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 asymptotically 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

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. Pediatric coronavirus disease-2019 (COVID-19) cases are estimated to be less than 8% of all confirmed cases. Among infected children, the proportion with severe or critical illness has ranged between 3.3% and 8%. Previous estimates of asymptotically infected children are estimated to be less than 8% of all confirmed cases.
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 COVID-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 | 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                    |         |
| 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 | 3.2 (2.6–4.3)         | 3.3 (2.2–4.5)        | .748    |
| Neutrophil count | 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)     | 2 (1–2)               | 3 (1–3)              | .196    |
| (median, IQR)    |                       |                      |         |
| 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)   | 196 (147–196)         | 169 (142–169)        | .215    |
| (median, IQR)    |                       |                      |         |
| ALT, (n = 126)   | 16 (13–16)            | 16 (13–161)          | .878    |
| (median, IQR)    |                       |                      |         |
| AST, (n = 122)   | 27 (20–27)            | 24 (20–24)           | .766    |
| (median, IQR)    |                       |                      |         |

TABLE 1 (Continued)

|                  | Asymptomatic (n = 91) | Mild disease (n = 43) | p-value |
|------------------|-----------------------|----------------------|---------|
| Albumin (n = 129) | 41 (38–41)            | 40 (38–40)           | .762    |
| Creatinine (n = 127) | 37 (30–37)        | 37 (27–37)           | .657    |
| Chest x-ray (n = 52) |                      |                      | .003    |
| Normal            | 29 (90.6%)            | 11 (55%)             |         |
| Increased         | 0                    | 4 (20%)              |         |
| bronchovascular marking |                |                      |         |
| 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,
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 may have important ramifications for public health pandemic containment efforts, including the need for broad testing of asymptomatic contacts of COVID-19 cases.

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CONFLICTS OF INTEREST
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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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