ORIGINAL RESEARCH

The Coronavirus Disease 2019 (COVID-19) in Children: A Study in an Iranian Children's Referral Hospital

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Background: Despite the worldwide spread of the coronavirus disease 2019 (COVID-19), the epidemiological and clinical patterns of the COVID-19 infection remain largely unclear, particularly among children. In this study, we explored the epidemiological characteristics, clinical patterns, and laboratory and imaging findings of pediatric patients with COVID-19.

Materials and Methods: From March 7 to March 30, 2020, there were a total of 35 patients who had confirmed COVID-19 infection by laboratory virus nucleic acid test (RT-PCR) assay with throat swab samples or typical chest CT manifestation compatible with COVID-19, in addition to a history of close contact with suspected or confirmed SARS-CoV-2 in family members. Information recorded included demographic data, medical history, exposure history, underlying comorbidities, symptoms, signs, laboratory findings and radiologic assessments, severity of disease, treatment, and mortality.

Results: The median age of the patients was 7.5 years (IQR=4–11; range=4 months to 15 years). A total of 63% were male. Cough was present in 80% of the patients, followed by fever (77%), nausea or vomiting (29%), diarrhea (26%), shortness of breath (29%), headache (20%), and myalgia (14%). Lymphopenia was present in 43% of the patients, thrombocytopenia in 9%, neutopenia in 8%, and leucopenia in 26%. We reported severe pneumonia in 40% of the hospitalized patients and 18 (51%) had underlying diseases. Of 35 patients, 11 had positive RT-PCR results (31%). The chest CT images of 24 patients (69%) suggested COVID-19, while their RT-PCR assays from throat swab samples were negative.

Conclusion: This study demonstrates different clinical findings of pediatrics compared to the previous reports of children. Since a high rate of false negative RT-PCR test was observed, early detection of children with COVID-19 infection by CT is conducive to reasonable management and early treatment.

Keywords: COVID-19, children, severe pneumonia, Iran

Introduction

The epidemic started in late December 2019 in Wuhan and swept across China and has spread through the world rapidly. According to the daily report of the World Health Organization, the epidemic of coronavirus disease 2019 (COVID-19) so far registered 7553182 cases and 423,349 deaths through the world. More than 182,545 cases of COVID-19 and 8659 deaths in Iran have been reported as of June 13, 2020.[1] Genetic analyses of novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), showed that SARS-CoV-2 viruses evolved into two major types of L and S. Although L type newly evolved from the ancient S type, the

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L type (~70%) is more prevalent and aggressive than the S type (70% vs 30%) and transmits or replicates faster in human populations.[2]

Despite the worldwide spread, the epidemiological and clinical patterns of the COVID-19 remain largely unclear, particularly among children.[3] Pediatric patients with COVID-19 have their own clinical features and therapeutic responses.[4] However, in contrast to adult patients, clinical manifestations of children with COVID-19 infection might be less severe.[3]

Children might be less likely to become infected or, if infected, may show milder symptoms.[5,6] It is suggested that children were less sensitive to COVID-19 due to several factors including the lower maturity and binding ability of Angiotensin converting enzyme II (ACE2), which is known as a cell receptor for SARS-CoV-2. In addition, higher levels of antibody against respiratory infection viruses including respiratory syncytial virus and different immune responses to pathogens than adults might be another possible explanation.[3] However, the mechanisms for the differences in clinical manifestations between children and adults are unclear.

Although the diagnosis of COVID-19 must be confirmed by reverse transcription polymerase chain reaction (RT-PCR), a total positive rate of RT-PCR for throat swab samples was about 30% to 60% at initial presentation. On the other hand, radiological characteristics can provide important evidence for the clinical diagnosis of COVID-19 and chest computed tomography (CT) might reveal pulmonary abnormalities consistent with COVID-19 even in patients with initial negative RT-PCR results.[7,9]

In the absence of specific therapeutic drugs or vaccines for COVID-19, early detection of children with SARS-CoV-2 infection is essential to decrease the risk of infecting a larger population. Sine clinical and imaging features of pediatric patients with COVID-19 infection in Iran are limited, in this study, we explored the epidemiological characteristics, clinical patterns, and laboratory and imaging findings of pediatric patients with COVID-19. The aim of this study was to investigate the consistency of chest CT in comparison to RT-PCR assay in COVID-19 in children.

Materials and Methods

This study was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (IR. TUMS.VCR.REC.1399.060) and signed informed consent was obtained from all patients who participated in the study or their parents/legal guardians. In cases that did not have the legal capacity or maturity to provide informed consent, their parents/legal guardians provided informed consent for themselves.

This study was performed in the Children's Medical Center, the hub of excellence in pediatrics in Iran. Approximately, more than 35,000 outpatients and 2500 inpatients are admitted to our hospital monthly. From March 7 to March 30, 2020, a total of 35 patients were included in the study. The inclusion criteria were a patient who had a confirmed COVID-19 infection by laboratory virus nucleic acid test (RT-PCR assay) with throat swab samples or typical chest CT manifestation compatible with COVID-19 in addition to a history of close contact with suspected or confirmed SARS-CoV-2 in family members. If both radiologic assessments and RT-PCR test were not performed for a patient, they were excluded from the study.

Information recorded included demographic data, medical history, exposure history, underlying comorbidities, symptoms, signs, laboratory findings and radiologic assessments, severity of disease, treatment, and mortality.

The presence of SARS-CoV-2 was detected by the RT-PCR method, as previously described[10] using nucleocapsid protein (N) 5′-GACCCCAAAATCAGCGAA AT-3′ (F) and 5′- TCTGGTTACTGCCAGTTGAATCTG-3′ (R) primers, and 5′-FAM-ACCCCGCAT TACGTTTGGTGGACC-3′ probe. Each sample was run duplicated with positive and negative controls. Throat swab samples were collected into a collection tube with 150 μL of virus preservation solution for extracting SARS-CoV-2 RNA from patients suspected of having SARS-CoV-2 infection. The RT-PCR assay was performed under the following conditions: at 50°C for 15 minutes and 95°C for 5 minutes, 40 cycles at 94°C for 15 seconds and at 55°C for 45 seconds. A cycle threshold value (Ct-value) of less than 37 was defined as a positive test result, and a Ct-value of 40 or more was defined as a negative result. Radiologic assessments including chest radiography or CT scan were performed, and all laboratory testing was performed according to the clinical care needs of the patient. Laboratory assessments consisted of a complete blood count, blood chemical analysis, coagulation testing, assessment of liver and renal function, and measures of electrolytes, C-reactive protein (CRP), procalcitonin, lactate dehydrogenase, creatine kinase, and erythrocyte sedimentation rate (ESR).

Severe pneumonia was defined by the presence of any of the following conditions:

1. Hypoxia: $SpO_2 \leq 93\%$ (<90% in premature infants).
2. Increased respiration rate: $RR \geq 70/min$ (≤1 year), $RR \geq 50/min$ (>1 year).
3. Blood gas analysis: $PaO_2 < 60$ mmHg, $PaCO_2 > 50$ mmHg.
4. Other manifestations.[11]

The CT features were evaluated as follows: ground-glass opacities, consolidations, nodules, pleural effusion, lymphadenopathy, unilateral or bilateral, number of affected lobes, and opacity distribution. The analysis of chest radiographic findings was based on density (ground-glass and consolidations), central to peripheral distribution, and lung involvements.

Statistical Analysis

All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 13.0 software (SPSS Inc). Categorical variables were described as frequency rates and percentages, and continuous variables were described using median and interquartile range (IQR) values. Normally distributed continuous variables were presented as means with standard deviations (SD). Comparison of the differences between the two groups was conducted using the *t*-test or Chi-square test. Variables with a two-tailed *P*-value<0.05 were considered statistically significant.

Results

The demographic and clinical characteristics of the patients are shown in Table 1. The median age of the patients was 7.5 years (IQR=4–11; range=4 months to 15 years). No differences by gender were observed, but there were more males in the study overall (63%).

Twenty-nine patients (83%) had an identified history of close contact with suspected or confirmed COVID-19 cases in family members. No patient had a history of international travel within 14 days before symptom onset. Seven patients (20%) required intensive care unit (ICU) admission. The median time to admission from development of symptoms was 7 days (interquartile range [IQR] =2–7 days). We reported severe pneumonia in 14 hospitalized patients (40%). The time from the onset of symptoms and the reference time to the hospital was higher in patients with severe disease than patients in the mild group (8.0±7.6 vs 5.3±4.5 days, *P*-value=0.19).

Table 1 Summary of Patient's Characteristics (n=35)

	N	%
Sex		
Female	13	37
Male	22	63
Age (years)		
<1	2	6
1–5	9	26
6–10	14	40
11–15	10	29
Blood group		
B	5	45
O	4	36
A	2	18
Presenting symptoms and signs		
Fever	27	77
Cough	28	80
Vomiting	10	29
Diarrhea	9	26
Tachypnea	4	11
Rhinorrhoea	3	9
Myalgia	5	14
Shortness of breath	10	29
Headache	7	20
Abdominal pain	4	11
Treatment		
Oseltamivir	30	86
Hydroxychloroquine	22	63
Azithromycin	18	51
Third-generation cephalosporins	17	49
Kaletra	3	9
Vancomycin	1	3

The duration of hospital stay was significantly higher in patients with severe disease than patients in the mild group (14.9±14.4 vs 4.3±3.7 days, *P*-value=0.003).

Cough was present in 80% of the patients, followed by fever (77%), nausea or vomiting (29%), diarrhea (26%), shortness of breath (29%), headache (20%), and myalgia (14%). Less common symptoms were tachypnea (11%), abdominal pain (11%), and rhinorrhea (8%).

The majority of cases were ≥5 years old (n=24, 69%). No significant differences between the clinical features and outcome were found between children aged <5 years and ≥5 years with and without severe disease. Fever was observed in only around half of the children <5 years (54.5%) and that was less than children ≥5 years (87.5%).

The presence of preexisting underlying medical conditions was found in 18 (51%) patients. Chronic kidney

diseases (n=4, 22%), neurological disorders (n=4, 22%), cardiovascular disease (n=2, 11%), liver cirrhosis (n=2, 11%), leukemia (n=2, 11%), polyarthritis (n=1, 6%), reactive airway disease, X-linked lymphoproliferative (XLP) syndrome (n=1, 6%), and human immunodeficiency virus (n=1, 6%) were the reported coexisting conditions.

Table 2 shows laboratory findings on admission. Lymphopenia was present in 43% of the patients, thrombocytopenia in 9%, neutopenia in 8%, and leucopenia in 26%. Most of the patients had elevated levels of ESR (83%). Most patients showed normal serum levels of procalcitonim (64%), and the CRP level was above the normal range in 59% of the cases. Lactate dehydrogenase and creatinine kinase were elevated in 31% and 9% of the cases, respectively, and anemia was found in 20% of the cases.

The white blood cell counts at admission did not differ significantly in patients with and without severe disease (median=7×10^9 cells per L vs 6.6×10^9 cells per L). Lymphopenia was observed at admission in 15 patients (43%), but did not differ significantly between those with and without severe disease (48% vs 36%, *P*-value=0.48).

Table 2 Laboratory Findings of the Patients with COVID-19 Infection on Admission

	Median (IQR)	Range
White blood cell count (×10^9 cells per L)	6.6 (3.5–10.4)	0.67–20.2
Neutrophil count (×10^9 cells per L)	4.0 (1.9–7.2)	0.01–16.8
Lymphocyte count (×10^9 cells per L)	1.5 (0.9–2.1)	0.14–4.18
Red blood cell count (×10^9 cells per L)	4.8 (4.3–5.1)	0.93–6.7
Haemoglobin (g/dL)	12.2 (11.3–13.5)	3.3–14.9
Platelet count (×10^9 cells per L)	273 (169–339)	36–543
Oximetry saturation (%)	87 (74.4–92.9)	22–99
Blood sugar (mg/dL)	109 (93–121)	76–207
Blood urea nitrogen (mg/dL)	11 (8–16.5)	4.0–95
Creatinine (µmol/L)	0.6 (0.5–7)	0.2–9.0
Creatine phosphokinase (U/L)	81 (62–149.7)	34–551
Lactate dehydrogenase (U/L)	594 (446–734)	273–1392
Calcium (mg/dL)	9.3 (8.6–10.2)	6.8–10.5
Phosphorus (mg/dL)	3.6 (8.6–10.2)	2.6–7.9
Magnesium (mg/dL)	1.95 (1.8–2.2)	1.6–4.1
Sodium (mmol/L)	136.5 (135–138.7)	131–143
Potassium (mmol/L)	4.1 (4–4.5)	3.0–6.0
Prothrombin time (s)	13.3 (12.5–14.8)	12.5–23.6
Partial thromboplastin time (s)	37 (32–46.5)	30–120
International normalized ratio	1.1 (1–1.3)	1–2.7
C-reactive protein (mg/L)	13 (3.8–42)	1–520
Erythrocyte sedimentation rate (mm/h)	26 (14–51.5)	5–83
Alanine aminotransferase (U/L)	22 (19.7–38.2)	14–247
Aspartate aminotransferase (U/L)	14 (10.5–26.7)	7–474
Procalcitonin (ng/mL)	0.01 (0.01–0.95)	0.01–9.0

Inflammatory markers (CRP: median=36 mg/dL vs 10 mg/dL; procalcitonin: median=0.7 ng/mL vs 0.15 ng/mL) were elevated at admission for patients with severe disease compared to patients with mild disease; however, the differences were not significant. Of 35 patients, 11 had positive RT-PCR results (31%). Of 35 CT scans that were performed at the time of admission, 91% revealed abnormal results (Table 3). The chest CT images of 24 patients (69%) suggested COVID-19, while their RT-PCR assays from throat swab samples were negative. A typical CT scan manifestation compatible with COVID-19 in addition to a history of close contact with suspected or confirmed cases in family members was considered as a decisive clue for pediatric COVID-19 in patients with a RT-PCR negative result.

The most common pattern on chest CT was ground-glass opacity (74%). Opacity and bilateral distribution were seen in 31% and 17% of cases, respectively; and 17 (49%) had involvement of two or more lobes at chest CT. The right lower lobe was involved in 14 (40%), the left lower lobe was involved in 13 (37%), the right upper lobe in 10 (29%), the right middle lobe was involved in six (1%), and the left upper lobe in four (11%) patients at initial CT scan.

Normal chest radiographic findings were found in 31% of patients; diffuse and central distribution was seen in 31% and 20% of cases, respectively (Table 3).

Most patients received antiviral therapy (oseltamivir, 30 [86%]), and many received antibacterial therapy including azithromycin (n=18, 51%), cefotaxime (n=11, 31%), and ceftriaxone (n=6, 17%). More than half of the patients (63%) received hydroxychloroquine therapy.

Most patients were discharged (31 [89%]) with a median length of stay of 4 days (range=12–46 days). Four deaths (11%) were reported among the pediatric cases included in this analysis.

In a patient with XLP syndrome infected with COVID-19 after bone marrow transplantation, his condition deteriorated in spite of treatment. Despite steady improvement being seen in a patient with Wilson disease and a patient with congenital heart defect, their COVID-19 RT-PCR was positive several times; however, finally in a patient with congenital heart defect the result of COVID-19 RT-PCR changed to negative, in a patient with Wilson disease it remained positive.

Discussion

This report, to our knowledge, is the largest study to date of hospitalized children with COVID-19 infection in Iran.

Table 3 Findings at Initial Chest CT and Radiographic Examination

Findings	N	%
CT scan		
Normal	3	9
Ground-glass opacities	26	74
Consolidation	6	17
Lobe involvement		
LLL	1	3
RLL	3	9
RML	1	3
RUL	2	6
LLL/RUL	5	14
RLL/LLL	4	11
RLL/RML	3	9
RLL/RML/LLL	1	3
RLL/RML/LUL	1	3
RUL/LLL/LUL	1	3
RUL/LUL/RLL	1	3
RLL/RUL/LLL/LUL	1	3
Opacity distributions	11	31
Bilateral lung disease	6	17
Pleural effusion	1	3
Lymphadenopathy	1	3
Chest radiography		
Normal	11	31
Consolidation	4	11
Ground-glass opacities	14	40
Central distribution	7	20
Diffuse distribution	11	31
Lobe involvement		
LLL	2	6
RLL	2	6
RML	1	3
RML/LLL	2	6
RUL/LLL	1	3
RUL/RML	2	6
RUL/RML/RLL/LLL	1	3

Abbreviations: RUL, right upper lobe; LUL, left upper lobe; LLL, left lower lobe; RLL, right lower lobe; RML, right middle lobe.

Since the early days of a COVID-19 infection outbreak, it has been thought that pediatric patients were not susceptible to COVID-19. However, along with widespread spread of the virus, the number of infected children has gradually increased.[7] In a recent report, among 1099 laboratory-confirmed cases, only nine patients (0.9%) were younger than 15 years of age.[12] Males seemto be more susceptible to COVID-19 infection, which is similar to the recent epidemiological studies.[3,5,12] A higher incidence rate of COVID-19 infection in males and in Asia might be due to the higher expression level of ACE-2.[13,14]

Our study is similar to previous reports indicating that the main clinical manifestations of COVID-19 are fever and cough.[3,12,15] Although fever was the most common symptoms at onset of illness in children, it was reported less than in adults.[10] Moreover, fever was more prevalent in children aged ≥5 years compared to the patients aged <5 years.

Diarrhea and vomiting were reported as uncommon symptoms in previous studies of children;[3,12,15] however, in our study nearly one third of our patients experiences diarrhea and/or vomiting.

It has been reported that clinical symptoms in pediatric patients are relatively milder compared with those in adults; however, there are limited data on the epidemiological and clinical patterns of COVID-19 in children. In contrast to previous reports of pediatrics in China,[3,11,12] we reported severe pneumonia in 40% of the hospitalized patients in the COVID-19 outbreak in Iran.

In laboratory examination results, most patients (80%) had normal or decreased white blood cell counts. In contrast to adults where lymphopenia is found in the majority of cases with COVID-19,[10] it was found in only 43% of cases. Nearly half of the patients (46%) had underlying diseases. Immunocompromised patients may be at high risk of developing a severe COVID-19 pneumonia.[16]

It has been reported that patients with chronic comorbidities are at higher risk of severe acute respiratory syndrome.[4] The underlying and chronic diseases may be linked to the pathogenesis of COVID-19, which might make individuals more susceptible to severe disease complications, probably due to the attenuation of the innate immune response, low immune function, and proinflammatory responses.[17]

Eighty-three percent of our cases had close contact with family members suspected or confirmed with COVID-19; therefore, family prevention is highly recommended to prevent the transmission of COVID-19 to children.

COVID-19 has not been described in organ transplant recipients or donors.[18] Although identifying of COVID-19 before donation in transplant donors for the consequent exclusion of positive cases was introduced, no specific indications for recipients of transplants in epidemic areas are available.[19] To our knowledge, this is a first report of COVID-19 in organ transplant recipients in children. We described COVID-19 in a liver transplant candidate that had no fever and did not meet the case definition for COVID-19 and she was tested before transplantation.

Chest CT is a sensitive tool to detect COVID-19 infection, especially in areas with a shortage of RT-PCR testing.[5] Since the diagnosis of COVID-19 must be confirmed by RT-PCR for respiratory specimens, pharyngeal swab COVID-19 nucleic acid has a low detection rate.[7] In addition, sampling errors and low virus load, and kit performance, might lead to negative results, especially in an early stage of disease.[8,20]

In our study only 31% of the cases had a positive RT-PCR result. The total positive rate of 30–60% for throat swab RT-PCR was reported at initial presentation of patients with COVID-19 infection.[21]

It has been reported that chest CT has a high sensitivity for diagnosis of COVID-19.[7] We observed that 69% of cases with COVID-19 infection had a false negative RT-PCR result of throat swab samples, so chest CT may be considered as a primary tool for the current COVID-19 detection in epidemic areas.[7] The sensitivity of chest CT based on positive RT-PCR results in suggesting COVID-19 was 97% (95% CI=95–98%) and 75% of patients with negative RT-PCR results had positive chest CT findings.[7]

Since COVID-19 is a novel disease and little has been described about the clinical course, risk factors for severity of disease and reappearance of SARS-CoV, especially in children,[22,23] plans should be made at local and regional levels for preventing transmission and slowing the rate of new infections.

On the other hand, reducing the risk of nosocomial outbreak by infection prevention and control precautions are of critical importance. Maintaining of appropriate distancing of at least 2 meters between patients with suspected or confirmed COVID-19 with other patients and health care workers as well as use of relevant personal protective equipment is highly recommended.

Several limitations have been observed in this paper. First, the sample size included in the study was small and the results cannot be really generalized on the whole child population in Iran. Moreover, prioritization of SARS-CoV-2 RT-PCR testing for symptomatic patients would result in overestimation of the percentage of patients with COVID-19 severe infection. The RT-PCR assay was performed on throat swab samples and the sensitivity of throat swab samples was not high enough and repeated RT-PCR tests on other samples including nasopharyngeal swab samples with higher sensitivity and compliance in children was not performed. Besides, although RT-PCR assay is considered as a confirmatory test for COVID-19, typical CT scan manifestation compatible with COVID-19 in addition to a history of

close contact with suspected or confirmed cases in family members was a decisive clue of pediatric COVID-19 in patients with a RT-PCR negative result.

In conclusion, this study demonstrated different clinical findings of pediatrics compare to the previous reports of children. Since a high rate of false negative RT-PCR test was observed, early detection of children with COVID-19 infection by CT is conducive to reasonable management and early treatment of pediatric patients.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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