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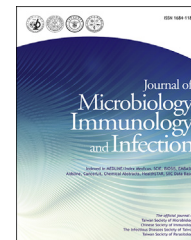
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Original Article

Novel coronavirus disease 2019 (COVID-19) outbreak in children in Iran: Atypical CT manifestations and mortality risk of severe COVID-19 infection



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Abstract *Background:* During the coronavirus disease 2019 (COVID-19) pandemic, Iran reported its first confirmed cases of syndrome coronavirus 2 (SARS-CoV-2) infections on 19 February 2020 in Qom. Although the numbers of cases are increasing, no report about clinical manifestations, laboratory results, and imaging findings of the children infected with COVID-19 in Iran has been published. The aim of this study was to evaluate the epidemiological, clinical, and radiological and laboratory findings of 24 children who had proven SARS-CoV-2 infection and performed chest computed tomographic (CT) in Qom, Iran.

Methods: Demographic information and clinical characteristics of the patients including signs and symptoms, chest CT scan manifestation, laboratory findings and clinical outcomes were collected. Diagnosing of the confirmed case was based on positive real-time reverse-transcriptase-polymerase-chain-reaction test for SARS-CoV-2.

Findings: During the first 3 months of the epidemic in Qom, Iran, 24 children with confirmed diagnosis of COVID-19 were included. The median age of the cases was 6 years [interquartile range 3.5–9.5 years]. The most common presenting symptoms were fever (100%), dry cough (62.5%), tachypnea (29%), abdominal pain (21%), and vomiting (21%). Three cases (12.5%) presented with a history of diarrhea in addition to fever and cough. According to

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the chest CT findings, 2 cases (8%) showed no abnormality. Typical CT findings were found in 6 patients (25%), 2 patients showed indeterminate appearance, and 14 patients (58%) showed atypical findings. Two children with SARS-CoV-2 infection manifested as a hyperinflammatory syndrome with multi-organ involvement similar to Kawasaki disease shock syndrome. Seventy-one percent of the patients showed severe SARS-CoV-2 infection and the mortality of 12.5% (3 cases) were reported.

Interpretation: High frequency of atypical chest CT finding in children should raise concern for pediatricians. Early recognition of patients with SARS-CoV-2 infection is of crucial importance in controlling of the outbreak and atypical imaging features should be interpreted with caution.

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Introduction

The Coronaviridae family of viruses includes seven known human-infecting coronaviruses. Although four of these coronaviruses cause only mild respiratory symptoms similar to the common cold, epidemics caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2002 and Middle East Respiratory Syndrome (MERS-CoV) in 2012, showed high mortality rates of 10% and 37%, respectively. The latest novel coronavirus named SARS CoV-2 is highly infectious and could be a significant health threat; however, the mortality rate of so far is lower than SARS-CoV in 2002 and MERS-CoV.¹

The Coronavirus disease 2019 (COVID-19) epidemic is evolving rapidly, and On March 11, the COVID-19 outbreak was characterized as a pandemic by the World Health Organization (WHO) and COVID-19 is considered as the sixth public health emergency of international concern.²

During the COVID-19 pandemic, Iran reported the first confirmed cases of COVID-19 on 19 February 2020 in Qom. Then, the number of cases has been increasing rapidly; by May 30, there were total 146,668 confirmed cases of COVID-19 pneumonia and 7677 deaths identified in Iran with the mortality rate of 5.2%.³

According to the previous report in China, only 2.1% laboratory-confirmed cases of COVID-19 were reported in cases ≤ 19 years of age.⁴ However, there is limited data on children in the literature, milder symptoms are reported in children compared with compared to the adults and rare death in children and adolescents has been reported.⁵ Here, we report the epidemiological, clinical, radiological and laboratory findings of 24 children with SARS-CoV-2 infection in Qom, Iran.

Material and methods

Demographic information and clinical characteristics including signs and symptoms, chest computed tomographic (CT) scan, laboratory findings and clinical outcomes of each patient were collected. Data collection was allowed by verbal consent with subsequent written consent provided by patients with positive results.

The nasopharyngeal swab samples were collected for SARS-CoV-2 real-time reverse-transcriptase-polymerase-chain-reaction (rRT-PCR) for all cases and diagnosing of the confirmed case was based on positive rRT-PCR test for SARS-CoV-2.⁶

The date of disease onset was defined as the day when the symptom was noticed. The durations from the onset of disease to performing of rRT-PCR and CT scan tests were also recorded.

Severe pneumonia was defined by presence of any following conditions⁷: hypoxia: $SpO_2 \leq 93\%$, increased respiration rate: $RR \geq 70/\text{min}$ (≤ 1 year), $RR \geq 50/\text{min}$ (>1 year), blood gas analysis: $PaO_2 < 60$ mmHg, $PaCO_2 > 50$ mmHg or other manifestations.

Laboratory tests were conducted at the first day of admission, including a complete blood count (leucocytes, neutrophils, lymphocytes, thrombocyte, hemoglobin), serum biochemistry (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), and creatinine), and albumin. In cases with hyperinflammatory syndrome with multiorgan involvement, additional tests including D-dimers, ferritin, triglycerides, and troponin were performed. Reference intervals for each tests were defined by Clinical and Laboratory Standards Institute (CLSI),⁸ Chest CT scan was performed for all the cases and reported by two expert radiologists. The findings were categorized in four groups.⁹

- a) No features of pneumonia
- b) Typical CT imaging features for COVID-19 that are frequently and more specifically seen in COVID-19 pneumonia including peripheral, bilateral, ground-glass opacification with or without consolidation or visible intralobular lines, multifocal ground-glass opacification or rounded morphology with or without consolidation or visible intralobular lines, or reverse halo sign or other findings of organizing pneumonia.
- c) Indeterminate appearance that are nonspecific features of COVID-19 pneumonia including presence of multifocal, diffuse, perihilar or unilateral ground-glass opacification with or without consolidation lacking a specific distribution that are non-rounded or non-peripheral, or few very small ground-glass opacification with a non-rounded and non-peripheral distribution.
- d) Atypical features are those that are reported to be uncommon or not occurring in COVID-19 pneumonia and are more typical of other diseases such as lobar or segmental consolidation in the setting of a bacterial pneumonia, lung cavitation, and tree-in-bud opacities with centrilobular nodules, or smooth interlobular septal thickening with pleural effusion.

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS version 18.0, SPSS Inc., Chicago, IL, USA). Categorical data were described as percentages and continuous data as median with interquartile range (IQR). 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

During the first 3 months of the epidemic in Qom, Iran, 24 children with the confirmed diagnosis of COVID-19 in Hazrat Masume Hospital, Qom University of Medical Sciences, Qom, Iran were included.

The characteristics of 24 patients who had rRT-PCR proven COVID-19 infection and performed chest CT are described in a [supplementary file](#). Among all children, there were 13 females (54%) and 11 males (46%), aged from 2 months to 15 years old (median 6 years [interquartile range 3.5–9.5 years]).

Three patients had a close contact history with family members with confirmed COVID-19 and one case was infected during hospitalization. All children were reported to be living in Qom during the outbreak period of COVID-19. Twenty-one patients were from Iran, while 3 cases were Afghan.

The most common presenting symptoms were fever (100%), dry cough (62.5%), tachypnea (29%), abdominal pain (21%), and vomiting (21%) (Table 1). Three cases (12.5%) presented with a history of diarrhea in addition to fever and cough.

Leukopenia was found in 5 (21%). A normal leukocyte count was found in 58% (N = 14), and 21% (N = 6) had an increased count relative to the locally defined reference limits. Among 24 patients, 16 (67%) had normal neutrophil counts, 6 patients (24%) above the normal range and neutropenia was found in 2 (8%) cases. Thrombocytopenia was reported in 10 patients (42%). A concentration of CRP was elevated in most patients (96%, 22 out of 23) and the elevated ESR was found in 87% of the cases.

In our study 71% of the patients showed severe SARS-CoV-2 infection. There were no significant differences between the age, leukocyte counts, neutrophil counts, lymphocyte counts, platelet counts, hemoglobin level, LDH, liver enzymes level, CRP, ESR level and severity of disease.

Elevated LDH, ALT, and AST were found in 4 cases and all of them showed severe pneumonia.

According to the chest CT findings, 2 cases (8%) showed no abnormality. Typical CT findings were found in 6 patients (25%), 2 patients showed indeterminate appearance, and 14 patients (58%) showed atypical findings ([supplementary file](#), Fig. 1).

The predominant features in cases with atypical CT findings was consolidation (n = 11, 79%) followed by ground-glass opacification (n = 7, 50%). Pleural effusion, cavitation, small nodules, and bilateral central peribronchovascular thickening was found in 36% (n = 5), 14% (n = 2), 7% (n = 1), and 7% (n = 1) of cases, respectively.

Table 1 Epidemiological data (symptom/signs and treatment) of children with COVID-19.

Epidemiological data	N	%
Symptom or sign		
Fever (body temperature >37 °C)	24	100
Dry cough	15	62.5
Tachypnoea	7	29
Abdominal pain	5	21
Vomiting	5	21
Myalgia	4	17
Rash	4	17
Diarrhoea	3	12.5
Tiredness	3	12.5
Chest pain	2	8
Conjunctivitis	2	8
Swollen hands and feet	2	8
Sore throat	1	4
Strawberry-red tongue	1	4
Treatment		
Ceftriaxone	17	71
Vancomycin	14	58
Azithromycin	10	42
Meropenem	2	8
Clindamycin	2	8
Hydroxychloroquine	20	83
Oseltamivir	14	58
Lopinavir/ritonavir	8	33

The mean age of the cases who died was higher than patients who discharged from hospital after recovery (10.7 ± 3.8 year vs. 5.9 ± 3.9 , p value = 0.069). No significant difference was found between CT findings and outcomes. A majority of cases with atypical CT findings were older than 5 years (79%) (Table 2).

Unfortunately, 3 patients died and all of them were Afghan. Two of three cases (67%) who died showed abnormal CT manifestations, while one of them had typical CT findings related to COVID-19. All of them were female aged older than 5 years and presented with fever. Chest pain, vomiting and diarrhea was found in 2 (67%), 2 (67%), and 1 (33%) of them.

Two children with SARS-CoV-2 infection manifested as a hyperinflammatory syndrome with multi-organ involvement similar to Kawasaki disease shock syndrome. One of these cases was admitted with fever, cough, and abdominal pain since 5 days before hospital admission. At admission, maculopapular rash and conjunctivitis and tachypnea were observed. Laboratory findings showed hypoalbuminemia and elevated concentrations of CRP (98 mg/L), liver enzymes, LDH (865 U/L), ferritin (2736 ng/mL), triglycerides (212 mg/dL), and D-dimers (4563 ng/mL). Another case was presented with fever, cough, vomiting, diarrhea, and abdominal pain, maculopapular rash, edema, and conjunctivitis. Laboratory findings showed hypoalbuminemia and elevated concentrations of CRP (75 mg/L), ESR (49 mm/h), troponin (6.6 ng/mL), and D-dimers (4563 ng/mL). These two patients were given intravenous immunoglobulin (2 g/kg) in the first 24 h.

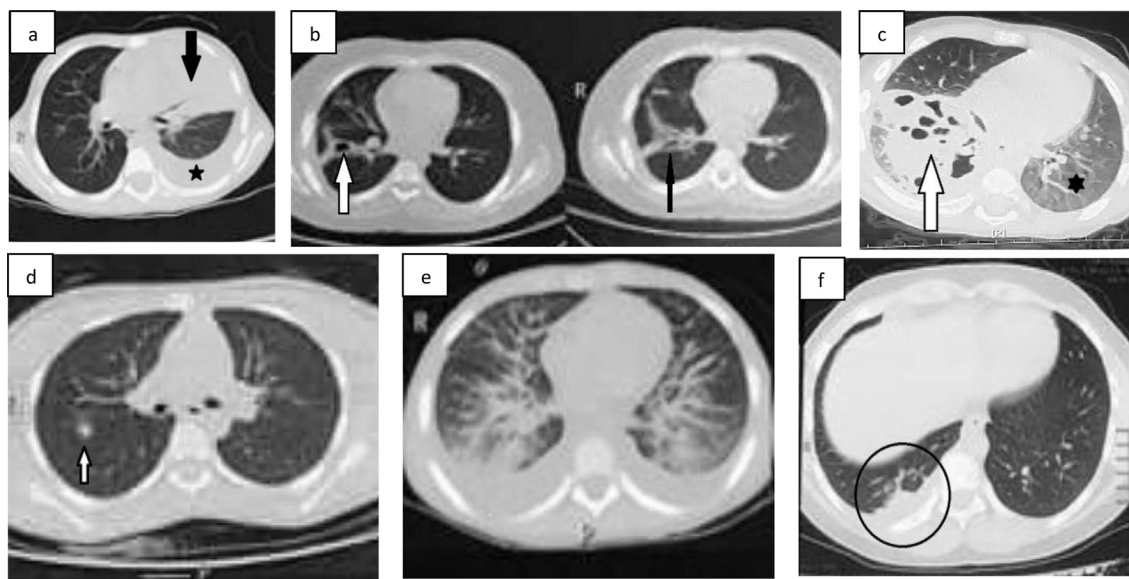


Fig. 1. Atypical CT scan findings: a) complete lobar consolidation in left upper lobe (arrow) with left side pleural effusion (asterisk); b) A small cavity (arrow) with adjacent consolidation (thin solid arrow) in right lower lobe, c) A large area of cavitation/bronchiectasis with surrounding consolidation in right lower lobe (arrow). Diffuse ground glass opacity (asterisk) is seen in left lower lobe, which later progresses to air space opacity (not shown); d) A small nodule with surrounding ground glass halo in upper portion of pulmonary right lower lobe; e) Ground glass/patchy air space opacities are seen in bilateral lower lobes. Reticular opacities are also seen in lower aspects of the lungs, with bilateral pleural effusion; f) Mid pleural effusion is seen posterior to lower aspect of right lung with adjacent small parenchymal band/atelectasis in right lower lobe.

Table 2 CT scan findings related to COVID-19 in 24 children.

CT scan findings related to COVID-19	N	Sex		Age		Severe pneumonia	Mortality
		Male	Female	≤5 year	>5 year		
		N (%)	N (%)	N (%)	N (%)		
Normal	2	1 (50)	1 (50)	0	2 (100)	0	0
Typical	6	4 (67)	2 (34)	5 (83)	1 (17)	5 (83)	1 (17)
Indeterminate	2	0	2 (100)	2 (100)	0	2 (100)	0
Atypical	14	6 (43)	8 (57)	3 (21)	11 (79)	10 (71)	2 (14)

The treatment options of the patients are shown in Table 1. Eighty-three percent of cases were given hydroxy-chloroquine. Antiviral agents including oseltamivir and lopinavir/ritonavir were prescribed in 58% and 33% of patients, respectively.

Discussion

COVID-19 is currently causing a severe outbreak of disease in Iran. This report, to our knowledge, is the largest study to date of hospitalized children with COVID-19 in Qom, Iran.

According to the recent review of 72,314 cases by the Chinese Center for Disease Control and Prevention, children younger than 10 years of age accounted for less than 1% of the cases.⁶ Despite that many articles have established the clinical features of COVID-19 patients in adults so far,^{9–11} there are limited data on laboratory findings, clinical and imaging manifestation of this infection in children.

Although a normal or decreased total white blood cell count has been reported in the early stage of the disease.^{12,13} In our study, more than half of the cases had normal leukocyte count and leukocytosis was found in 21% of the patients. Similar to the previous reports, the majority of patients had normal neutrophil counts.^{6,13} Increased concentrations of CRP were elevated and ESR in the majority of patients.

In April 2020, children with SARS-CoV-2 infection manifesting with hyperinflammatory shock and multi-organ involvement features similar to Kawasaki disease were reported.¹⁴ In this study, we reported two cases with severe SARS-CoV-2 infection with similar clinical presentation to this syndrome. The CT finding of one of these cases showed atypical finding of bilateral central peribronchovascular thickening and mostly central ground glass opacity/consolidation in lower lobes with bilateral pleural effusion mostly in right side. The CT finding of other case showed indeterminate appearance related to COVID-19 including bilateral perihilar, peribronchovascular thickening and ground glass opacities.

In the context of typical clinical presentation with COVID-19, CT imaging may be strongly helpful for suspicious to COVID-19 infection despite negative RT-PCR results.^{6,15} However, the CT imaging in children differ from what has been reported until now.^{9,16}

In our study, atypical CT findings were found in 58% of the cases. Although, pleural effusion, pericardial effusion, CT halo sign, cavitation, small nodules and pneumothorax are not common findings of CT scan, they might be related with disease progression.¹⁷ Developments of atypical CT manifestations including pleural effusions and progression to a mixed pattern of ground-glass opacification and consolidative opacities have been observed in later disease stages.^{1,17,18} The correlation between CT findings and disease severity and mortality are not completely explained; however; in our study, 3 deaths occurred in patients with severe COVID-19, while no significant difference was found between CT findings and outcomes.

The rapid progression of the disease might be due to the cytokine storm after COVID-19 infection. It has been reported that cytokine storm can induced following SARS-CoV-2 infection.¹⁹

In our study, only 2 cases (8%) with positive SARS-CoV-2 rRT-PCR showed normal chest CT. In the study of Chung et al., chest CT was negative for viral pneumonia of COVID-19 in 14% of the cases.⁹ In contrast to the recent studies of China that reported the most pediatric patients had mild symptoms without fever or pneumonia,^{18,20,21} in our study, a majority of cases had fever and 71% showed severe SARS-CoV-2 infection. Although it has been reported that gastrointestinal symptoms might be seen in young children,^{22,23} in this study 21% of the patients had gastrointestinal symptoms.

So far, rare severe COVID-19 in children and death has been reported in the pediatric population⁵; however, in our study 71% of the patients showed severe SARS-CoV-2 infection and the mortality of 12.5% (3 cases) was reported. All of the cases who died were Afghan; therefore, the severity of COVID-19 as well as presentation of atypical CT scan findings might be influenced by ethnicity.²⁴

In conclusion, high frequency of atypical chest CT manifestations in the children should raise a concern for pediatricians; therefore, early recognition of children with SARS-CoV-2 infection is of crucial importance in controlling of the outbreak and atypical imaging features should be interpreted with caution.

Declaration of competing interest

The authors have no conflict of interest relevant to this paper to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jmii.2020.07.019>.