Epidemiological, clinical, laboratory and imaging finding of children with COVID-19 in Yazd, Iran; a single center historical cohort study.

Farzad Ferdosian[1]*, Zahra Nafei[1], Mehran Karimi[1], Marzie Vaghefi[1], Farimah Shamsi[2], Danial Chaleshi[3], Amir Pasha Amel Shahbaz[4], Elahe Akbarian[1]

[1]Department of Pediatrics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

[2]Department of Biostatistics and Epidemiology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

[3]Department of Science, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

[4]Department of Radiology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Abstract

Background: Following the onset of the novel Coronavirus Disease 2019 (COVID-19) in China and its rapid spread worldwide, numerous clinical manifestations and laboratory findings of this disease have been reported in adults and to a lesser extent, in children. It seems that COVID-19 has different clinical manifestations, less severity and in some cases, more complications in children than adults. Therefore, this study was conducted to investigate clinical symptoms and laboratory and imaging findings of children under 18 years of age hospitalized with COVID-19.

Methods: This historical cohort study was conducted from February 2020 to July 2021 on children under 18 years of age with suspected, probable and definite COVID-19 who were hospitalized in Shahid Sadoughi hospital, Yazd, Iran

Results: Of 191 patients, 133, 26 and 32 patients were diagnosed as confirmed, probable, and suspect cases of COVID-19 disease, respectively. The participants included 95 (49.7%) boys and 96 (50.3%) girls with an average age of 6.5 years. Most patients (45.6%) were in the age range of 1 to 59 months. Patients' most common clinical presentation at the time of hospitalization was general symptoms (40.4%), such as fever, weakness and fatigue, followed by respiratory symptoms (28.7%). During hospitalization, 82 patients underwent chest Computed Tomography (CT) scan of which ground glass opacities were reported in 41 cases.

Conclusion: The most common clinical manifestations in children with COVID-19 were fever, weakness and fatigue. The disease was more severe in patients with fever for more than five days. Furthermore, consolidation on chest CT scan was related to the severity of the disease.

Keywords: COVID-19, Children, Epidemiology, Symptom, Laboratory

Abbreviations: COVID-19: Coronavirus Disease in 2019; PCR: Polymerase Chain Reaction; MIS-C: Multisystem Inflammatory Syndrome; in Children; CRP: C-Reactive Protein; PT: Prothrombin Time; GGO: Ground Glass Opacity; PICU: Pediatric Intensive Care Unit; CT: Chest Computed Tomography; LV: Left Ventricle

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Introduction

Since the beginning of the Coronavirus Disease in 2019 (COVID-19) in Wuhan, China and its exponential spread worldwide 55,5446,890 people have been infected and 6,353,692 patients died until July 14, 2022 [1]. Up to this date, more than 7 million people have been infected and more than 140 thousand patients died in Iran [2].

Although many studies have focused on the different aspects of COVID-19 in adults, few studies have reflected on the epidemiological aspects, clinical manifestations and laboratory findings of this disease in people under 20. It seems that COVID-19 shows mild clinical presentations and better outcome in children than adults [3,4].

Some studies showed that the disease severity and mortality were significantly higher in children with COVID-19 and underlying diseases [5,6].

In addition, children are susceptible to severe disease in the form of Multisystem Inflammatory Syndrome in Children (MIS-C). It seems Obesity, hypoxia, lymphopenia and increased C-Reactive Protein (CRP) during the hospitalization period predicts the occurrence of MIS-C [7].

Therefore, in children and adolescents, factors such as the variety of clinical symptoms of COVID-19, the existence of diarrhoea as a relatively common symptom, the negative Polymerase Chain Reaction (PCR test in many patients, mild symptoms and the long incubation period of the disease indicates the need to pay more attention to the different aspects of this disease in this age group.

The present study was conducted to examine different dimensions of the disease, including symptoms before and during hospitalization, as well as paraclinical findings in 191 children hospitalized in a referral hospital in Yazd (central Iran).

Materials and Methods

This historical cohort study has been conducted from February 2020 to July 2021 on children under 18 years of age with suspected, probable and definite COVID-19 who was hospitalized in Shahid Sadoughi hospital, Yazd, Iran.

Ethical approval was obtained through the ethical committee of Shahid Sadoughi university of medical sciences (IR.SSU.REC. 1399.312). Informed consent was waived because of the historical cohort design.

Baselines characteristics including age and sex were collected. Also clinical, laboratory and imaging data were extracted from hospital information system. Also, the parents were contacted and asked about the persistence of the clinical symptoms after the patients were discharged.

Again, the images were reviewed by a radiologist. Moreover, the parents were contacted and asked about the persistence of the clinical symptoms after the patients were discharged. The severity of lung involvement in the CT scan graded from 0 to 25 so that a score of 0 to 5 was assigned for each lung lobe (of five lobes) based on the degree of involvement. The mild, moderate and severe was considered as ≤ 7, 8-17 and ≥ 18 respectively [8].

The data were analysed with SPSS-26 software and using descriptive statistics of frequency and percentage. The analytical statistics, including the *Chi-square* test and Fisher's exact test, were used to compare the frequency of qualitative variables. To check the normality of quantitative data, the Kolmogorov Smirnov test was conducted. Later, t-test and one way ANOVA were administered to compare the average of quantitative variables in terms of qualitative variables.

Definitions

Suspect COVID-19: A child with a history of dry cough, chills or sore throat with shortness of breath; with or without fever that cannot be explained by other etiological factors; with fever or respiratory symptoms of any severity, with a history of close contact with a probable/confirmed case of COVID-19 within 14 days before the onset of the disease symptoms.

Possible COVID: Radiological findings are strongly suggestive of the disease; the person has developed pneumonia with an inappropriate clinical response despite proper treatment; the patient's clinical conditions become more acute and worse; the person dies unusually and unexpectedly, and the result of PCR test is not known, or negative.

Definite COVID: A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Critical disease: When the patient needs medical support to survive and has an acute respiratory failure or severe infection and septic shock.

Severe disease: When the patient's blood oxygen level is less than 90% in ambient air, respiratory rate is more than 30/min in adults, the respiratory rate is higher than the normal level based on age (more than 60/min in 2 months ≥, more than 50/min for 2-12 mo., more than 40/min for 1-4 years, more than 30/min for 5 years and more) or the patient has symptoms of severe respiratory failure.

Non-severe disease: When the patient has no symptoms of severe or critical illness.

Results

The present study was conducted on 191 children under 18 years old hospitalized with COVID-19. The results indicated that 133 (69.6%), 32 (16.8%) and 26 (13.6%) patients were diagnosed as confirmed, suspect and probable cases of COVID-19 disease, respectively. Among them, 95 (49.7%) cases were male and the patients' mean age was 6.5 years. The majority of patients (45.5%) were between the ages of one month and five years and residents of Yazd province (76.5%).

The most common clinical manifestations were fever (n=105, 54.9%), cough (n=51, 26.7%), diarrhoea (n=43, 22.5%) and respiratory distress (n=32, 16.8%), respectively (Table 1). There was a significant relationship between fever ≥ 5 days and the severity of the disease. (p=0.019). The patients' laboratory findings at the time of hospital admission showed that 43 (22.5%) had lymphopenia, 35 (19.7%) had thrombocytopenia and 41 had impaired Prothrombin Time (PT). Other laboratory findings are entirely shown in Table 2. Chest CT scan was performed for 82 patients, showing that the most and least common findings were ground glass opacity (n=41, 50%) and pleural effusion (n=7, 8.5%), respectively. In our study, 42 cases of CT patients were evaluated in terms of severity of lung involvement indicating 8 (19%), 23 (54.7%), and 11 (26.1%) cases of mild, moderate and severe lung involvement. Out of 49 echocardiograms, abnormal results were reported in 18 patients and the most common finding was left ventricle systolic dysfunction in 13 people (26.5%).

44 patients diagnosed with MIS-C were treated during hospitalization and there was a significant relationship between the severity of the disease at the time of hospitalization and MIS-C (P=0.001).

42.4% of patients had at least an underlying disease, the most common of which were neurological diseases (13.1%), followed by malignancies (7.9%). A significant association was found between the type of underlying disease and the

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severity of COVID-19 so patients with heart disease experienced more severe and critical conflicts (P: 0.02).

It is worth noting that 49.2% of the patients had severe and critical illness. Also, 47.1% of patients underwent oxygen therapy; only 14 cases (7.3%) required intubation and 26.7% were hospitalized in Pediatric Intensive Care Unit (PICU). The mean duration of hospitalization was 11.1 days (range: 1-36 days).

The results of our study showed that 24 patients (12.5%) died and the most common symptoms of them at admission time were general symptoms such as weakness, fatigue, fever (50%) followed by respiratory symptoms (16.6%).

The most common symptoms after discharge from the hospital were weakness and fatigue (10.1%), followed by respiratory symptoms (9.5%).

Table 1. *The baseline and clinical characteristics of patients with COVID-19.*

Characteristics	Number (%)
Gender	
Male	95 (49.7%)
Female	96 (50.3%)
Age group	
<1 month	8 (4.2%)
1 month-5 years	87 (45.5%)
5-13 years	60 (31.4%)
13-18 years	36 (18.8%)
Severity of disease	
Critical	26 (13.6%)
Sever	68 (35.6%)
Not sever	97 (50.8%)
Case definition	
Confirmed	133 (69.6%)
Probable	26 (13.6%)
Suspected	32 (16.8%)
Hospital length to stay	
<1 week	143 (74.9%)
1-2 week	33 (17.2%)
>2 weeks	15 (7.9%)
Maximum respiratory support	
Noninvasive respiratory support	90 (47.1%)
Invasive mechanical ventilation	14 (7.3%)
Medical therapy	
Intravenous immunoglobulin	6 (3.1%)
Steroid therapy	58 (30.4%)
Remdesivir	53 (27.7%)
Kaletra	29 (15.2%)
Hydroxychloroquine	23 (12%)
Signs and symptoms at admission	
Fever	105 (54.9%)
Cough	51 (26.7%)
Diarrhea	43 (22.5%)
Chest discomfort	32 (16.8%)
Comorbidities	
Neurologic	25 (13.1%)
Malignancy	15 (7.9%)
Hematologic	9 (4.7%)
Heart conditions	7 (3.7%)
Nephrologic	7 (3.7%)

Chronic lung disease	5 (2.6%)
Gastrointestinal disease	4 (2.1%)
Others	9 (4.7%)
Chest CT scan (N: 82)	
Ground glass opacity	41 (50%)
Consolidation	24 (29.2%)
Atelectasis	12 (14.6%)
Plural effusion	7 (8.5%)
No specific findings	19 (23.1%)
Echocardiography (N:49)	
Normal	31 (63.2%)
Depressed LV function	3 (6.1%)
Coronary artery abnormality	3 (6.1%)
MR	1 (2%)
MR+depressed EF	2 (4%)
Depressed EF+pericardial effusion	1 (2%)
MR+depressed EF+Coronary abnormality	3 (6.1%)
MR+myocarditis+depressed EF	4 (4%)
Endocarditic	1 (2%)

Table 2. *Laboratory data of patients with COVID-19.*

Laboratory data	N/total N (%)
Na (mEq/L, NR:135-145)	
Hyponatremia	61/164 (37.1%)
Hypernatremia	4/164 (2.9%)
K (mEq/L, NR: 3.5-5.5)	
Hypokalemia	13/157 (8.2%)
Hyperkalemia	5/157 (3.3%)
Platelets (×10^6/L, NR:150000-450000)	
Thrombocytopenia	35/177 (19.7%)
Thrombocytosis	25/177 (11.3%)
WBC (× 10^9/L, NR: 5000-15000)	
Leukopenia	37/178 (20.7%)
Leukocytosis	31/178 (17.6%)
Lymphopenia	43/150 (22.5%)
Ca (mg/dl, NR: 8.8-10.8)	
Hypocalcemia	45/94 (47.8%)
Hypercalcemia	1/94 (1.2%)
P (mg/dl, NR: 3-6)	
Hypophosphatemia	7/55 (12.7%)
Hyperphosphatemia	4/55 (7.3%)
PTT (seconds, NR<36)	
Increased	14/55 (25.5%)
PT (seconds, NR<12)	
Increased	41/55 (74.5%)

SGPT (U/L, NR<35)	
Increased	44/109 (40.4%)
SGOT (U/L, NR<45)	
Increased	47/110 (42.8%)
ESR (mm/h)	
Increased	46/98 (47%)
CPK>200	12/79 (15.2%)
BS (NR: 60-200)	
Hypoglycemia	3/103 (2.9%)
Hyperglycemia	6/103 (5.9%)
LDH>500	46/97 (47.4%)
CRP ≥ ++	68/154 (44.1%)
D dimer>200	14/28 (50%)

Discussion

This study showed that the demographic characteristics and mean age of children were consistent with other studies in Iran and the world. In such a way that the studies conducted in Iran on hospitalized children with COVID-19, more than half of the patients were boys and less than 5 years of age [9,10].

Clinical symptoms

Our study showed that the most common clinical symptoms of children on admission included fever, weakness, lethargy, fatigue and headache. In most similar studies, fever, cough and headache were common clinical symptoms [11-13]. Lee, et al. reviewed the studies on the clinical characteristics of children with COVID-19 and discovered that the most common symptoms were fever (47%) followed by cough (42%), while 23% of the children were asymptomatic [14]. Another study on 402 children aged 2 to 17 years with COVID-19 in India acquainted that the most common symptoms were fever (38.2%), cough and sore throat (20%), as well as abdominal pain and vomiting (less than 10%) [15]. Some studies introduced gastrointestinal problems as the most common symptoms [16]. This discrepancy in the findings can be attributed to the variety in the research methodologies, locations, inpatient or outpatient cases and probably different strains of the virus.

Disease severity

Nearly half of the patients in this study had a severe and critical illness, which is justified considering the studied population, which included hospitalized and referred patients from other hospitals. In a study conducted in Canada on 544 hospitalized children due to COVID-19, 29.7% of the children had severe disease [17]. We noted a significant relationship between the duration of fever before admission and the disease severity during hospitalization. In other terms, patients who experienced fever for more than five days had severe diseases [18,19].

MIS-C is a late manifestation of SARS-CoV-2 infection in children characterized by fever, systemic inflammation and dysfunction of multiple organs [20]. The researchers found a significant association between MIS-C and the severity of the disease, which is compatible with our findings [21,22]. In addition to inflammatory symptoms such as fever, weakness and fatigue; respiratory symptoms were commonly observed in this study. But in similar studies, gastrointestinal and cardiovascular symptoms were more common [23,24]. In addition, in our study, 80% of patients with MISC had a positive PCR test, while in Dinah's study, positive PCR test was reported in more than 99% of patients [25].

Imaging findings

In this study, 76.8% of the patients had an abnormal chest CT scan, of which 41 (50%) and 24 (22%) had a Ground Glass Opacity (GGO) and consolidation view. Similarly Mahmoudi, et al. reflected that only 9% had normal, but 91% had abnormal chest CT scan results. They declared that the GGO was the most frequent view (74%) in the chest CT scan [26]. Rahimi, et al. research demonstrated that bilateral GGO and sub pleural involvement were observed most commonly, and 16.1% had normal chest CT scan.

Also, our results showed that out of 49 echocardiograms, abnormal results were reported in 18 patients and the most common finding was Left Ventricle (LV) systolic dysfunction (n=13, 26.5%). In another study, among 114 patients with COVID-19, LV systolic dysfunction and Coronary artery dilation were seen in 47.4% and 10.5%, respectively, which is comprehensible with the present study [27].

Laboratory findings

Although our study's biochemical findings were unavailable for all patients, lymphopenia was observed in 22.5% of cases and increased CRP and LDH were noted in more than 40% of the patients, which is consistent with other literature results [28]. In a systematic review, 31.5% of children with COVID-19 had leukopenia and 9.1% had lymphopenia. The main laboratory findings in Yasuhara J, et al. study were lymphopenia (33%) increased D-dimer (52%) and increased CRP (40%). Another study in Congo indicated that in children with moderate to severe disease, CRP, D-dimer, creatinine and BUN increased significantly. In the present study, nearly half of the patients had elevated liver enzymes, which is in line with a study on 1100 patients with COVID-19 in Peru [29].

Underlying diseases

The high frequency of underlying diseases among children hospitalized with COVID-19 was reported in several countries (39% in Oman) and (37% in the United States of America), which is compatible with our findings (42.4%). The most common frequent underlying disease was the neurological condition, supported by the literature; however, some studies had conflicting results with this study [30]. Also, in our study, a significant number of deaths were observed in children with underlying diseases, which is compatible with another study in Iran.

The mean duration of hospitalization was 5.9 days in pediatric wards and 11.1 days in PICU, which are consistent with similar studies. However, a study in Oman maintained that the mean duration of hospitalization was two days in the pediatric ward and PICU was 3 days. This difference could be because our study was conducted in a referral hospital.

Conclusion

Our findings demonstrated that the most common clinical symptoms of children on admission included fever, weakness, lethargy, fatigue and headache. Also, patients who had fever for more than five days, consolidation in their chest CT scan and underlying diseases, especially cardiovascular diseases, experienced the more severe disease.

Ethics Approval and Consent to Participate

The present study was approved by the medical ethics committee of the academy, Shahid Sadoughi university of medical sciences, Iran.

Consent for Publication

Not applicable.

Competing Interests

Authors declare that they have no competing interests.

Authors Contribution

Zahra Nafei: Substantial contribution to conceptualization and design, data collection, data analysis and interpretation, drafting of the article and review of the article before submission.

Mahran Karimi: Project administration, conceptualization and design, data collection, data analysis and interpretation, drafting of the article and review of the article before submission.

Fazad Ferdosian: Organizing and supervising the course of the article writing and taking the responsibility.

Marzie Vaghefi: Collaboration in data analysis and interpretation, article writing and editing.

Farimah Shamsi: Data analysis and interpretation, method planning and writing a part of the article.

Danial Chaleshi: Original draft preparation, article writing and editing.

Amir Pasha Amel Shabaz: Investigation and data collection and writing a part of the article.

Elahe Akbarian: Data collection, methodology and validation, project coordinator and original draft preparation.

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Not applicable.

Availability of Data and Materials

The findings, dataset used and the analysis during the present study are available on request from the corresponding author. They are not publicly available due to privacy and ethical restrictions.

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*Correspondence to

Farzad Ferdosian

Department of Pediatrics,

Shahid Sadoughi University of Medical Sciences,

Yazd,

Iran

E-mail: *Ferdosian@ssu.ac.ir*