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A Comparison Between Chinese Children Infected with COVID-19 and with SARS

Xiaoli Xiong, MD, Gilbert T. Chua, MBBS, FHKAM(Paed), Shuiqing Chi, MD, Mike Yat Wah Kwan, MSc(Applied Epidemiology) CUHK, FHKAM(Paed), Wilfred Hing Sang Wong, PhD, Aifen Zhou, MD, Chi Chiu Shek, FHKAM(Paed), FRCPCH, Keith TS. Tung, MPH, Huan Qin, MMSc, Rosa S. Wong, PhD, Xue Li, PhD, Peng Chen, MBBS, Shuai Li, MD, Celine S. Chui, PhD, Winnie WY. Tso, MBBS, BSc(Hons), Marco HK. Ho, MD, FRCP, Ian CK. Wong, PhD, FRCPCH(Hon), Godfrey CF. Chan, MD, FRCPCH (UK), Yu Lung Lau, MD (Hon), FRCPCH, Kenneth KY. Wong, PhD(Lond), FRCS(Edin), Patrick HY. Chung, MS(HK), FRCSEd(Paed), Hui Li, Paul KH. Tam, FRCS(Eng, Edin, Glas, and Ire), FRCPCH, Shao-tao Tang, MD, Patrick Ip, MPH, FRCPCH(UK)

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A Comparison Between Chinese Children Infected with COVID-19 and with SARS

Authors

Xiaoli Xiong[1¶], MD, Gilbert T Chua[2¶], MBBS, FHKAM(Paed), Shuiqing Chi[3], MD, Mike Yat Wah Kwan[4], MSc(Applied Epidemiology) CUHK, FHKAM(Paed), Wilfred Hing Sang Wong[2], PhD, Aifen Zhou[5], MD, Chi Chiu Shek[4], FHKAM(Paed), FRCPCH, Keith TS Tung[2], MPH, Huan Qin[6], MMSc, Rosa S Wong[2], PhD, Xue Li[2,7], PhD, Peng Chen[8], MBBS, Shuai Li[3], MD, Celine S Chui[2,7], PhD, Winnie WY Tso[2], MBBS, BSc(Hons), Marco HK Ho[2], MD, FRCP, Ian CK Wong[7,9], PhD, FRCPCH(Hon), Godfrey CF Chan[2], MD, FRCPCH (UK), Yu Lung Lau[2], MD (Hon), FRCPCH, Kenneth KY Wong[10], PhD(Lond), FRCS(Edin), Patrick HY Chung[10], MS(HK), FRCSEd(Paed), Hui Li[11], Paul KH Tam[10,12], FRCS(Eng, Edin, Glas, and Ire), FRCPCH, Shao-tao Tang[3], MD, Patrick lp, MPH, FRCPCH(UK)[2]

[¶] Contributed equally

Affiliations

1. Department of Integrated Chinese and Western Medicine, Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
2. Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong SAR, China
3. Department of Pediatric Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
4. Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital, Hong Kong SAR, China
5. Department of Maternal Healthcare, Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

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6. Institute of Maternal and Child Health, Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China,
7. Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong SAR, China
8. Department of Respiratory Medicine, Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
9. Research Department of Practice and Policy, UCL School of Pharmacy, University College, London, United Kingdom
10. Division of Paediatric Surgery, Department of Surgery, The University of Hong Kong, Hong Kong SAR, China
11. Department of Hematology, Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
12. Dr. Li Dak Sum Research Centre, The University of Hong Kong-Karolinska Institutet Collaboration in Regenerative Medicine, The University of Hong Kong

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Contact Information of Corresponding Author

Dr. Patrick Ip

Clinical Associate Professor

Department of Paediatrics and Adolescent Medicine

The University of Hong Kong

Hong Kong SAR

Tel: (852) 2255-4090

Fax: (852) 2855-1523

Email: patricip@hku.hk

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Objectives

To compare the clinical and laboratory features of severe acute respiratory syndrome 2003 (SARS) and coronavirus disease 2019 (COVID-19) in two Chinese pediatric cohorts, given that the causative pathogens and are biologically similar.,

Study design

This is a cross-sectional study reviewing paediatric patients with SARS (n = 43) and COVID-19 (n=244) who were admitted to the Princess Margaret Hospital in Hong Kong and Wuhan Children's Hospital in Wuhan, respectively. Demographics, hospital length of stay, clinical and laboratory features were compared

Results

Overall, 97.7% of patients with SARS and 85.2% of patients with COVID-19 had epidemiological associations with known cases. Significantly more patients with SARS developed fever, chills, myalgia, malaise, coryza, sore throat, sputum production, nausea, headache, and dizziness than patients COVID-19. No SARS patients were asymptomatic at the time of admission. 29.1% and 20.9% COVID-19 patients were asymptomatic on admission and throughout their hospital stay, respectively. More SARS patients required oxygen supplementation than COVID-19 patients (18.6 vs. 4.7%, *P* = .004). Only 1.6% COVID-19 and 2.3% SARS patients required mechanical ventilation. Leukopenia (37.2% vs. 18.6%, p=0.008), lymphopenia (95.4% versus 32.6%, p<0.01), and thrombocytopenia (41.9% vs 3.8%, p<0.001) were significantly more common in SARS than COVID-19 patients. The duration between positive and negative nasopharyngeal aspirate and the length in

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hospital stay were similar in COVID-19 patients regardless of whether they were asymptomatic or symptomatic, suggesting a similar duration of viral shedding.

Conclusions

Children with COVID-19 were less symptomatic and had more favorable hematological findings than children with SARS.

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The outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China in December 2019. Subsequently, more patients with COVID19 were diagnosed in other parts of Mainland China, nearby regions and countries in Asia and beyond. It was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. [1] The first severe acute respiratory syndrome (SARS) patient was reported in Mainland China in 2003, and subsequently other COVID-19 patients were diagnosed in other parts of the world. Significantly fewer people were affected by SARS-CoV within the 6-month epidemic, and only 8096 cases and 774 deaths were reported worldwide.[2] There have been no known reported cases of SARS since 2004.

Both SARS-CoV and SARS-CoV-2 belong to the *betacoronavirus* genus and are phylogenetically related to bat SARS-like coronavirus, but relatively more distantly to MERS-CoV. Both SARS-CoV and SARS-CoV-2 share 79% genetic similarity[3]. They also share similar infection pathophysiology in humans, as they both bind to the same human receptor, angiotensin-converting enzyme 2 (ACE2), for entry into host cells. However, SARS-CoV-2 has higher transmissibility, with a higher reproductive number (R_0) of 2-2.5 compared with 1.7-1.9 for SARS-CoV.[4] Studies from Wuhan describing the clinical characteristics of 171 COVID-19 children showed that 15.8% of patients in their cohort were asymptomatic carriers, and only one patient required intensive care with ventilator support.[5] In contrast, previous studies summarizing the clinical characteristics of pediatric SARS patients showed they were almost all symptomatic.[4] A serological study showed that asymptomatic SARS cases in children was rare.[6] Furthermore, compared with other coronavirus infections that cause milder diseases, both SARS and COVID-19 have significantly higher morbidity and mortality.[7] Nevertheless, studies providing a direct comparison of clinical and laboratory features between children infected with SARS and COVID-19 are lacking. In this study, we investigated the clinical and laboratory features in two representative Chinese pediatric cohorts with SARS and COVID-19. Understanding the differences and similarities in the clinical phenotypes and laboratory measures in pediatric

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patients with SARS and COVID-19 will guide us in the identification, quarantine, and management of infected children in a timely manner.

Methods

This was a comparative study examining the clinical and laboratory features of Chinese children (aged ≤18 years at admission) with SARS in Hong Kong and COVID-19 in Wuhan, China. In Hong Kong, pediatric patients diagnosed with SARS and admitted to Princess Margaret Hospital (PMH) from March 1 to April 30, 2003 were included in the study. Princess Margaret Hospital is a key public hospital that served as the major center for managing SARS patients in Hong Kong at the beginning of the SARS-CoV outbreak in 2003. Over one-third (36%) of pediatric SARS patients in Hong Kong were admitted and managed in PMH. The case definitions and clinical characteristics have been previously published in a peer-reviewed journal.[8] In Wuhan, pediatric patients who tested positive for SARS-CoV-2, as confirmed by nasopharyngeal aspirate (NPA) specimen using a reverse-transcriptase polymerase chain reaction (RT-PCR) test, and who were admitted to the Wuhan Children's Hospital between January 21 and March 20, 2020 were included in this study. The Wuhan Children's Hospital is the main center assigned by the central government for treating children diagnosed with SARS-CoV-2 infection in Wuhan.[5] Children in both cohorts were tested if symptomatic, or if in contact with a confirmed SARS or COVID-19 case. Those with a positive test were hospitalized regardless of symptoms. Those with SARS or SARS-CoV-2 infection are referred to as SARS or COVID-19 cases respectively, regardless of symptoms. Hospital records and laboratory results from both SARS and COVID-19 cohorts were retrieved and analyzed. Demographics, clinical symptoms, days between positive and negative NPA, length of stay (LOS) in hospital, need for oxygen and mechanical ventilation, and laboratory tests were compared between the two cohorts. Duration between positive and negative NPA was defined as the time between the first SARS-CoV-2 positive NPA specimen and the first of two consecutive NPA negative specimens. Asymptomatic

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patients were defined in Wuhan as no clinical symptoms and no abnormal computed tomography (CT) findings, as all COVID-19 patients received CT scan of the thorax prior transferral or after admission to the Wuhan Children's Hospital.[9] Both COVID-19 and SARS patients were discharged after resolution of the clinical symptoms and after receiving two consecutive negative NPA tests for SARS-CoV-2 and SARS-CoV, respectively. SARS patients were also mandated to stay in the hospital for 21 days from symptoms onset.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) and analysed by independent t-test or Mann-Whitney U test where appropriate. Categorical variables for SARS, symptomatic COVID-19, and asymptomatic COVID-19 groups were expressed as number (%) and analysed by Chi-square test, Fisher exact test, or ANOVA. Age- and sex-matched references from Chinese children were used for comparing blood measures. A two-sided α of <0.05 was considered statistically significant. Patients with missing data will not be analysed for the particular variables. Statistical analyses were performed using SPSS software version 19 (Armonk, New York, USA), Microsoft Excel® (Microsoft, Redmond, Washington, USA), and Statistical Analysis System® v9.4 (SAS Institute Inc., Cary, NC).

Ethics

The study protocol was approved by the University of Hong Kong/Hospital Authority Hong Kong West Cluster Institutional Review Board (Reference number: UW 20-292) and the Research Ethics Board of the Wuhan Children's Hospital (Reference number: WHCH 2020022).

Results

Patient demographics

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A total of 43 SARS and 244 COVID-19 pediatric patients were recruited into the study. Demographic and clinical characteristics are shown in Table I. The median age of the COVID-19 cohort was 82 months and the SARS cohort was 160.8 months (Figure 1). There were a total of 85 (34.8%) asymptomatic COVID-19 patients compared with no asymptomatic SARS patients at presentation ($p<0.001$). Among asymptomatic COVID-19 patients, 94.1% (48/51) had family members with COVID-19, and were identified by screening after family members had been confirmed positive. Among the 85 clinically asymptomatic COVID-19 patients at presentation, 34 of them were considered symptomatic by definition after admission. 26.5% (9/34) developed clinical symptoms including cough, nasal congestion, vomiting, diarrhea, poor feeding. 73.5% (25/34) of symptomatic patients were found to have mild abnormalities on CT imaging, including ground glass opacities and pneumonic changes; only one patient had both clinical symptoms and CT abnormalities.

Overall, 97.7% (42/43) SARS and 85.2% (208/242) COVID-19 cases had identifiable epidemiologic links in known cases. In the COVID-19 cohort, a 10-month-old boy died of intussusception and multi-organ failure, which has been reported elsewhere.[5] No mortality was reported in the SARS cohort. There were no significant differences in the time from positive to negative NPA between symptomatic and asymptomatic COVID-19 groups (mean 8.2 days versus 8.9 days, $p=0.434$). There were also no significant differences in the LOS in hospital between symptomatic and asymptomatic COVID-19 patients (mean 13.0 days versus 11.4 days, $p=0.066$), but the LOS in the SARS cohort (all symptomatic) was significantly longer than in the symptomatic COVID-19 cohort (mean 20.6 days versus 12.9 days, $p<0.001$).

Clinical Symptoms

Comparison of symptoms between the SARS and COVID-19 cohorts are presented in Table 1 and Figure 2. Compared with COVID-19 patients, significantly more SARS patients developed fever ($p<0.001$), chills ($p<0.001$), myalgia ($p<0.001$), malaise ($p<0.001$), coryza ($p<0.001$), sore throat ($p=0.019$), sputum production ($p<0.001$), nausea ($p=0.015$), headache ($p<0.001$), and dizziness

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(p=0.006). Almost all SARS patients developed fever compared with only 51.3% of COVID-19 patients. Cough symptoms occurred similarly in both cohorts. More SARS patients required oxygen supplementation than COVID-19 patients (18.6% versus 4.7%, p=0.004), whereas only 1.6% and 2.3% of COVID-19 and SARS patients required mechanical ventilatory support, respectively.

Laboratory Test Results

Laboratory testing results for SARS and symptomatic COVID-19 patients are presented in Table 2. SARS patients had significantly lower total white blood cell count (p=0.043), lymphocyte count (p<0.001), and platelet (p<0.001) count, and lower albumin (p<0.001), higher globulin (p<0.001), higher ALT (p=0.01), and lower D-Dimer (p<0.001) levels. We further explored the number of children with leukopenia, lymphopenia and thrombocytopenia using age- and sex-matched reference ranges for Chinese and Asian children.[10-12] Leukopenia (37.2% versus 18.6%, p=0.008), lymphopenia (95.4% versus 32.6%, p<0.01), and thrombocytopenia (41.9% versus 3.8%, p<0.001) were significantly more common in SARS than in COVID-19 patients. The laboratory test results for the asymptomatic COVID-19 patients were normal.

Discussion

In our study of Chinese children infected with COVID-19 and SARS in representative paediatric cohorts from Wuhan and Hong Kong. COVID-19 patients experienced fewer symptoms than SARS patients. Almost all SARS patients presented with fever compared with only half of COVID-19 patients, which suggests screening by body temperature will potentially miss half of the children infected with COVID-19. Although a similar percentage of patients in both cohorts had a cough, significantly more SARS patients had other symptoms including fever and respiratory difficulties.[8 13] A study comparing the replication, cell tropism, and immune activation profile of SARS-CoV-2 and SARS-CoV infections in human lung tissue showed that SARS-CoV-2 infection generated 3.2 times more virus particles, yet induced significantly less type I, II, and III interferons and other pro-inflammatory cytokines,[14] which might explain the relatively milder phenotype in COVID-19.

Only a few children in both cohorts required oxygen therapy and mechanical ventilation. In contrast to adult patients, our results echo that children infected by either SARS-CoV-2 or SARS-CoV had a good prognosis.[15 16] Indeed, studies have shown that a higher percentage of older adults with COVID-19 develop complications including pneumonia, acute myocardial injury, and acute respiratory distress syndrome, with an overall mortality of up to 11% in some populations.[17] Similar observations were reported during the SARS-CoV epidemic in 2003, which had 7% and 17% mortality in Mainland China and Hong Kong, respectively.[2] The majority of the patients who died from SARS and COVID-19 were older patients with underlying chronic illnesses or who were immunocompromised.[18] A study comparing published data in the literature also concurred with our findings that SARS and COVID-19 infected children had favorable outcomes.[19] One possible explanation why children are less affected by both SARS and COVID-19 is the different expressions of ACE2 in children and adults. The ACE2 receptor is crucial for both SARS-CoV and SARS-CoV-2 to enter into host cells.[20] It has been demonstrated that ACE2 expression can influence the infectivity of SARS-CoV in vitro.[21] Nevertheless, studies demonstrating age variation of ACE2 expression currently are lacking.

Our study also showed there were significantly more asymptomatic carriers in the pediatric COVID-19 group, but none in the paediatric SARS group. This finding was consistent with studies in adults with SARS, which found only a few asymptomatic adults or healthcare workers who tested antibody-positive after the epidemic,[22] or had only mild and self-limiting symptoms.[23] To the contrary, asymptomatic COVID-19 infections were reported to be common among adults and younger adults without co-morbidities.[24] Asymptomatic transmission of SARS-CoV-2 may be one of the key factors leading to the pandemic.[25] In our study, the average time to achieve a negative NPA and hospital LOS were similar for symptomatic and asymptomatic COVID-19 patients, which indicates that clearance of COVID-19 virus may be similar for symptomatic and asymptomatic patients. A difficulty in concluding this is that dating of the first specimen at the onset in symptomatic patients cannot be replicated in asymptomatic patients. Although we found the LOS in hospital for the SARS cohort was

significantly longer than that for the symptomatic COVID-19 cohort (20.6 days versus 11.4 days, p<0.001), a difference in the isolation policy between the two outbreaks likely confounded this observation. In the SARS outbreak in 2003, the mandatory hospitalization for patients was 21 days from symptoms onset in addition to a negative NPA and resolution of symptoms. More importantly, our study also revealed that 35.6% of children infected with SARS-CoV-2 were asymptomatic on admission and 14.9% of them subsequently became symptomatic. These asymptomatic patients are still carriers of the virus and have the potential to spread the disease to others leading to further burdens on public health systems. Public health measures such as the universal use of facemasks, social distancing, early quarantine, and identification and tracing of asymptomatic carriers of COVID-19 have already been widely adopted in places with less severe outbreak such as Hong Kong, Macau, and Taiwan. Studies have shown that frequent and proper use of facemasks in public areas was associated with a 60% lower risk of contracting SARS-CoV compared with infrequent use during the SARS outbreak in 2003.[26] Repeated RT-PCR testing for SARS-CoV-2 should also be performed in those highly suspected of infection where there is an initial possible false-negative result. Given the evidence of a significant proportion of asymptomatic COVID-19 carriers and experience from Asia, strict preventive measures should be enacted to control the spread of COVID-19.

We found that the COVID-19 cohort had more favorable hematologic and biochemical findings, with fewer COVID-19 patients having abnormal test results compared with SARS patients. The mean total white blood cell, lymphocyte, and median platelet counts in SARS patients were all significantly lower than in COVID-19 patients. Potential mechanisms include direct infection of haematopoietic progenitor cells via cell surface CD13 or CD66a that possibly induces growth inhibition and apoptosis.[27] Although the COVID-19 cohort was significantly younger than the SARS cohort, significantly fewer children in the COVID-19 cohort had hematological abnormalities when using age- and sex-matched references. Lymphopenia was observed during the early phase of the SARS epidemic,[28] predominantly CD4+ and CD8+ lymphopenia,[29] and adult SARS-CoV patients who were clinically more severe or died had significantly more severe CD4+ and CD8+ lymphopenia. In COVID-

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19 infection, the degree of lymphopenia was reported to be a prognostic indicator for older patients.[30] The significantly lower proportion of pediatric COVID-19 patients with lymphopenia may explain the milder phenotype compared with the SARS group.

This study had several limitations. First, this was retrospective observational study design, which may have potential recall or sampling bias. Nevertheless, the majority of COVID-19 children under the age of 18 in Wuhan were admitted to the Wuhan Children's Hospital, whereas the majority SARS pediatric patients in Hong Kong were admitted to PMH. Wuhan and Hong Kong were among the most seriously affected cities in the COVID-19 and SARS outbreaks, respectively. Therefore, they are representative pediatric cohorts for these two infections. Second, not all family contacts of SARS cases were tested in 2003. Nevertheless, in the study conducted by Lee et al, only 0.57% of asymptomatic children from the Amoy Garden were positive for SARS-CoV antibody. None of the 14 asymptomatic children who had contacts with SARS patients were seropositive.[6] The Amoy Garden was one of the housing estates in Hong Kong with major community outbreak. It was also where the majority of the SARS-infected children in this cohort were recruited. Therefore, despite the lack of close contact screening in 2003, SARS asymptomatic carriage was considered to be rare. Third, younger COVID-19 patients may not be able to describe their subjective symptoms, such as anosmia that is considered a novel symptom of COVID-19,[31] which may lead to under-reporting of these symptoms. Fourth, CT and other radiologic findings were not reported in details as the majority of the SARS patients did not have CT performed and therefore was considered out of the scope of this manuscript. Radiologic findings of some of the patients from Wuhan's Children Hospital have been reported elsewhere.[9] Fifth, a recent phylogenetic network study showed that the predominant SARS-CoV-2 variant (type B) in East Asia is genetically different from the variants in Europe and America (type A and C). Whether such differences lead to different clinical characteristics between Asia and the West remains uncertain, and one must be cautious in extrapolating clinical characteristics of COVID-19 in Asia to other geographic areas.[32] Finally, we did not observe any children developing Kawasaki-like hyperinflammatory shock that was reported in European COVID-

19 children in our Chinese cohort.[33 34] Future studies combining and comparing data from international clinical centers will be meaningful to examine the demographics and clinical spectrum of pediatric COVID-19 patients on a global perspective, and to further identify the risk factors for these severe diseases.

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List of Abbreviations

ACE2 – angiotensin-converting enzyme 2

COVID-19 – Coronavirus disease 2019

HCW – healthcare workers

IQR – interquartile range

NPA – nasopharyngeal aspirate

R_0 – reproductive number

RT-PCR – reverse-transcriptase polymerase chain reactions

WHO – World Health Organization

SARS – severe acute respiratory syndrome

SARS-CoV – severe acute respiratory syndrome coronavirus

SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2

SD – standard deviation

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Figure 1. Age distribution of COVID-19 and SARS patients

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Figure 2. COVID-19 and SARS symptoms comparison

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Table 1. Characteristics and symptoms in paediatric patients with COVID-19 and SARS-CoV

	Wuhan COVID-19 2020 n= 244			Hong Kong SARS-CoV 2003 n = 43	p-value[##]
	Symptomatic n = 193	Asymptomatic n = 51	p-value[#]		
Demographics and epidemiology					
Age, months, median (IQR)	67.0 (106)	116.0 (71)	**<0.001**	160.8 (90)	**<0.001**
Male, n (%)	120 (62.2)	30 (58.8)	**0.746**	20 (46.5)	**0.0852**
Epidemiological link identified, n (%)	160 (82.9)	48 (94.1)	**0.047**	42 (97.7)	**0.0083**
Duration of NPA turning negative, days, mean ± SD	8.2 ± 5.8	8.9 ± 5.1	**0.434**	-	**-**
Length of hospital stay, days, mean ± SD	13.0 ± 6.0	11.4 ± 5.2	**0.066**	20.6±3.6	**<0.001**
Symptoms, n(%)					
Fever	99 (51.3)	-	-	42 (97.7)	**<0.001**
Chills	2 (1.0)	-	-	14 (32.6)	**<0.001**

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Myalgia	9 (4.7)	-	-	16 (37.2)	**<0.001**
Malaise	9 (6.5)	-	-	25 (58.1)	**<0.001**
Poor feeding	8 (4.1)	-	-	3 (7.0)	**0.426**
Coryza	24 (12.4)	-	-	17 (39.5)	**<0.001**
Sore throat	10 (5.2%)	-	-	7 (16.3)	**0.019**
Cough	120 (62.2)	-	-	28 (65.1)	**0.862**
Sputum	25 (13.0)	-	-	17 (39.5)	**<0.001**
Diarrhoea	15 (7.8)	-	-	7 (16.3)	**0.141**
Nausea	23 (11.9)	-	-	12 (27.9)	**0.015**
Abdominal pain	4 (2.1)	-	-	3 (7.0)	**0.116**
Headache	10 (5.2)	-	-	15 (34.9)	**<0.001**
Dizziness	3 (1.6)	-	-	5 (11.6)	**0.006**
Supportive care, n(%)					
Use of oxygen supplementation	9 (4.7)	-	-	8 (18.6)	**0.004**
Use of mechanical ventilation support	3 (1.6)	-	-	1 (2.3)	**0.559**

[#] Comparison between the COVID-19 symptomatic and asymptomatic groups;

[##] Comparison between the COVID-19 symptomatic and SARS groups.

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Table 2 Laboratory test results in paediatric patients with COVID-19 (symptomatic cases) and SARS.

	Wuhan COVID-19 2020 N = 193				Hong Kong SARS-CoV 2003 N = 43				
	Mean / Median	**SD / IQR**	**Range**	**N**	**Mean / Median**	**SD / IQR**	**Range**	**N**	***p* - value**
White cell count, x10^9/L	7.1	2.7	0.75 - 13.8	183	6.0	4.4	2.2 - 23.2	43	**0.043**
Haemoglobin, g/dL	12.4	1.5	6.7 - 18.3	183	16.1	18.0	7.6 - 131.0	43	**0.193**
Platelet, x10^9/L	291.5	128.8	14.0 -751.0	183	212.0	76.5	168.0 - 580.0	43	**<0.001**[#]
Lymphocyte, x10^9/L	3.4	1.9	0.2 - 11.7	184	2.1	2.8	0.6 - 9.4	43	**<0.001**
Albumin, g/L	45.0	3.5	34.7 - 55.9	192	43.4	6.5	29.0 - 52.0	40	**<0.001**
Globulin, g/L	22.8	5.0	11.1 - 32.2	187	34.0	5.5	23.0 - 44.0	40	**<0.001**
ALT, U/L	16.0	17.0	4.0 - 596.0	193	17.0	20.0	12.0 - 80.0	41	**0.010**[#]

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LDH, U/L	239.0	94.2	142.0 - 656.0	189	262.0	168.5	147.0 - 1143.0	36	**0.285**[#]
DD, mg/L FEU	1.2	8.9	0.01 - 100.8	140	-0.11	0.18	-0.2 - 0.2	11	**<0.001**[#]
APTT, seconds	34.3	28.6	23.4 - 353.0	169	32.0	4.2	25.9 - 37.3	29	**0.827**

 # Mann-Whitney U test, results presented as median (IQR)

ALT – alanine aminotransferase; APTT – Activated Partial Thromboplastin Time; DD – D-dimer; FEU – fibrinogen equivalent units; IQR – interquartile range; LDH – lactate dehydrogenase; SD – standard deviation

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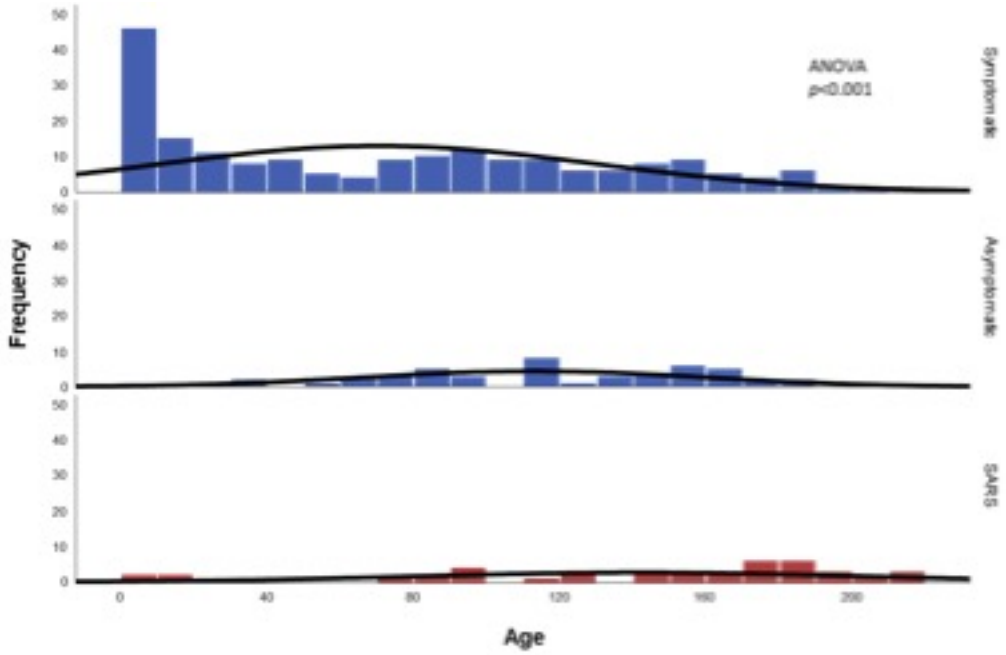

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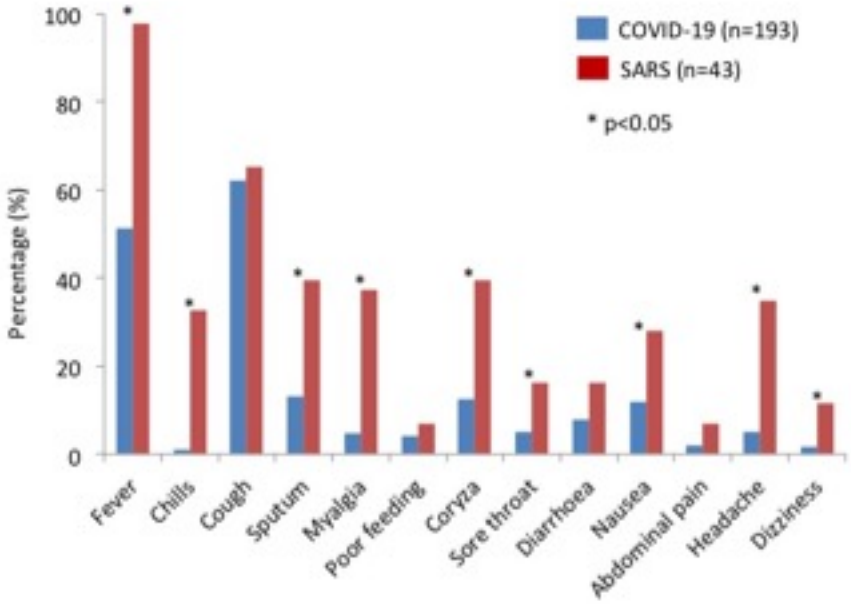

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