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Date:
2021-12-01

Citation:
Du Berry, C., Saunders, T., McMinn, A., Tosif, S., Shanthikumar, S., Vandeleur, M., Harrison, J., Burgner, D., Ranganathan, S., Crawford, N. & Wurzel, D. (2021). Is cardiorespiratory disease associated with increased susceptibility of SARS-CoV-2 in children?. Pediatric Pulmonology, 56 (12), pp.3664-3668. https://doi.org/10.1002/ppul.25642.

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Is Cardiorespiratory Disease associated with increased susceptibility of SARS-CoV-2 in Children?

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This is the author manuscript accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ppul.25642.

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Key words: SARS-CoV-2, COVID-19, Child, Paediatric lung disease, Asthma, Cardiac

Declaration of interest: All authors state that they have no competing interests to declare.

Abstract

Background

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

Method

Prospective cohort with nested case-control study of all children tested by 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% female, median age 3.5 yrs, range 0.1 to 19.0 yrs) were matched to 391 SARS-CoV-2[-] children (42% female, median age 3.7 yrs, range 0.1 to 18.3 yrs). The commonest co-morbidities 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 amongst children with and without cardiorespiratory comorbidities (n = 12, 75% vs n = 103, 57%, p = 0.35). A high proportion of children hospitalised with SARS-CoV-2 infection had cardiac comorbidities (23.8%).

Conclusions

In this single site dataset, 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 amongst hospitalised children with COVID-19 warranting further research to inform vaccine prioritisation.

Introduction

There are limited data in paediatric 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 prioritisation. 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 paediatric cohort attending a major tertiary paediatric 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.

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 1st February and 31st October 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 was 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 congenital heart disease (CHD) ranging from septal defects to cyanotic congenital heart disease. Respiratory disease

was defined as previously diagnosed asthma, obstructive sleep apnoea (OSA), bronchopulmonary dysplasia (BPD), cystic fibrosis (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 summarise 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, College Station, Texas, USA). Pearson's chi-square 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.

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% female, median age 3.5 yrs). They were matched to 391 SARS-CoV-2[-] children (42% female, median age 3.7 years). Of the children with PCR-confirmed SARS-CoV-2 infection, 16/179 (8.9%) had a previously documented cardiorespiratory co-morbidity. 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%). 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%; $p = 1.0$) were observed between groups. No patient with BPD, CF PCD, ILD, bronchiectasis or neuromuscular weakness presented with SARS-CoV-2 infection. Amongst 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 to 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 to 226 of 391 (57.8%) in the SARS-CoV-2[-] group. Rates of symptomatic infection observed in the SARS-CoV-2[+] cohort were similar amongst children with and without cardiac and/or respiratory comorbidities (60% vs 55.2%, p = 0.879). All asymptomatic infection in the SARS-CoV-2[+] group occurred in children undergoing contact tracing or mandatory testing of international arrivals as part of the state wide public health response.

Approximately one in ten (n=21/179; 11.7%) SARS-CoV-2[+] children were subsequently hospitalised as a result of their infection, with six (28.6%) having a history of any cardiac and/or respiratory disease (4 had CHD requiring previous surgical intervention, 1 had atrial septal defect that did not require surgical intervention as well as asthma and 1 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 hospitalised 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 congenital heart disease), one had paediatric multi-system 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.

Discussion

In this single centre prospective cohort study with nested case-control, similar rates of cardiac and respiratory disease were observed in children infected with SARS-CoV-2 compared to 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 hospitalised children with SARS-CoV-2[+] infection had a history of cardiac disease (23.8%). Recent data suggests that pre-existing cardiac disease in children is associated with hospitalisation, 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 hospitalisation. Cardiac disease was also shown to be associated with ICU admission in a recent European multicentre study [11]. In contrast, whilst asthma was relatively common in the SARS-CoV-2[+] cohort, two (9.5%) children who were hospitalised 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 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 hospitalised 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 analysed responses from 174 Paediatric centres, Moeller et al. also demonstrated low rates of severe COVID-19 illness in asthmatic patients hospitalised with SARS-CoV-2 [13]. Interestingly, despite being a tertiary care centre, 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]. Whilst 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 (table 1) 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 diarrhoea 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 versus 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. Firstly, testing was performed in a single paediatric hospital where healthcare workers and laboratory staff adhere to strict guidelines of sample collection and processing. Second, compared to 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 co-morbidities may have preferentially presented to the RCH over their local testing centre, potentially introducing selection bias. Also, as this was a single centre 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 dataset 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 co-morbidities in paediatric 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 to those without, respiratory diseases had similar rates of symptomatic COVID-19. The high rates of pre-existing cardiac disease observed in hospitalised children with SARS-CoV-2 infection warrants further study.

Funding/Support: This study was supported by Murdoch Children's Research Institute, Centers of Excellence in Influenza Research and Surveillance - Cross-Center Southern Hemisphere Project, The Influenza Complications Alert Network Surveillance System, Paediatric Active Enhanced Disease Surveillance and Sentinel Travelers and Research Preparedness Platform for Emerging Infectious Disease.

References

1. Choi, Y.J., et al., *Effect of Asthma and Asthma Medication on the Prognosis of Patients with COVID-19.* Eur Respir J, 2020.

2. Colombo, C., et al., *Impact of COVID-19 on people with cystic fibrosis.* The Lancet Respiratory Medicine, 2020. **8**(5): p. e35-e36.

3. McClenaghan, E., et al., *The global impact of SARS-CoV-2 in 181 people with cystic fibrosis.* Journal of Cystic Fibrosis, 2020.

4. Green, I., et al., *COVID-19 Susceptibility in Bronchial Asthma.* J Allergy Clin Immunol Pract, 2020.

5. Lu, X., et al., *SARS-CoV-2 Infection in Children.* N Engl J Med, 2020. **382**(17): p. 1663-1665.

6. Castagnoli, R., et al., *Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review.* JAMA Pediatr, 2020. **174**(9): p. 882-889.

7. Patel, N.A., *Pediatric COVID-19: Systematic review of the literature.* Am J Otolaryngol, 2020. **41**(5): p. 102573.

8. Ludvigsson, J.F., *Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults.* Acta Paediatr, 2020. **109**(6): p. 1088-1095.

9. Sanna, G., et al., *Children's heart and COVID-19: Up-to-date evidence in the form of a systematic review.* Eur J Pediatr, 2020. **179**(7): p. 1079-1087.

10. Williams, N., et al., *COVID-19 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review of critically unwell children and the association with underlying comorbidities.* Eur J Pediatr, 2021. **180**(3): p. 689-697.

11. Götzinger, F., et al., *COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study.* The Lancet Child & Adolescent Health, 2020. **4**(9): p. 653-661.

12. Kompaniyets, L., et al., *Underlying Medical Conditions Associated With Severe COVID-19 Illness Among Children.* JAMA Netw Open, 2021. **4**(6): p. e2111182.

13. Moeller, A., et al., *COVID-19 in children with underlying chronic respiratory diseases: survey results from 174 centres.* ERJ Open Res, 2020. **6**(4).

14. AIHW. *Asthma*. 2020 25 Aug 2020 [cited 2021 19 Aug]; Available from: https://www.aihw.gov.au/reports/chronic-respiratory-conditions/asthma/contents/asthma.

15. Sze, S., et al., *Ethnicity and clinical outcomes in COVID-19: A systematic review and meta-analysis.* EClinicalMedicine, 2020. **29**: p. 100630.

16. Chao, J.Y., et al., *Clinical Characteristics and Outcomes of Hospitalized and Critically Ill Children and Adolescents with Coronavirus Disease 2019 at a Tertiary Care Medical Center in New York City.* J Pediatr, 2020. **223**: p. 14-19 e2.

17. Mehta, N.S., et al., *SARS-CoV-2 (COVID-19): What Do We Know About Children? A Systematic Review.* Clin Infect Dis, 2020. **71**(9): p. 2469-2479.

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

Data presented as n, n (%) and median (range)

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
Diarrhoea	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

Data presented as n, n (%) and median (range)