

Comparative Analysis of Symptomatic and Asymptomatic SARS-CoV-2 Infection in Children

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Abstract

Introduction: In this study, a comparison of clinical, epidemiological and laboratory parameters between symptomatic and asymptomatic children with SARS-CoV-2 infection was performed. **Materials and Methods:** Data from all children with laboratory confirmed SARS-CoV-2 infection admitted to KK Women's and Children's Hospital (KKH), Singapore, from January to May 2020 were analysed. **Results:** Of the 39 COVID-19 children included, 38.5% were asymptomatic. Household transmission accounted for 95% of cases. The presenting symptoms of symptomatic children were low-grade fever (54.2%), rhinorrhoea (45.8%), sore throat (25%), diarrhoea (12.5%) and acute olfactory dysfunction (5.4%). Children of Chinese ethnicity (37.5% vs 6.7%), complete blood count (45.8% vs 6.7%) and liver enzyme abnormalities (25% vs 7.7%) were more common in symptomatic versus asymptomatic children. All children had a mild disease course and none required oxygen supplementation or intensive care. **Conclusions:** The high proportion of asymptomatic infected children coupled with household transmission as the main source of paediatric COVID-19 infection underscores the importance of early screening and isolation of children upon detection of an index case of COVID-19 in a household. Symptomatic children were more likely to have abnormal laboratory parameters but they did not have a poorer outcome compared to asymptomatic cases.

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Key words: COVID-19, Paediatric, Pandemic, Singapore

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an enveloped, single-stranded RNA virus that belongs to the betacoronavirus genus which includes 2 other RNA viruses that have caused recent important epidemics: SARS caused by SARS-CoV-1, and Middle East Respiratory Syndrome (MERS) by MERS-CoV. In late December 2019, the first cases of COVID-19 were reported in Wuhan, Hubei Province, China.¹ COVID-19 rapidly spread across the globe,

and the World Health Organization (WHO) declared the SARS-CoV-2 outbreak a pandemic on 11 March 2020.^{2,3} Globally, there are now more than 15 million cases and over 619,000 deaths due to COVID-19.⁴

Singapore confirmed its first case of COVID-19 on 23 January 2020 in a Chinese national from Wuhan, and its first paediatric case on February 4, 2020.^{5,6} As of 24 July 2020, Singapore has reported 49,071 cases of COVID-19.⁷ Singapore initiated a comprehensive surveillance, testing and contact tracing strategy as

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part of its public health response to contain and mitigate the spread of COVID-19.⁸ Close contacts were placed under compulsory quarantine for 14 days, and were assessed by telephone for fever or respiratory symptoms by public health officials during the quarantine period. Contacts who became symptomatic were transferred to a hospital for further evaluation.⁹ From March 2020, as an additional measure for children, all asymptomatic paediatric close contacts of adults with COVID-19 were also screened for SARS-CoV-2 infection via nasopharyngeal (NP) sampling.

Several case series have described COVID-19 in children, the largest from China, with most describing a milder course of illness than in adults.^{2,6,10,11} However, the differences in characteristics between asymptomatic and symptomatic SARS-CoV-2 infection in children have not been well described. A better understanding of this differentiation will provide insight into the transmission dynamics of COVID-19, identify predictors of severity and guide clinical management of children infected with SARS-CoV-2.⁸ In this investigation, we compared the clinical findings, epidemiology and laboratory parameters between symptomatic and asymptomatic paediatric COVID-19 cases.

Materials and Methods

Study Setting and Participants

KK Women's and Children's Hospital (KK Hospital) is the single public specialist women's and children's hospital in Singapore with 830 beds. It is the main isolation hospital for paediatric COVID-19 cases in Singapore. We included all children with confirmed SARS-CoV-2 infection diagnosed via real-time reverse transcriptase-polymerase chain reaction (RT-PCR) from 2 January 2020 to 9 May 2020. Cases were classified as asymptomatic only if they had no clinical signs or symptoms throughout the course of their infection.

Clinical Data Collection

Demographic, clinical and laboratory data from electronic health records of children with SARS-CoV-2 infection were collected using a standardised data collection form. All cases were confirmed via RT-PCR test of nasopharyngeal (NP) samples.¹² The hospital has in place a standardised protocol for the clinical management of all confirmed COVID-19 cases. Complete blood counts (CBC) and liver enzymes were performed as part of standard of care. Blood samples

for SARS-CoV-2 RT-PCR were also obtained during admission. Stool and urine samples were taken for a subset of cases mainly during the early phases of the epidemic but these were subsequently discontinued. NP samples for respiratory pathogens by multiplex PCR (BioFire FilmArray RP2 Panel, Salt Lake City, UT, USA), serum samples for C-reactive protein (CRP), procalcitonin and blood cultures were collected based on clinical indication. Chest radiographs (CXR) were performed if there was a clinical suspicion of pneumonia. Children were discharged from hospital when they had negative SARS-CoV-2 PCR results from NP samples on 2 consecutive days.¹³

The study was approved by the institutional ethics review board. Written informed consent was waived in light of the need to inform public health outbreak control policies.

Data and Statistical Analysis

SPSS statistical software (version 23; IBM, Armonk, NY, USA) was used for statistical analysis. Continuous variables were expressed as mean if normally distributed. For categorical clinical and demographic variables, differences between groups were evaluated using the chi-square test or Fisher's exact test when appropriate. The independent student t-test was applied for comparisons involving scale variables. A *P*-value of *P* < 0.05 was considered statistically significant. We also performed age-stratified analysis using 3 age categories: 0–4 years, 5–9 years, 10–16 years.

Results

Clinical and Epidemiological Features

39 children with laboratory confirmed SARS-CoV-2 infection were admitted for isolation between 2 January 2020 and 9 May 2020. This represented approximately 70% of all paediatric cases detected in Singapore.¹⁴ Household transmission accounted for 95% of cases in our cohort (Table 1). The most common symptoms associated with COVID-19 in children were fever (54.2%), rhinorrhoea (45.8%), sore throat (25%) and cough (16.7%) (Table 1). The mean maximum recorded temperature amongst children with a fever was 38.6°C (range 38.0–41.0°C), and the mean total duration of fever was 2.6 days (range 1–6 days). Three children (12.5%) had diarrhoea as part of their clinical manifestation. In addition, two children (5.4%) aged 11 and 14 years also reported loss or reduced sense of smell and taste followed by fever as their only symptoms. This lasted until day 10 of illness

for one and continued until discharge (day 17 of illness) for the other. None of the children reported shortness of breath or chest discomfort, and none developed tachypnoea, tachycardia, hypotension or signs suggestive of Kawasaki disease during their illness.

Of the 39 paediatric cases, 19 (49%) were asymptomatic at presentation, 18 (95%) of whom were detected via testing of asymptomatic household contacts of adults with COVID-19. Subsequently, 4 of the 19 children developed symptoms during admission and hence the proportion who remained

asymptomatic throughout their course of illness was 38.5% (15/39). The mean ages of symptomatic and asymptomatic cases were 7.8 and 8.3 years respectively ($P = 0.67$) (Table 1). Similarly, there was a larger proportion of symptomatic children from 0–4 years of age (75%) as compared to older children (53% in children 5–9 years and 64% in children 10–16 years) (Table 1), but this was not statistically significant ($P = 0.55$). Children of Chinese ethnicity were most common in symptomatic COVID-19 children (37.5%), and children of Indian ethnicity were most common

Table 1. Demographic and Clinical Features of Symptomatic and Asymptomatic Children with SARS-CoV-2 Infection

Characteristic	Symptomatic	Asymptomatic	Total	P-value
Number, n (%)	24 (61.5)	15 (38.5)	39	
Mean age (years)	7.8	8.3		0.67
0–4 years	6 (75)	2 (25)	8 (20.5)	0.55
5–9 years	9 (52.9)	8 (47)	17 (43.5)	
10–16 years	9 (64.3)	5 (35.7)	14 (35.9)	
Males, n (%)	15 (62.5)	8 (53.3)	23 (60)	0.74
Ethnicity, n (%)				0.08
Chinese	9 (37.5)	1 (6.7)	10 (25.6)	
Malay	6 (25.0)	5 (33.3)	11 (28.2)	
Indian	4 (16.7)	7 (46.7)	11 (28.2)	
Others	5 (20.8)	2 (13.3)	7 (17.9)	
Comorbidities present, n (%)	9 (37.5)	1 (6.7)		0.06
Index is positive family member, n (%)	22 (91.7)	15 (100)	37 (94.9)	0.37
Father	10 (41.7)	5 (33.3)	14 (35.9)	
Mother	4 (16.7)	7 (46.7)	10 (25.6)	
Grandmother	3 (12.5)	1 (6.7)	4 (10.2)	
Older sibling	1 (4.2)	0	1 (2.6)	
More than 1 family member	4 (16.7)	2 (13.3)	6 (15.4)	
Presenting symptoms, n (%)				
Fever	13 (54.2)			
Blocked nose or rhinorrhoea	11 (45.8)			
Sore throat	6 (25)			
Cough	4 (16.7)			
Sneezing	3 (12.5)			
Loose stools	3 (12.5)			
Anosmia or hyposmia	2 (5.4)			

amongst asymptomatic children (46.7%), but the differences were not statistically significant ($P = 0.08$). Comorbidities were more likely to be present in symptomatic COVID-19 cases compared to asymptomatic (37.5% vs 6.7%, $P = 0.06$). The most common comorbidities included asthma (30%), epilepsy (20%), and hypothyroidism (20%).

Laboratory Parameters, Clinical Investigations and Outcomes

Abnormalities in CBC and liver enzymes were more frequently detected on admission in symptomatic children (Table 2). On admission, 11 of 24 (45.8%) symptomatic cases had at least an abnormal white blood cell or platelet count versus 1 of 15 (6.7%) asymptomatic cases ($P = 0.01$). Neutropenia for

age (25%) followed by leukopenia for age (12.5%) were the most common CBC abnormalities detected amongst symptomatic cases. The only abnormal CBC parameter detected in asymptomatic cases was neutropenia, which was detected in 1 patient. The proportion of cases with abnormal liver enzymes was similarly higher in symptomatic cases compared to asymptomatic cases (25% versus 7.7% respectively, $P = 0.22$). A raised alanine transaminase (ALT) level was the most likely abnormal liver enzyme especially amongst symptomatic cases (29.2%). Both mean ALT and aspartate transaminase (AST) were higher in symptomatic children (22.6 and 31.2 U/L respectively) compared to that in asymptomatic children (15.8 and 25.6 U/L respectively) (Table 2). All haematological and liver enzyme abnormalities detected in this cohort

Table 2. Laboratory Features and Investigations of Symptomatic and Asymptomatic Children with SARS-CoV-2 Infection

Characteristic	Symptomatic	Asymptomatic	Total	P-value
Number, n (%)	24 (61.5)	15 (38.5)	39	
Initial CBC, n (%)				
Leukopenia for age	3 (12.5)	0		0.27
Thrombocytopenia	2 (8.3)	0		0.51
Neutropenia for age	6 (25)	1 (6.7)		0.22
Lymphopenia for age	2 (8.3)	0		0.51
Lymphocytosis for age	2 (8.3)	0		0.51
Liver enzymes				
Raised ALT for age, n (%)	7 (29.2)	1 (6.7)		0.12
Mean ALT, U/L (range)	22.6 (10–60)	15.8 (9–34)		0.07
Raised AST for age, n (%)	1 (4.2)	0		
Mean AST, U/L (range)	31.2 (16–62)	25.6 (16–43)		0.14
Stool for SARS-CoV-2 RT-PCR, n (%)				
Patients with test performed	9 (37.5)	4 (26.7)	13 (33.3)	
No. with positive stool	7 (77.8)	3 (75)	10 (76.9)	0.42
Mean day of illness / infection of last positive stool (range)	13.5 (10–21)	9.7 (9–10)		0.3
Respiratory multiplex PCR* n (%)				
Test performed	21 (87.5)	7 (46.7)	28 (71.7)	
Positive for other pathogens	0	2 (13.3)		0.06

ALT: Alanine transaminase; AST: Aspartate transaminase; CBC: Complete blood count; PCR: Polymerase chain reaction; RT-PCR: Real-time polymerase chain reaction; WBC: White blood cell count.

*FilmArray RP2 Panel (BioFire, Salt Lake City, UT, USA)

of paediatric COVID-19 cases resolved by day 29 and day 18 of illness respectively.

Thirty-five children (89.7%) had blood tested for SARS-CoV-2 RT-PCR, of whom only 1 (2.6%) returned positive.⁶ Of 39 children with SARS-CoV-2 infection, 13 (33.3%) had stool tested for SARS-CoV-2 RT-PCR with a positivity rate of 76.9% (10/13) (Table 2). Symptomatic children also had a longer duration of viral shedding in stool compared to asymptomatic children (mean 13.5 days and 9.7 days respectively), though this was not statistically significant ($P = 0.3$) (Table 2). Six children (15.4%) had urine tested for SARS-CoV-2 RT-PCR, and all results were negative.

Twenty-eight children (71.8%) had NP samples screened via multiplex PCR for other respiratory pathogens (Table 2). Only 2 were positive for alternative pathogens (rhinovirus/enterovirus and respiratory syncytial virus) and both cases were asymptomatic. CRP was determined in 5 of 24 (20.8%) symptomatic children for the main indication of significant temperature during admission, with a mean value of 2.4 mg/L. Only one child had an abnormal CRP value of 8.2 mg/L. Of the 4 children who had a CXR performed during admission, 3 were normal and 1 showed perihilar infiltrates.

All children received supportive care and symptomatic treatment, including antipyretics and antihistamines. None required oxygen supplementation or ventilatory support, and none received antiviral therapy, interferon, or corticosteroids. All 39 children were discharged well from hospital, with a mean length of stay of 15 days (standard deviation 6.5 days, range 3–30 days).

Discussion

The proportion of symptomatic and asymptomatic paediatric COVID-19 cases was 61.5% and 38.5% respectively in our cohort. We found that children of Chinese ethnicity (37.5%) were more likely to present with COVID-19 symptoms while Indian children were more likely to be asymptomatic (46.7%), but these differences were not statistically significant. More data and research are needed to ascertain if there are differences in response to SARS-CoV-2 due to host genetic variations. The main presenting symptoms of symptomatic children in our case series were low-grade fever (54.2%), rhinorrhoea (45.8%), sore throat (25%), and diarrhoea (12.5%). We also noted acute olfactory

dysfunction (anosmia or hyposmia) and dysgeusia as presenting symptoms in 2 (5.4%) children. We did not observe major differences in clinical outcome between COVID-19 children with symptoms and those without.

The proportion of asymptomatic children with laboratory-confirmed SARS-CoV-2 infection in the paediatric literature ranged from 12.9%–28% , lower than that reported in our cohort (38.5%).^{11,15,16} Our data may provide a more accurate estimate of the population asymptomatic rate in children due to the comprehensive surveillance, contact tracing and testing of exposed children regardless of symptom status as part of Singapore's public health control strategy. Although the infectivity of asymptomatic children is poorly understood, transmission from pre-symptomatic and asymptomatic adults has been described.^{17, 18} We noted a higher proportion of symptomatic cases in the 0–4 years age category, in contrast to the closer proportions reported in the older age categories (75% symptomatic in 0–4 years versus 52.9% in 5–9 years and 64.3% in 10–16 years) (Table 1).

Paediatric studies from China found that household transmission accounted for 70–100% of cases.^{19,20} Similarly, in our series, we found that family members were the main source of infection for children (95%). The high proportion of asymptomatic children infected by household members underscores the importance of early screening and isolation of children upon detection of an index case of COVID-19 in a household.^{21,22} In settings where testing capabilities may be limited, it might be useful to isolate or quarantine all paediatric household contacts regardless of presence of symptoms once a confirmed COVID-19 case is detected to curb further community transmission of SARS-CoV-2.²³ The proportion of asymptomatic infected individuals in mixed adult and paediatric studies varies greatly from 1–43%.^{2,24} The estimated proportion of asymptomatic infections is a key parameter in epidemiological modelling studies currently used to inform public health strategy.²⁵ There may be a need to incorporate age-stratified estimates of asymptomatic infection into modelling studies to provide more accurate estimates.^{8,26–28}

The reported symptoms in our cohort were similar to that reported in other paediatric case series, where the most common presenting symptoms were also fever (36–41%), cough (19–48.5%), sore throat (36–46.2%), and diarrhoea (8.8%).^{11,15,29} However, the proportion of children reporting cough in our cohort was much lower

(16.7%). The reason for this is unclear but it could be the result of our limited sample size. Acute olfactory dysfunction (anosmia or hyposmia) and dysgeusia have been identified as early symptoms of SARS-CoV-2 infection in adults.³⁰ Two children in our cohort reported these symptoms and this proportion is at the lower end of the range reported in adult COVID-19 cases (5.1–85.6%).³¹ For one of our cases, hyposmia was the only presenting complaint at presentation. Therefore, it will be useful to include loss of smell or taste in screening criteria for paediatric COVID-19 cases as per adults. Presence of symptoms did not influence the outcome or treatment required, and all children in our cohort had a mild course of illness. Children have been noted to have a milder course of illness compared to adults, similar to paediatric MERS and SARS disease.^{10,32–35} However, recent reports of Kawasaki-like disease and multisystem inflammatory syndrome in children (MIS-C) from Europe and USA described in children with asymptomatic or mildly symptomatic SARS-CoV-2 infection is worrying.³⁶ To date, no such reports have been identified in Asia. At the time of writing, children with COVID-19 in this cohort were well at follow-up, and have not been admitted to our institution for symptoms suggestive of Kawasaki disease or MIS-C after their initial discharge.

The majority of haematological and liver enzyme abnormalities were observed amongst symptomatic children, and almost all asymptomatic children (except 1 child) had normal laboratory parameters. This suggests that infection may be localised to the nasopharynx and systemic involvement was absent in asymptomatic children. Leukopenia and neutropenia were the most common haematological abnormalities in this paediatric cohort (7.7% and 18% respectively). These abnormalities were consistent with that reported in other paediatric studies, and normalised on repeat testing.³⁷ Alternative pathogens in NP samples were detected in 2 asymptomatic children. Unlike previous paediatric case series which described a more severe course of illness in children with SARS-CoV-2 and co-infections with other respiratory viruses, our patients remained asymptomatic and clinically well.^{38,39} More studies are required to determine how co-infections with other respiratory viruses influence severity of illness in children with COVID-19.

The poor yield of blood and urine for SARS-CoV-2 by PCR has been described previously.^{39,40} Of the 35 children in this case series who had blood tested for SARS-CoV-2 by RT-PCR, only one infant was

positive. Viremia in the infant did not result in more severe clinical manifestation as the infant remained clinically well apart from one fever spike during the course of the illness.⁶ The stool SARS-CoV-2 RT-PCR positivity rate of 77% in our cohort was close to the 80–100% reported in other paediatric studies.^{19,41,42} In our cohort, stool positivity was detected up to 21 days of illness with longer duration noted in symptomatic cases. Persistent fecal detection of SARS-CoV-2 by RT-PCR after consecutive negative NP samples has been described, with viral detection in stool reported as late as day 33 of illness.^{19,40,43} Until more information is available on the viral replicability of SARS-CoV-2 isolated from stool in the late course of illness, quarantine and infection control measures should take into consideration the late shedding of SARS-CoV-2 in stool of children regardless of presence of symptoms, especially in young children and those with special needs who require caregivers to handle toileting requirements.

The major limitation of this study was its limited sample size. However, our cohort was based on a standardised national public health surveillance and comprehensive contact tracing strategy to actively identify cases, and represented 70% of all paediatric cases detected in Singapore. SARS-CoV-2 testing was performed using pre-determined case definitions for suspect cases.⁹ Furthermore, our protocol to proactively test all paediatric household contacts independent of symptom status provided a more accurate rate for asymptomatic cases in children. We also utilised a standardised clinical management and basic blood parameter testing protocol for all our admitted cases.

Conclusion

Household transmission remains a major mode of transmission of SARS-CoV-2 infection in the paediatric population. A significant proportion (38.5%) of paediatric patients with SARS-CoV-2 infection remain asymptomatic, with minimal evidence of systemic involvement. The high proportion of asymptomatic infected children coupled with household transmission as the main source of paediatric COVID-19 infection underscores the importance of early screening and isolation of children upon detection of an index case of COVID-19 in a household. Although symptomatic children were more likely to have abnormal laboratory parameters, they did not have a poorer outcome compared to asymptomatic children, and all children in our cohort recovered from SARS-CoV-2 infection.

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