Clinical, Laboratory, and Chest CT Features of Severe Versus Non-Severe Pediatric Patients with COVID-19 Infection Among Different Age Groups

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Abstract

Background: The aim of this study was to compare the clinical, laboratory, and chest computed tomography (CT) findings between severe and non-severe patients as well as between different age groups of pediatric patients with confirmed COVID-19.

Method: This study was performed on 55 pediatric patients with confirmed COVID-19 hospitalized in Namazi and Ali Asghar Hospitals, Shiraz, Iran. Patients were divided into severe (n=27) and non-severe (n=28) groups. Also, they were categorized into three age groups: aged less than two years, 3-12 years and 13-17 years. CT scans, laboratory, and clinical features were taken from all patients at the admission time. Abnormal chest CT in COVID-19 pneumonia was found to show one of the following findings: ground-glass opacities (GGO), bilateral involvement, peripheral and diffuse distribution.

Result: Fever (79.2%) and dry cough (75.5%) were the most common clinical symptoms. Severe COVID-19 patients showed lymphocytosis compared to non-severe ones ($P = 0.028$). C-reactive protein (CRP) was shown to be significantly lower in patients aged less than two years than those aged 3-12 and 13-17 years old ($P = 0.009$). It was also shown that O_2 saturation was significantly increased, as age increased ($P = 0.015$). Also, severe patients had significantly higher CT abnormalities compared to non-severe ones (48.0% compared to 17.9%, respectively) ($P = 0.019$).

Conclusion: Lymphocytosis and abnormal CT findings are among the factors most associated with COVID-19 severity. It was, moreover, showed that the severity of the COVID-19, O_2 saturation, and respiratory distress were improved as the age of confirmed COVID-19 pediatric patients increased.

Background

An outbreak of unexplained viral infection named coronavirus 2019 (COVID-19) began in Wuhan, China in December 2019 [1, 2]. It has become a worldwide pandemic, causing infection in more than 28 million people (as of September 2020).

The number of affected children is on the rise according to recent studies. Pediatric patients most commonly represent with fever and cough [3, 4]. However, clinical, laboratory, and imaging findings in the pediatric population remain unclear. To date, the data suggests that children and young adults are less likely to become severely ill than adults [5]. However, the recent increase in the reports of children with systemic inflammatory response requiring intensive care has made explicit the need for prompt diagnosis [6]. Given that several cases with severe symptoms and even death have been observed among such patients, rapid and accurate diagnosis in the pediatric population assumes the utmost significance [7].

Although the reverse transcriptase-polymerase chain reaction (RT-PCR) is characterized as a reference standard diagnostic test, computed tomography (CT) scan has turned into an important diagnostic tool, along with other clinical and laboratory features [8]. Bilateral ground-glass opacities (GGOs) with posterior and peripheral distribution in CT scan is known as the hallmark of COVID-19 pneumonia [9–11]. The main findings obtained from the abnormal CT scans of the pediatric population are peripherally located GGOs. Also, lower attenuation and a more localized extent of the GGOs are noted in pediatric patients [12]. In some studies, CT scan findings were shown to be similar to those of the infected adult patients [12, 13]. Nevertheless, given the lower severity of COVID-19 pneumonia in pediatric patients, imaging findings, the pattern of involvement and the role of CT imaging may be different from those commonly observed in adults.

In adults, COVID-19 manifestations range from asymptomatic infection to severe respiratory failure [14, 15]. Nonetheless, few studies have examined the severity of disease among pediatrics and tried to make a distinction between severe and non-severe children with COVID-19 infection in clinical, laboratory, and radiological findings. This study was conducted aiming to identify the clinical and paraclinical characteristics of the pediatric population with COVID-19, make a comparison between different age groups of pediatric patients, as well as to make a comparison between severe and non-severe COVID-19 hospitalized pediatric patients hospitalized in terms of their clinical, laboratory, and CT features.

Methods

Patients and Study Design

In this cross-sectional and multi-center study, a total number of 55 pediatric patients with confirmed diagnosis of COVID-19 were admitted to the isolation wards of two Hospitals, multispecialty healthcare university settings affiliated to Shiraz University of Medical Sciences between March 1, 2020 and May 30, 2020. The diagnosis was confirmed according to interim guidance for novel coronavirus pneumonia published by the National Health Commission of the People's Republic of China [16]. The patients included in the study were categorized based on the severity of the disease. Severity was defined in this study in accordance with that presented by the New Coronavirus Pneumonia Prevention

and Control Program (6th edition) published by the National Health Commission of China [17]: [1] mild: no detection of pneumonia in imaging (CT); [2] moderate: pneumonia diagnosed based on patients' symptoms and imaging examination; [3] severe: one of the following factors observed: (i) respiratory rate equal to or larger than 30/min; (ii) resting pulse oxygen saturation (SpO_2) equal to or smaller than 93%; (iii); the division of partial pressure of oxygen (PaO_2) by the fraction of inspired oxygen (FiO_2) equal to or smaller than 300 mmHg (1 mmHg = 0.133 kPa); (iv) more than 50% lesion progression in 24–48 hours on imaging shown by multiple pulmonary lobes; [4] critical: if one of the following criteria are met: (i) the need for mechanical ventilation due to respiratory failure; (ii) shock; (iii) other complications requiring patents' admission into intensive care unit (ICU). Patients with mild or moderate disease were included in the “non-severe group” and severe or critical patients were categorized as the “severe group”. Moreover, patients were categorized in different age groups [18]: 1) patients under two years old (Class I); 2) patients aged between 3–12 years old (Class II); and 3) patients aged between 13–17 years old (Class III). The study was carried out in compliance with the edicts of the *Declaration of Helsinki* and was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (IR.SUMS.REC.1081).

Data Collection

In order to approve that patients were infected with the virus, reverse-transcription polymerase chain reaction (RT-PCR) was utilized to detect traces of SARS-CoV-2 nucleic acid in all patients. Also, endotracheal aspirate, bronchoalveolar lavage, nasopharyngeal swab, or oropharyngeal swab were employed to obtain RT-PCR samples. Chest CT was performed to diagnose pneumonia. The clinical manifestations, laboratory findings, and chest CT images were all extracted from electronic medical records. The obtained data was then reviewed and abstracted by two experienced radiologists.

Ct Scanning Protocol

The following scanners were employed to scan all the patients: 16-MDCT Philips brilliance (Philips healthcare, United States), with 120–130 kvp, Ave 75 mAs, tubal current 103–147, pitch 1.1–1.2, slice thickness 5 mm, and reconstruction thickness 5 mm. Patients were scanned in the supine position and during a breath-hold after inhalation.

Image Viewing And Evaluation

The analysis of all the CT images was performed separately by two radiologists with chest-imaging experience exceeding five years. Any disagreement was resolved with a consensus. Likewise, another radiologist (with 25 years of experience in chest imaging) confirmed CT results by reviewing.

Then, the patterns extracted from CT images were grouped into three principal categories including lung, bronchial, and pleural changes. Each category was then narrowed down to further subcategories. The changes in patients' lungs were organized into the following eight subcategories: ground-glass opacities (GGO; high degrees of reduction while the underlying lung vessels were not obscured), consolidation (the intensity of lung parenchyma was homogeneously increased through obscuring the underlying vessels), crazy paving (GGO with septal thickening), reverse halo (central GGO was surrounded by more dense consolidation), tree-in-bud pattern (centrilobular nodules with a linear branching pattern), centrilobular nodule, solid nodule (well defined larger than 3 mm). Also, the changes concerning bronchial were divided into two subcategories: air bronchogram (an air-filled image of bronchus in lung lesions) and bronchus distortion. Moreover, the pleural changes were classified into three subcategories: thickening of the pleura and pleural effusion. The distribution of the lung lesions was divided to 4 patterns: (1) predominantly peripheral (principally including the peripheral region which was made up of one-third of the lung), (2) central (or the central region constituting two-thirds of the lung), or (3) peribronchovascular (accompanied by bronchovascular bundle) and (4) diffuse. Recently, it has been shown that the abnormal CT findings in COVID-19 include consolidation, GGO, bilateral involvement, peripheral and diffuse distribution [8, 19, 20].

Results

Basic And Demographic Findings

A comparison of basic clinical and laboratory characteristics of severe and non-severe patients is presented in Table 1. The patients' mean age was 9.58 ± 5.35 years, ranging from two months to 17 years, and most patients were female (31 females (58.5%) and 22 (41.5%) male). In the present study, a total of 25 and 28 patients were labeled as severe and non-severe patients, respectively. Patients in the severe group were found to be younger (8.33 ± 5.51 years) than the non-severe group (10.69 ± 5.05 years). No significant age and sex differences were found between the severe and non-severe groups ($P = 0.118$, and $P = 0.442$, respectively). As shown in Table 2, after the patients were grouped based

on their age, a number of seven, 27, and 19 subjects were placed in class I (≤ 2 years), class II (3–12 years), and class III (13–17), respectively. Five (71.4%), 14 (51.9%), and six (31.6%) patients showed severe signs in the age-specified class I, II, and III, respectively (P = 0.154). In addition, there was no significant sex difference between the three age-stratified groups (P = 0.269). The mean time from the illness onset to the hospital admission was 4.47 ± 3.55 days, and six patients were admitted to the ICU. Besides, the hospitalization process lasted considerably more in severe patients (7.16 ± 5.09 days) than in non-severe (3.78 ± 2.39 days) ones (P = 0.003).

Table 1
Comparison of clinical and laboratory features between severe and non-severe pediatric patients with COVID-19

		Total		Severe		Non severe		P-value
		N	Mean (SD)/percentage	N	Mean (SD)/percentage	N	Mean (SD)/percentage	
Age, year		53	9.58 (5.35)	25	8.33 (5.51)	28	10.69 (5.05)	0.118
Sex	**Male**	22	41.5%	9	36.0%	13	46.4%	0.442
	Female	31	58.5%	16	64.0%	15	53.6%	
Disease onset to hospital admission duration		53	4.47 (3.55)	25	4.92 (3.80)	28	4.07 (3.32)	0.383
Hospital duration		53	5.37 (4.22)	25	7.16 (5.09)	28	3.78 (2.39)	**0.003**
ICU duration		53	0.69 (2.46)	25	1.48 (3.45)	28	0.00 (0.00)	**0.007**
ICU admission	**Yes**	6	11.3%	6	24.0%	0	0.0%	**0.006**
	No	47	88.7%	19	76.0%	28	100.0%	
Fever	**Yes**	42	79.2%	19	76.0%	23	82.1%	0.582
	No	11	20.8%	6	24.0%	5	17.9%	
Dry cough	**Yes**	40	75.5%	21	84.0%	19	67.9%	0.173
	No	13	24.5%	4	16.0%	9	32.1%	
Nasal congestion	**Yes**	5	9.4%	3	8.0%	2	10.7%	0.736
	No	48	90.6%	23	92.0%	25	89.3%	
Poor feeding	Yes	2	28.6%	1	20.0%	1	50.0%	0.427
	No	5	71.4%	4	80.0%	1	50.0%	
Body pain	Yes	14	30.4%	4	20.0%	10	38.5%	0.177
	No	32	69.6%	16	80.0%	16	61.6%	
Nausea	Yes	12	26.1%	6	30.0%	6	23.1%	0.596
	No	34	73.9%	14	70.0%	20	76.9%	
Diarrhea	**Yes**	5	9.4%	4	16.0%	1	3.6%	0.122
	No	48	90.6%	21	84.0%	27	96.4%	
Vomiting	**Yes**	11	20.8%	5	20.0%	6	21.4%	0.898
	No	42	79.2%	20	80.0%	22	78.6%	
Abdominal pain	**Yes**	3	6.5%	2	10.0%	1	3.8%	0.402
	No	43	93.5%	18	90.0%	25	96.2%	
Distress	**Yes**	23	43.4%	23	92.0%	0	0.0%	**< 0.001**
	No	30	56.6%	2	8.0%	28	100.0%	
Outcome	**Dead**	1	1.9%	1	4.0%	0	0.0%	0.285
	Alive	52	98.1%	24	96.0%	28	100.0%	
Leukocyte count, $\times 10^9$/L		53	9232.08 (4755.19)	25	10064.00 (4477.06)	28	8489.29 (4951.64)	0.096
Leukopenia ($< 3.5 \times 10^9$/L)	**Yes**	3	5.7%	0	0.0%	3	10.7%	0.092
	No	50	94.3%	25	100.0%	25	89.3%	

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

P-value less than 0.05 was considered as significant.

		Total		Severe		Non severe		P-value
		N	Mean (SD)/percentage	N	Mean (SD)/percentage	N	Mean (SD)/percentage	
Leukocytosis	**Yes**	17	32.1%	11	44.0%	6	21.4%	0.079
(> 11 × 10^{9}/L)	**No**	36	67.9%	14	56.0%	22	78.6%	
Lymphocyte, %		53	26.249 (13.17)	25	29.22 (15.61)	28	23.59 (10.11)	0.250
Lymphopenia (< 20%)	**Yes**	21	39.6%	8	32.0%	13	46.4%	0.284
	No	32	60.4%	17	68.0%	15	53.6%	
Lymphocytosis	**Yes**	7	13.2%	6	24.0%	1	3.6%	**0.028**
(> 40%)	**No**	46	86.8%	19	76.0%	27	96.4%	
CRP, mg/L		53	40.13 (45.93)	25	45.64 (52.01)	28	35.21 (40.08)	0.823
ESR, mm/h		16	34.75 (29.03)	5	43.00 (41.72)	11	31.00 (22.77)	0.865
O_2 saturation, %		51	93.61 (5.89)	25	90.44 (6.85)	26	96.65 (2.19)	**< 0.001**
Respiratory rate		52	32.48 (13.36)	25	37.88 (15.66)	27	27.48 (8.35)	**0.008**
Antiviral therapy	**Yes**	11	20.8%	4	16.0%	7	25.0%	0.420
	No	42	79.2%	21	84.0%	21	75.0%	
Antibacterial therapy	**Yes**	49	92.5%	23	92.0%	26	92.9%	0.906
	No	4	7.5%	2	8.0%	2	7.1%	
Comorbid disease								
Comorbid disease	**Yes**	20	37.7%	12	48.0%	8	28.6%	0.145
	No	33	62.3%	13	52.0%	20	71.4%	
G6PD deficiency	**Yes**	4	7.5%	3	12.0%	1	3.6%	0.246
	No	49	92.5%	22	88.0%	27	96.4%	
Cardiovascular	**Yes**	3	5.7%	2	8.0%	1	3.6%	0.486
	No	50	94.3%	23	92.0%	27	96.4%	
Gastrointestinal	**Yes**	3	5.7%	2	8.0%	1	3.6%	0.486
	No	50	94.3%	23	92.0%	27	96.4%	
Other comorbid diseases	**Yes**	6	11.3%	2	8.0%	4	14.3%	0.471
	No	47	88.7%	23	92.0%	24	85.7%	

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

P-value less than 0.05 was considered as significant.

Table 2
Comparison of clinical and laboratory features among different age groups in pediatric patients with COVID-19

		Total		Age class 1 (0–2)		Age class 2 (3–12)		Age class 3 (13–17)		P-value
		N	Mean (SD)/percentage	N	Mean (SD)/percentage	N	Mean (SD)/percentage	N	Mean (SD)/percentage	
Severe	Severe	25	47.2%	5	71.4%	14	51.9%	6	31.6%	0.154
	Non-severe	28	52.8%	2	28.6%	13	48.1%	13	68.4%	
Sex	Male	22	41.5%	1	14.3%	13	48.1%	8	42.1%	0.269
	Female	31	58.5%	6	85.7%	14	51.9%	11	57.9%	
Disease onset to hospital admission duration		53	4.47 (3.55)	7	4.43 (4.31)	27	4.70 (3.58)	19	4.16 (3.38)	0.889
Hospital duration		53	5.37 (4.22)	7	4.00 (2.16)	27	6.07 (3.94)	19	4.89 (5.08)	0.074
ICU duration		53	0.69 (2.46)	7	0.85 (1.57)	27	1.00 (3.26)	19	0.21 (0.91)	0.306
ICU admission	Yes	6	11.3%	2	28.6%	3	11.1%	1	5.3%	0.250
	No	47	88.7%	5	71.4%	24	88.9%	18	94.7%	
Fever	Yes	42	79.2%	4	57.1%	24	88.9%	14	73.7%	0.138
	No	11	20.8%	3	42.9%	3	11.1%	5	26.3%	
Dry cough	Yes	40	75.5%	7	100.0%	17	63.0%	16	84.2%	0.069
	No	13	24.5%	0	0.0%	10	37.0%	3	15.8%	
Nasal congestion	Yes	5	9.4%	2	28.6%	3	11.1%	0	0.0%	0.079
	No	48	90.6%	5	71.4%	24	88.9%	19	100.0%	
Poor feeding	Yes	2	3.8%	2	28.6%	-	-	-	-	-
	No	51	96.2%	5	71.4%	-	-	-	-	
Body pain	Yes	14	30.4%	-	-	5	18.5%	9	47.4%	**0.036**
	No	32	69.6%	-	-	22	81.5%	10	52.6%	
Nausea	Yes	12	26.1%	-	-	8	29.6%	4	21.1%	0.514
	No	34	73.9%	-	-	19	70.4%	15	78.9%	
Diarrhea	Yes	5	9.4%	0	0.0%	3	11.1%	2	10.5%	0.656
	No	48	90.6%	7	100.0%	24	88.9%	17	89.5%	
Vomiting	Yes	11	20.8%	0	0.0%	8	29.6%	3	15.8%	0.182
	No	42	79.2%	7	100.0%	19	70.4%	16	84.2%	
Abdominal pain	Yes	3	6.5%	-	-	2	7.4%	1	5.3%	0.772
	No	43	93.5%	-	-	25	92.6%	18	94.7%	
Distress	Yes	23	43.4%	5	71.4%	13	48.1%	5	26.3%	0.093
	No	30	56.6%	2	28.6%	14	51.9%	14	73.7%	
Outcome	Dead	1	1.9%	0	0.0%	1	3.7%	0	0.0%	0.612
	Alive	52	98.1%	7	100.0%	26	96.3%	19	100.0%	
Leukocyte count, $\times 10^9$/L		53	9232.08 (4755.19)	7	10085.71 (2848.05)	27	9085.19 (5532.67)	19	9126.32 (4251.64)	0.483
Leukopenia ($< 3.5 \times 10^9$/L)	Yes	3	5.7%	0	0.0%	3	11.1%	0	0.0%	0.216

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. P-value less than 0.05 was considered as significant.

		Total		Age class 1 (0–2)		Age class 2 (3–12)		Age class 3 (13–17)		P-value
		N	Mean (SD)/percentage	N	Mean (SD)/percentage	N	Mean (SD)/percentage	N	Mean (SD)/percentage	
	No	50	94.3%	7	100.0%	24	88.9%	19	100.0%	
Leukocytosis	Yes	17	32.1%	4	57.1%	9	33.3%	4	21.1%	0.212
(> 11×10^{9}/L)	No	36	67.9%	3	42.9%	18	66.7%	15	78.9%	
Lymphocyte, %		53	26.24 (13.17)	7	30.95 (12.65)	27	26.67 (13.71)	19	23.90 (12.71)	0.373
Lymphopenia	Yes	21	39.6%	1	14.3%	10	37.0%	10	52.6%	0.192
(< 20%)	No	32	60.4%	6	85.7%	17	63.0%	9	47.4%	
Lymphocytosis	Yes	7	13.2%	2	28.6%	3	11.1%	2	10.5%	0.435
(> 40%)	No	46	86.8%	5	71.4%	24	88.9%	17	89.5%	
CRP, mg/L		53	40.13 (45.93)	7	4.57 (5.71)	27	50.93 (45.82)	19	37.89 (48.80)	**0.009**
ESR, mm/h		16	34.75 (29.03)	2	22.50 (2.12)	10	46.20 (31.55)	4	12.25 (3.86)	0.051
O_2 saturation, %		51	93.61 (5.89)	7	87.14 (9.70)	26	93.62 (4.99)	18	96.11 (2.90)	**0.015**
Antiviral therapy	Yes	11	20.8%	1	14.3%	4	14.8%	6	31.6%	0.348
	No	42	79.2%	6	85.7%	23	85.2%	13	68.4%	
Antibacterial therapy	Yes	49	92.5%	7	100.0%	26	96.3%	16	84.2%	0.224
	No	4	7.5%	0	0.0%	1	3.7%	3	15.8%	
Comorbid disease										
Comorbid disease	Yes	20	37.7%	3	42.9%	10	37.0%	7	36.8%	0.956
	No	33	62.3%	4	57.1%	17	63.0%	12	63.2%	
G6PD deficiency	Yes	4	7.5%	1	14.3%	1	3.7%	2	10.5%	0.530
	No	49	92.5%	6	85.7%	26	96.3%	17	89.5%	
Cardiovascular	Yes	3	5.7%	2	28.6%	1	3.7%	0	0.0%	**0.016**
	No	50	94.3%	5	71.4%	26	96.3%	19	100.0%	
Gastrointestinal	Yes	3	5.7%	0	0.0%	2	7.4%	1	5.3%	0.748
	No	50	94.3%	7	100.0%	25	92.6%	18	94.7%	
Other comorbid diseases	Yes	6	11.3%	0	0.0%	3	11.1%	3	15.8%	0.529
	No	47	88.7%	7	100.0%	24	88.9%	16	84.2%	

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. P-value less than 0.05 was considered as significant.

Clinical Findings

The most common symptoms at the time of patients' admission were fever (42 (79.2%)), followed by dry cough (40 (75.5%)). It was reported that 23 patients showed signs of respiratory distress (43.4%) in the course of their hospital admission. The mean level of O_2 saturation was 93.61 ± 5.89%. Upper respiratory symptoms such as nasal congestion were uncommon and were observed only in five patients (9.4%). Generally, it was reported that the severe and non-severe groups did not differ significantly in terms of the clinical symptoms such that 19 and 23 severe patients showed fever and dry cough compared to 21 and 19 non-severe patients, respectively (P = 0.582 and P = 0.173, respectively). Similarly, dry cough and fever were the most prevalent clinical symptoms demonstrated in different age groups.

Comorbidities, Treatments And Outcomes

Eleven (20.8%) and 49 (92.5%) patients received antivirals and antibiotics. Twenty (37.7%) patients were shown to have comorbidities such that glucose-6-phosphate dehydrogenase (G6PD) deficiency (4 (7.5%)), CVD (3 (5.7%)), and gastrointestinal disorders (3 (5.7%)) were the most common ones. Twelve of the severely infected patients (12/25, 48.0%) had underlying diseases, while eight non-severe patients (8/28, 28.6%) had comorbidities ($P = 0.145$). Additionally, fifty-two patients (94.5%) showed clinical improvement after two weeks (mortality rate = 5.5%). A 12-year-old patient showing fever, vomiting, abdominal pain, lymphopenia, high CRP (150 mg/dl), and G6PD deficiency with GGO chest finding died from COVID-19.

Laboratory Findings

A number of 21 (39.6%) and seven (13.2%) patients showed lymphopenia and lymphocytosis, respectively. Moreover, patients with severe COVID-19 infection showed lymphocytosis compared to non-severe patients ($P = 0.038$). Yet, in comparison with non-severe patients, the severe ones did not differ significantly in terms of leukocyte count, leukopenia, and leukocytosis ($P > 0.05$). Moreover, no significant differences were observed between the severe and non-severe groups regarding CRP and ESR ($P = 0.823$ and $P = 0.865$, respectively). Moreover, regarding age-specified grouping, apart from CRP, which was significantly lower in patients aged lower than two years than those with 3–12 and 13–17 years of age ($P = 0.009$), no significant differences were found among other laboratory findings between the three age-specified groups ($P > 0.05$). Albeit, the ESR level difference between different age groups inclined towards being statistically significant ($P = 0.051$).

Chest Ct Findings

Chest CT scan findings were compared with regard to the disease severity and the three different age-specified groups as presented in Table 3 and Table 4, respectively. Chest CT findings were normal in 36 (67.9%) patients; moreover, severe group (12 (48.0%)) were reported to have a higher number of abnormal CT findings in comparison with non-severe (5 (17.9%)) ones ($P = 0.019$). Moreover, GGOs (12 (22.6%)) and consolidation (10 (18.29%)), followed by subpleural sparing (5 (9.4%)), were the dominant findings in abnormal CT scans. A comparison of each CT item showed that CT findings were not significantly different between severe and non-severe infected patients ($P > 0.05$). One severe patient and another non-severe one, aged more than 12 years showed peripheral halo on their chest CT scans. In the group with patients aged under two years, only a two-year-old patient showed abnormal chest CT findings of GGO, consolidation, and subpleural sparing. GGO was detected in one (14.3%), six (22.2%), and five (26.3%) patients from class I, class II, and class III age groups, respectively ($P = 0.807$). Moreover, consolidation was reported in one (14.3%), three (11.1%), and six (28.6%) patients from class I, class II, and class III age groups, respectively ($P = 0.206$).

Table 3
Comparison of chest CT features between severe and non-severe pediatric patients with COVID-19

		Total		Severe		Non severe		P-value
		N	Mean (SD)/percentage	N	Mean (SD)/percentage	N	Mean (SD)/percentage	
CT	**Normal**	36	67.9%	13	52.0%	23	82.1%	**0.019**
	Abnormal	17	32.1%	12	48.0%	5	17.9%	
Ground Glass Opacity	**Yes**	12	22.6%	7	28.0%	5	17.9%	0.378
	No	41	77.4%	18	72.0%	23	82.1%	
Peripheral halo	**Yes**	2	3.8%	1	4.0%	1	3.6%	0.935
	No	51	96.2%	24	96.0%	27	96.4%	
Consolidation	**Yes**	10	18.9%	7	28.0%	3	10.7%	0.108
	No	43	81.1%	18	72.0%	25	89.3%	
Subpleural sparing	**Yes**	5	9.4%	2	8.0%	3	10.7%	0.736
	No	48	90.6%	23	92.0%	25	89.3%	

P-value less than 0.05 was considered as significant.

Table 4
Comparison of chest CT features among different age groups in pediatric patients with COVID-19

		Total		Age class I (0–2)		Age class II (3–12)		Age class II (13–17)		P-value
		N	Mean (SD)/percentage	N	Mean (SD)/percentage	N	Mean (SD)/percentage	N	Mean (SD)/percentage	
CT	Normal	36	67.9%	6	85.7%	18	66.7%	12	63.2%	0.539
	Abnormal	17	32.1%	1	14.3%	9	33.3%	7	36.8%	
Ground Glass Opacity	Yes	12	22.6%	1	14.3%	6	22.2%	5	26.3%	0.807
	No	41	77.4%	6	85.7%	21	77.8%	14	73.7%	
Peripheral halo	Yes	2	3.8%	0	0.0%	0	0.0%	2	10.5%	0.156
	No	51	96.2%	7	100.0%	27	100.0%	17	89.5%	
Consolidation	Yes	10	18.9%	1	14.3%	3	11.1%	6	31.6%	0.206
	No	43	81.1%	6	85.7%	24	88.9%	13	68.4%	
Subpleural sparing	Yes	5	9.4%	1	14.3%	2	7.4%	2	10.5%	0.840
	No	48	90.6%	6	85.7%	25	92.6%	17	89.5%	

P-value less than 0.05 was considered as significant.

Discussion

Coronaviruses are enveloped RNA viruses of the family *Coronaviridae* that cause a variety of diseases in mammals and birds, such as human respiratory syndrome [21]. A variety of studies have revealed that pediatric patients infected with COVID-19 show a mild respiratory infection compared to the adult population [22, 23]. COVID-19 disease is of utmost significance in children and in the physiological differences between this population and adults. Thus, this study was performed on 53 pediatric patients with RT-PCR confirmed COVID-19 who were admitted to the hospital. After their admission, their clinical, laboratory, and radiological findings were evaluated. The results showed that patients in the severe group had more respiratory distress, hospital and ICU duration, lymphocytosis, and lower O_2 saturation than non-severe patients. Severe patients also presented more number of abnormal CT findings, particularly GGO and consolidation findings. Besides, CRP levels were normal in patients under two years of age, while it was significantly higher in both other groups consisting of older patients. Also, it was found that of chest CT findings, GGO, and consolidation had higher frequency.

In line with the previous studies, the most commonly observed symptoms were fever and dry cough [22, 24, 25], like other viral respiratory infections that affect children [26]. In this regard, both dry cough and fever were the most common clinical manifestations in each age group class. Additionally, the findings of this study showed that a small percentage of patients were admitted to the ICU, which is consistent with that of other studies [4, 25]. A systematic review study revealed that comorbidities with the highest frequency in children with COVID-19 were asthma, immunosuppression, and cardiovascular disease (CVD) [3], while in our study the most common comorbidities included G6PD deficiency, CVD, and gastrointestinal disease. Furthermore, regarding the different age-specified groups in this study, class I showed more cardiovascular comorbid disease than class II and III. Besides, patients in age class II showed the highest percentages of fever and the longest hospital duration, implying the higher severity of this pneumonia in this age group.

Different and conflicting laboratory findings have recently been reported as with the different age groups with COVID-19-confirmed patients [1, 27]. Similar to many other viral infections, coronavirus infection is expected to lead to an increased number of lymphocytes, although most studies have contrarily shown a decrease in lymphocytes in these patients [20, 21, 28]. This finding suggests that one of the causes may be lymphocyte consumption. Yet, in our study, the severe group showed significant lymphocytosis, which was consistent with results found in the study by Sun et.al. on COVID-19-diagnosed infants aged lower than one year [29]. Also, in a meta-analysis conducted on a pediatric population with COVID-19, lymphocytosis, and leukopenia were introduced as the main indices for pediatric inpatients [30]. It is worthy of note that the stage of the disease seems to play a crucial role in how lymphopenia or lymphocytosis are developed. Generally, lymphocytosis emerges at the early stages of the disease. Moreover, at the late stages, lymphopenia occurs due to lymphocyte consumption in the activation against virus and as a result of apoptosis. Therefore, it is important to pay attention to the stage of the disease in the lymphocyte count and immune cells in general to the extent that disregarding this issue can lead to conflicting results in various studies. In the groups formed based on the patients' age, it was revealed that as the patients' age increased, O_2 saturation decreased. On the other hand, nasal congestion, dry cough, respiratory distress, and disease severity were more common in the age class I than class II and III. The average CRP was normal in class I, but it suddenly

increased in classes II and III. Therefore, it seems that CRP could not be a reliable marker for showing the severity of the disease in COVID-19 infant patients. Rather, it is an effective index in children aged more than two years.

This study included four children with G6PD deficiency, three of whom were placed in the severe group. Infections such as COVID-19 can trigger hemolysis of red blood cells in G6PD deficiency patients [31–33]. Wu et.al. showed that G6PD deficiency enhances human coronavirus infection in cell culture [34]. Hydroxychloroquine, used as an effective drug to treat COVID-19 in many medical centers, has pro-hemolytic effects [31, 35, 36]. A number of COVID-19 patients have been reported that showed hemolysis symptoms after the use of hydroxychloroquine [32, 37]. However, none of the patients with G6PD deficiency in this study received hydroxychloroquine. Accordingly, suggesting that this drug should be used with caution in COVID-19 patients who suffer from G6PD deficiency or use any other alternative drug.

Although no specific clinical or radiologic finding is available for COVID-19 diagnosis, a chest CT scan is useful in identifying the severity of lung lesions in patients with pneumonia [38]. In the present study, approximately two-thirds of patients were presented with normal chest CT scans and demonstrated a mild, non-deteriorating course of infection. Patients in the severe group showed more chest CT findings such as consolidation and GGO compared to non-severe patients, though it was not statistically significant. In addition, a significant difference was seen in severe patients compared to the non-severe group. In agreement with the present study is the fact that the destruction of pulmonary parenchyma in radiological findings manifests itself as GGO and consolidation [4, 13, 39, 40]. Also, the presence of consolidation is indicative of the infiltration of inflammatory cells into the lungs and, consequently, damage to the pulmonary parenchyma. However, the age groups did not differ significantly in terms of chest CT findings. All in all, the use of CT findings, especially GGO and consolidation, along with other clinical findings, can be effective in the early detection of severe COVID-19.

To the best of the authors' knowledge, this is the first study that compares the clinical, laboratory, and CT findings of severe and non-severe COVID-19 pediatric patients among different age groups. Although the present study was conducted on a larger sample size compared to the similar studies on pediatric COVID-19 patients, one of the limitations of this study is the small sample size, especially in the age group consisting of patients aged less than two years. Due to the prevalence of some respiratory infections in children and the similarities and overlaps between radiological findings of these infections and coronavirus infection, more comprehensive and epidemiological studies are needed to find differential radiologic findings between these infections. It is suggested that further studies with larger sample sizes as well as comparisons with adult populations be conducted so as to shed more light on the differences in the symptoms and pathogenesis of coronavirus in the pediatric population.

Conclusion

There is a crucial need to better recognize the full laboratory spectrum of COVID-19 in different pediatric populations in order to establish an early diagnosis of the disease. Moreover, it is believed also to be the first attempt in comparing the aforementioned findings in different age groups. Findings revealed that lymphocytosis and abnormal CT findings (GGO and consolidation) are the most reliable factors associated with COVID-19 severity. Also, it was found in this study that the severity of the COVID-19 and respiratory distress decreased with age (in the group with patients aged less than 17 years).

Abbreviations

COVID-19
Coronavirus Disease 19; SARS-CoV-2:Severe Acute Respiratory Syndrome Coronavirus 2; CT:Computed Tomography; GGO:Ground-glass Opacity; RT-PCR:Reverse Transcriptase-polymerase Chain Reaction; ICU:Intensive Care Unit; G6PD:Glucose 6 Phosphatase Dehydrogenase

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (IR.SUMS.REC.1081). Individual informed consent was waived by the ethics committee listed above because this study used currently existing samples collected during the course of routine medical care and did not pose any additional risks to the patients. All patient data were anonymized prior to the analysis.

Consent for publication

Not applicable

Availability of data and materials

The dataset analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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None.

Authors' contributions

MH, SE, and AT set up the study design and interpreted the data. SH and RJL interpreted imaging. FGS and FR performed the statistical analyses, interpreted the data and drafted the manuscript. AT, MH and RJL revised the manuscript critically and provided continuous guidance throughout the study. RJ and SE collecting the data. All authors read and approved the final manuscript.

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