Received: 28 July 2020 | Revised: 14 September 2020 | Accepted: 19 November 2020

DOI: 10.1002/jmv.26684

SHORT COMMUNICATION

JOURNAL OF MEDICAL VIROLOGY WILEY

Clinical characteristics of pediatric SARS-CoV-2 infection and coronavirus disease 2019 (COVID-19) in Kuwait

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Abstract

Clinical presentation of coronavirus disease-2019 (COVID-19) ranges from asymptomatic to severe and life-threatening. National-level registries found that children, generally, have less severe disease when compared with adults. However, most asymptomatically infected children will not present to hospital and may be missed. We aimed to describe the clinical characteristics in pediatric COVID-19 patients in Kuwait, and to estimate the potential duration of viral shedding. A retrospective cohort study was performed in Jaber Alahmad Hospital (JAH) from February 29 to April 30, 2020. During the study period and as part of the public health measures, all severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients from 1 month to 18 years old, regardless of symptoms, were hospitalized at JAH, and were included. Polymerase chain reaction (PCR) negativity was defined as having two consecutive negative PCR results from a respiratory specimen. Descriptive statistics and multivariable regression analyses were performed. We found that 67.9% (95% CI, 59.4%–75.3%) of 134 SARS-CoV-2-infected children were asymptomatic. Median PCR positivity was 15 days and did not vary with symptoms. Among patients who had laboratory investigations and chest imaging, symptomatic infection was associated with elevated C-reactive protein and procalcitonin, and radiographic pneumonia. Asymptomatic SARS-CoV-2 infection is very common in children. Among symptomatic patients, the disease seems to be mild. Children exhibit substantial duration of viral shedding, regardless of symptoms.

KEYWORDS

coronavirus<virus classification, epidemiology, SARS coronavirus<virus classification, shedding<pathogenesis

1 | INTRODUCTION

Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) has caused a pandemic with high morbidity and mortality, especially in older adults. Children are believed to have decreased susceptibility to SARS-CoV-2 infection compared with adults.[1] Pediatric coronavirus disease-2019 (COVID-19) cases are estimated to be less than 8% of all confirmed cases.[2–4] Among infected children, the proportion with severe or critical illness has ranged between 3.3% and 8%.[5–7] Previous estimates of asymptomatically

infected children may be inaccurate because of a lack of systematic testing and longitudinal follow-up. In the largest pediatric cohort reported in China including more than 2000 children, it was found that 4.4% patients were asymptomatic and 50.9% and 38.8% had mild and moderate disease, respectively.[7]

Understanding the duration of SARS-CoV-2 viral shedding is important to control transmission and define the isolation period in the pediatric population. In one study at Wuhan Children's Hospital, researchers found a median of 15 days of viral RNA shedding in upper respiratory tract specimens. In addition, symptomatic infection, fever, pneumonia, and lymphopenia were identified as significantly with prolonged viral shedding in children with COVID-19.[8]

The first pediatric COVID-19 case in Kuwait was reported on February 29, 2020. Since then, and until April 30, 2020, all confirmed pediatric SARS-CoV-2 infections older than 1 month of age and regardless of symptoms were admitted to Jaber Alahmad hospital, the designated hospital in Kuwait for patients with COVID-19. During that time, daycare centers, schools, and commercial establishments, including shopping centers, dine-in restaurants, and gyms, were closed. Cases were identified through systematic household and close contact tracing, screening of all returning travelers, and testing of all suspected COVD-19 cases. This setting created a unique opportunity to evaluate COVID-19 characteristics and duration of viral shedding measured by reverse-transcription polymerase chain reaction (RT-PCR) done on upper respiratory samples. Also, we aimed to identify predictors for symptomatic pediatric COVID-19 cases.

2 | METHODS

2.1 | Study design

We performed a retrospective cohort study at Jaber Alahmad Hospital (JAH) from February 29 to April 30, 2020. All PCR-confirmed pediatric SARS-CoV-2 infections from 1 month to 18 years old were included. During the study period, all patients, regardless of symptoms were evaluated on a daily basis by a pediatrician, and vitals were checked at least 3 times daily. Initially, all COVID-19 cases were admitted until two consecutive nasopharyngeal or paired nasopharyngeal/oropharyngeal samples were negative by RT-PCR. However, on April 15, 2020, hospital discharge policy was changed due to bed capacity limits; patients could be discharged to institutional quarantine, where RT-PCR testing continued. Subjects were identified using admission records from medical records and virology laboratory information system. Patients admitted for suspected COVID-19 but with negative RT-PCR results were excluded.

Patient charts were reviewed to collect data on patient demographics, clinical history, significant underlying chronic comorbidities, laboratory investigations, and medical management. Daily symptoms as reported in the admission and progress notes were recorded. Disease severity categorization was based on the World Health Organization classification.[9] Results of laboratory investigations and chest radiography done at admission were collected. Data entry was reviewed by two investigators to ensure accuracy.

Normal ranges for neutrophil and lymphocyte counts were based on established parameters.[10] Manufacturer's defined cutoff values were followed to determine high procalcitonin (PCT) and C-reactive protein (CRP) values (Elecsys BRAHMS, Roche diagnostics, and IMMAGE immunohistochemistry system, Beckman Coulter Inc).

Nasopharyngeal specimens were collected using Xpert Nasopharyngeal sample collection kit (SWAB/B-100; Cepheid), and oropharyngeal swabs used were Transystem 139C (COPAN Italia). Upper respiratory specimens were first repeated after 12 days of admission. Then, it was repeated after 24 h if the result was negative, or every 3 days if it was positive. Nucleic acid extraction and RT-PCR were performed on MagNA Pure and LightCycler 480 (Roche™). Cycle threshold (Ct) value for E and RdRP genes were measured using Tib MolBiol's LightMix (Roche™).

Data were analyzed using descriptive statistics. Differences between the asymptomatic and the symptomatic patients were analyzed using Fisher's exact test for categorical variables and Mann–Whitney U test for continuous variables. The Kaplan–Meier method was used to assess duration to negative RT-PCR and log-rank test was performed to compare different clinical patient groups. Statistical analysis was performed using STATA/IC 14 (STATA Corp), and a two-tailed $p < .05$ was considered statistically significant.

2.2 | Ethics

This study was approved by the ethics committee of the Ministry of Health in Kuwait (reference no. 2020/1452).

3 | RESULTS

We identified 134 pediatric patients with COVID-19. This represented 3.3% of all COVID-19 cases (pediatric and adult) in Kuwait. The median age was 8.8 years (interquartile range [IQR]: 4.7–12.4 years), and there were slightly more males (55.2%). Most infections (82.4%) were acquired from a household contact (Table 1). The median hospitalization duration was 14 days (7–21 days).

The majority of patients (91, 67.9%; 95% CI, 59.4%–75.3%) were asymptomatic and 43 (32%) had mild illness or pneumonia. Three patients were admitted before symptom development. None in the cohort developed WHO criteria for severe disease or needed intensive care admission. One patient was readmitted with a diagnosis of multisystem inflammatory syndrome in children (MIS-C) 21 days after initial discharge. The most frequently reported symptoms were cough (74.4%) and fever (55.8%). Eleven patients (25.6%) had gastrointestinal symptoms with or without respiratory symptoms. Most of the cohort (89%) reported no comorbidities.

Neutropenia and lymphopenia were found in 11% and 8.5% of subjects, respectively. Twelve patients had abnormal chest x-ray findings. Of those, three asymptomatic patients had unilateral patchy infiltrates.

TABLE 1 Demographic data, clinical characteristics, laboratory, and radiological findings of the study population

	Asymptomatic (n = 91)	Mild disease (n = 43)	p-value
Age (median, IQR)	9.11 (5–9.11)	7.5 (1.7–7.5)	.329
Less than 1 year	2 (2.2%)	6 (13.9%)	.065
Gender			
Male	52 (57.1%)	22 (51.2%)	.516
Female	39 (42.9%)	21 (48.8%)	
Source of exposure			
Travel-related	19 (20.9%)	0	.001
Close contact	70 (76.9%)	41 (95.3%)	
unknown	2 (2.2%)	2 (4.7%)	
Fully vaccinated (n = 99)	54 (85.7%)	34 (94.4%)	.319
Comorbidities			
Asthma	3 (3.3)	0	.551
Prematurity	3 (3.3%)	1 (2.3%)	1
Type 1 diabetes	1 (1.1%)	0	1
Malignancy	1 (1.1%)	0	1
Epilepsy	1 (1.1%)	1 (2.3%)	.540
Congenital heart	1 (1.1%)	3 (7%)	.098
WBC (n = 128) (median, IQR)	7.7 (6–9)	7.1 (5.3–9.5)	.621
Lymphocyte count (median, IQR)	3.2 (2.6–4.3)	3.3 (2.2–4.5)	.748
Neutrophil count (median, IQR)	3 (2.1–4.1)	2.7 (1.7–3.4)	.078
Lymphopenia (n, %)	5 (5.8%)	6 (14%)	.597
Neutropenia (n, %)	7 (8.2%)	7 (16.2%)	.224
CRP (n = 79) (median, IQR)	2 (1–2)	3 (1–3)	.196
Abnormal CRP (n, %)	2 (3.8%)	7 (26.9%)	.005
PCT, (n = 99)	0.043 (0.03–0.059)	0.048 (0.03–0.095)	.131
(median, IQR)			
Abnormal PCT	3 (4.6%)	7 (20.6%)	.029
Coagulation profile (n = 77)			
INR (median, IQR)	0.99 (0.94–0.99)	0.96 (0.92–0.96)	.173
PT (median, IQR)	13 (12.6–13)	13 (12.4–13)	.958
aPTT (median, IQR)	31.9 (30–31.9)	31.5 (29.4–31.5)	.503
Liver enzymes			
ALK, (n = 128) (median, IQR)	196 (147–196)	169 (142–169)	.215
ALT, (n = 126) (median, IQR)	16 (13–16)	16 (13–161)	.878
AST, (n = 122) (median, IQR)	27 (20–27)	24 (20–24)	.766
Albumin (n = 129) (median, IQR)	41 (38–41)	40 (38–40)	.762
Creatinine (n = 127) (median, IQR)	37 (30–37)	37 (27–37)	.657
Chest x-ray (n = 52)			.003
Normal	29 (90.6%)	11 (55%)	
Increased bronchovascular marking	0	4 (20%)	
Unilateral infiltrate	3 (9.4%)	4 (20%)	
Bilateral infiltrate	0	1 (5%)	
Time to negative RT-PCR (median, IQR)	15.5 (14–21)	15 (13–19)	.543

Abbreviations: ALK, alkaline phosphatase; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CRP, C-reactive protein; INR, international normalized ratio; IQR, interquartile range; PCT, procalcitonin; PT, prothrombin time; WBC, white blood cells.

Among patients in whom these investigations were performed, high CRP (odds ratio [OR] 9.4; 95% CI, 1.8–49.2), high PCT (OR 5.3; 95% CI, 1.3–22.3), and abnormal chest x-ray (OR 7.9; 95% CI, 1.8–34.7) on admission were associated with symptomatic infection. Stepwise multivariable logistic regression analysis was attempted but failed to achieve good model fit.

The median duration of viral shedding, represented by having two consecutive negative RT-PCR results, was 15 days (IQR: 14–21 days) for asymptomatic and 15.5 days (IQR: 13–19 days) for symptomatic patients (Figure 1). RT-PCR positivity persisted beyond 40 days in two asymptomatic patients. We did not identify variables that were associated with prolonged RT-PCR positivity.

Eleven patients received antibiotics, and only one patient had microbiologically confirmed bacterial infection (urine culture grew *Klebsiella pneumoniae*, 60,000 CFU/ml). Eight patients received combination antibiotic therapy (all were azithromycin and ceftriaxone). Among the 10 symptomatic patients who received antibiotics, eight patients had chest radiograph done, which was abnormal.

4 | DISCUSSION

Most SARS-CoV-2 infections in children are nonsevere. We describe a cohort of the first 134 PCR-confirmed pediatric patients with COVID-19 identified through systematic testing of suspected COVID-19 cases, contact tracing and screening of returning travelers in Kuwait. During in-hospital follow-up of a median of 14 days,

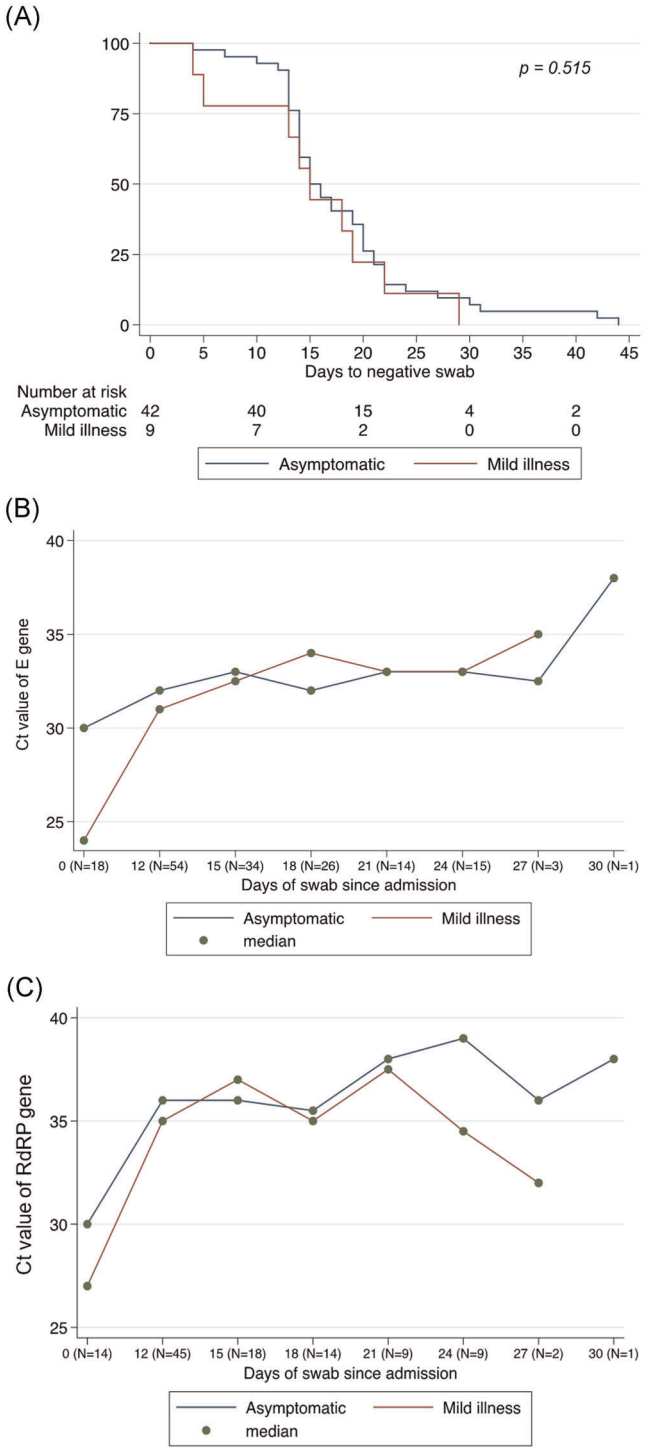

FIGURE 1 (A) Kaplan–Meier estimates of proportion reverse-transcription polymerase chain reaction positive from upper respiratory specimen. (B) Median cycle threshold (Ct) value of E gene in asymptomatic and symptomatic patient. (C) Median cycle threshold (Ct) value of RdRP gene in asymptomatic and symptomatic patient

twothirds (67.9%) of patients were asymptomatic and none required respiratory support. Both symptomatic and asymptomatic children had substantial duration of RT-PCR positivity from upper respiratory specimen.

Children are less likely to develop severe disease when compared with adults.[11,12] It is estimated that less than 3% of children will develop severe or critical illness.[2,5,13] In our study, none developed severe or critical disease. On the other hand, 67.9% of study subjects were asymptomatic. This finding is much higher than what has previously been reported. The estimates of asymptomatic SARS-CoV-2 in children varied according to study design and setting, but ranged between 12.9% and 27.7%, according to a systematic review by de Souza et al.[5] We believe that our findings may represent a more accurate estimate for the proportion of asymptomatic SARS-CoV-2 infection in children. Subjects in our cohort were identified through active case finding, and were admitted and their clinical status assessed daily for a median of 14 days, which thus enabled us to distinguish asymptomatic cases from presymptomatic individuals that eventually develop symptoms.

We found that children have substantial duration of RT-PCR positivity from an upper respiratory sample. Lu et al.[3] found that viral shedding was longer in symptomatic patients when compared with asymptomatically infected children (17 vs. 11 days).[3] In our study, we observed that viral shedding as detected by RT-PCR did not differ according to symptoms, lasting for a median of 15.5 and 15 days in asymptomatic and symptomatic children, respectively. Our findings are in-line with a recent study from Korea that showed no significant difference in RT-PCR positivity in relation to the presence or severity of symptoms.[14] Other factors beyond viral shedding can influence an individual's propensity to transmit infection, and the relationship between SARS-CoV-2 viral RNA shedding and transmission risk is not yet clear. Nevertheless, our data suggest that asymptomatic SARS-CoV-2-infected children have the potential to act as silent transmitters of the virus.

Identifying factors that are associated with symptomatic patients may help primary care and emergency room physicians to appropriately triage patients for further management. We identified that CRP, PCT, and abnormal chest x-ray, all done on admission, to be associated with symptom development. However, unlike other reports, we did not find age or white blood cell count (including neutrophil and lymphocyte counts) to be associated with symptomatic patients.[3] Due to the small number of patients with abnormal CRP, PCT, and chest radiography, as well as the absence of severe cases in out cohort, larger studies are needed to confirm our findings. Also, performing routine testing on asymptomatically infected children may not be cost effective and identification of abnormal laboratory or imaging findings may lead to unnecessary antimicrobial therapy.[15]

There are limitations to this national-level retrospective cohort study. First, patient information was dependent on accuracy of data recorded in the patient chart. In addition, it was difficult to ascertain reasons behind performing certain investigations, especially in asymptomatic patients. Also, during the first 10 days of the study, samples for RT-PCR were sent-out to a reference laboratory. For that reason, these Ct values were not accessible to us. However, our finding that asymptomatic SARS-CoV-2 infection is very common in

children may have important ramifications for public health pandemic containment efforts, including the need for broad testing of asymptomatic contacts of COVID-19 cases.

ACKNOWLEDGMENT

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICTS OF INTEREST

Jesse Papenburg has received consulting/honoraria fees from AbbVie, Cepheid and Seegene, and research grant funding outside of the current work from AbbVie, BD Diagnostics, Sanofi Pasteur, and MedImmune.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Alsharrah D, Alhaddad F, Alyaseen M, et al. Clinical Characteristics of Pediatric SARS-CoV-2 Infection and Coronavirus Disease 2019 (COVID-19) in Kuwait. *J Med Virol*. 2021;93:3246–3250. https://doi.org/10.1002/jmv.26684