the relationship between cardiac and respiratory comorbidities in pediatric populations is limited, our findings are consistent with published literature,[10,13,16,17] adding further support to our findings.

In conclusion, pre-existing cardiac or respiratory disease did not appear to increase likelihood of testing positive to SARS-CoV-2. Furthermore, children with, compared with those without, respiratory diseases had similar rates of symptomatic COVID-19. The high rates of pre-existing cardiac disease observed in hospitalized children with SARS-CoV-2 infection warrants further study.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Cassidy Du Berry: Conceptualization (equal); formal analysis (lead); investigation (equal); methodology (equal); project administration (lead); software (equal); writing original draft (lead); writing review & editing (equal). **Thomas Saunders**: Conceptualization (equal); data curation (equal); investigation (equal); methodology (equal); project administration (supporting); resources (equal). **Alissa McMinn**: Conceptualization (supporting); funding acquisition (supporting); project administration (supporting); writing review & editing (supporting). **Shidan Tosif**: Conceptualization (supporting); data curation (supporting); investigation (supporting); writing review & editing (supporting). **Shivanthan Shanthikumar**: Conceptualization (supporting); writing review & editing (supporting). **Moya Vandeleur**: Conceptualization (supporting); data curation (supporting); writing review & editing (supporting). **Joanne Harrison**: Conceptualization (supporting); data curation (supporting); resources (supporting); writing review & editing (supporting). **David Burgner**: Conceptualization (supporting); writing review & editing (supporting). **Nigel Crawford**: Conceptualization (equal); funding acquisition (equal); supervision (supporting); writing review & editing (supporting).

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